Faculty of Health Sciences
Department of Surgery

CONTROVERSIES AND PROBLEMS IN SURGERY

16TH SYMPOSIUM

05-06 OCTOBER 2012

THEME: "THE ROLE OF SURGERY IN MODERN CANCER THERAPY"

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA
Denkleiers • Leading Minds • Dikgopolo tša Dihlalefi

Department of Surgery

Leading Minds

MESSAGE FROM THE DEAN

It is my privilege as Dean of the Faculty of Health Sciences to welcome you to the University of Pretoria and our 16 Symposium on Controversies and Problems in Surgery. This symposium fits the University's goals of being an institution that will advance science and clinical practice in the interests of humanity. It also fits with our goal of being a venue of choice for academic discourse and for advancing the practice of Medicine, in this case, Surgery. It also affords our younger Specialists and Registrars the opportunity of hearing and engaging with those at the top of the discipline and helps to develop the thinking and analytic skills that go with being a top practitioner.

It is our privilege to host and welcome such a specialist group of Surgeons to our University. We trust that this symposium, as with those before and indeed those that will follow will add great value to advancing Surgery in our country. By exploring the controversies and the problems and engaging at this high level, quality of care will be the main beneficiary.

A special thank you to all my staff that have committed time and effort to organizing the symposium.

Yours sincerely,

PROF ERIC BUCH
DEAN: FACULTY OF HEALTH SCIENCES

WELCOME MESSAGE

We should like to welcome you all to this 16th Annual Controversies and Problems in Surgery Symposium.

This Controversies Symposium has become a fixture in the National Surgical Academic Calendar since it was introduced by Professor Carel Mieny several years back while still the Chair of the Academic Department of Surgery here at the University of Pretoria. He continued to convene it annually except for the two occasions when Professor Mokoena and Professor Franz acted in his stead. He therefore has left his remarkable branding on the congress and we hope to keep this if only to polish it from time to time in order to retain its lustre. Thank you Professor Mieny.

This year we chose a theme on the Role of Surgery in Modern Management of Cancer. Specifically we sought to discuss surgical treatment of advanced cancer that presents to General Surgeons. We particularly wanted to address disseminated intraperitoneal metastases including Mesothelioma and Pseudomyxoma Peritonei for which there has been a nihilist attitude among clinicians. We are pleased to welcome our two European guests, Prof Kurt van der Speeten from Belguim and Prof Marcello Deraco from Italy. We look forward to what we believe would be practice changing input from themon these difficult clinical pathology cases.

We should also welcome and thank our national and local speakers. We know that preparations for these meetings tax your time which you give gladly and willingly. Without your input the proceeding and the discourse would be sterile and hollow.

Let us welcome and thank our Trade colleagues who have shown us their loyalty to the Controversies Symposium and continue to support us even in these very trying economic times. Thank you each and every one of you.

We should further thank all the members of staff of the Department of Surgery especially the secretarial staff for their sterling work during the preparation for this conference.

Lastly we welcome you, the delegates and thank you for your support. We know that there are a number of competing interests for your precious time but you chose us. We trust we in turn will deliver you a memorable if not practice modifying academic programme.

We encourage you to engage and debate robustly without fear but still with civility.

Enjoy!

PROF TAOLE MOKOENA **PROF MESHACK NTLHE**

Professor Kurt van Der Speeten MD PhD

Professor van der Speeten is currently Professor of Pharmacology at the University Hasselt in Belguim. He is also a staff-surgeon at Ziekehuis Oost – Limburg and Head of Department of Surgical Oncology.

A medical graduate of Katholieke Universiteit Leuven, Belgium, he continued to read for post graduate Doctor of Medicine degree (MD) at the same university both awarded *summa cum laude*. His further academic training and research was in pharmacology of per-operative chemotherapy at Washington Cancer Institute and Uppsala University graduating from latter with PhD on Perioperative Cancer Chemotherapy in Patients with Peritoneal Carcinomatosis.

Professor van der Speeten is a trained General Surgeon most of which was in UZ Leuven. During his training he spent nearly two years in the Department of Surgery at University of Pretoria as part of his broader surgical training. His professional surgical work has been devoted to Oncology.

He has published many papers on a wide range of surgical topics but the thrust of his later publications is around oncology and especially intraperitoneal cytoreductive surgery.

Professor van der Speeten is a Board member of Belgian Society of Surgical Oncology, a member of Editorial Board of Acta Chirurgica Belgica and a reviewer of a number of leading oncology journals from Britain, Europe and North America.

Professor Marcello Deraco MD

Professor Deraco is currently Professor of Surgery of Digestive Tract at University of Roma and Surgical Oncologist responsible for peritoneal malignancies at Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy.

Professor Deraco obtained his medical degree *cum laude* from the Universityof Messina, Italy where he continued to train in General Surgery where was also awarded*cum laude.*

He further trained and done research in Oncology at the Univesity of Paris IX and Department of Surgery at Gustave Roussy Institut Villejuif , France. He has devoted much of his research on peritoneal malignancies focussing principally on mesothelioma but also on pseudomyxoma peritonei. He has published extensively on these topics generally and on cytoreductive surgery and intraperitoneal hyperthermic chemotherapy perfusion in treatment of peritoneal carcinomatosis from variety of cancers including ovarian, gastric, pseudomyxoma peritonei and colorectal malignancies.

Professor Deraco is a member of Italian Surgical Society, Italian Surgical Oncology Society and Society of Surgical Oncology. He is secretary of Italian Society for Loco-regional Cancer Therapy, serves on executive board of International Peritoneal Surface Oncology Group and Italian Mesothelioma Group. He received a number of awards for his outstanding scientific work.

Thank you to our sponsors and exhibitors

BAYER
MEDIQUIP

LEGACY

MPS

EQUITY

ARROW/TELEFLEX

MGB

ACROTEQ

ENDOVISIONS

SA BIOMEDICAL/SABIO MEDICAL

FRESENIUS KABI

NATIONAL BIO PRODUCTS

NORVATIS

ANMARATE

BETA (ONLY SPONSORING WINE)

KARL STORZ (SPONSORING BAGS)

UMSINSI

SMITH & NEPHEW

HITECH

MANTA MEDICAL

DRAWTEX

SURGICAL INNOVATIONS

TECMED

Valid at going to press

Provisional Programme Controversies and Problems in Surgery Symposium - University of Pretoria

16TH SYMPOSIUM 05-06 OCTOBER 2012

Theme: **Role of Surgery in Modern Cancer Therapy**
Venue: Boerhaave Hall-Faculty of Health Sciences

FRIDAY 05 OCTOBER 2012

07h30	**Registration and Coffee**		
08h00	**Introduction and Welcome**	*Convenor*	***Prof T Mokoena***
	Opening Address	*Dean*	***Prof E Buch***
	BREAST CANCER **Chairman: Prof Apffelstaedt**		
08:20	**Is bilateral mastectomy justified for treatment of breast cancer with bilateral axillary lymphadenopathy but detectable primary lesion in only one breast.**	*Speakers*	***Pro: Dr H Jekel*** ***Con: Dr I Buccimazza***
08:40	**Opposing Oncologic and Cosmetic challenges for breast conserving surgery for retro-areolar primary cancer lesion.**	*Speaker:*	***Con: Dr I Buccimazza*** ***Pro: Dr C Benn/Prof P Coetzee***
09:00	**Role of Surgery in isolated hepatic metastasis from breast carcinoma, melanoma or sarcoma**	*Speaker:*	***Prof J Ramos***
09:20	**What is the ideal neo-adjuvant chemotherapy for breast cancer.**	*Speaker:*	***Dr R Khanyile***
09:30	**What is the justification of the return of radical surgery for advanced breast cancer.**	*Speakers*	***Pro: Dr H Jekel*** ***Con: Dr C Benn***
09:50	**Does neo-adjuvant treatment really down stage breast cancer- what is the evidence?**	*Speakers:*	***Con: Prof Apffelstaedt*** ***Pro: Dr R Khanyile***
10:10	**Panel discussion**	*Panellists*	***All Speakers***
10:40 – 11:10	**TEA**		
11:10	**HEAD AND NECK PLUS MELANOMA** **Chairman: Prof J Pretorius**		
11:10	**Management of metastatic squamous cell carcinoma cervical lymphadenopathy with "occult" primary** **i). How hard should "occult" primary be sought.** **ii). The role of surgery in such patient management**	*Speakers*	***Pro: Prof J Pretorius*** ***Con: Dr G Fetter***
11:30	**Problems of melanoma on the back of the trunk** **i). Search for "sentinel" lymph nodes and lymph node management** **ii). Management options for metastatic melanoma** **a) role of surgery** **b) immune therapy and chemotherapy**	*Speakers :*	***Prof S Smit*** ***Prof J Apffelstaedt*** ***Dr R Khanyile***
11:50	**Management of advanced head and neck squamous cell carcinoma** o **Role of surgery** o **Role of radiotherapy**	*Speakers :*	***Con: Prof P Coetzee*** ***Pro: Dr G Fetter*** ***Dr A Hocepied***
12:10	**Panel discussion**	*Panellists*	***All Speakers***

FRIDAY 05 OCTOBER 2012

12:10 – 12:40	***LUNCH***		
	ADVANCED INTRA –ABDOMINAL CANCERS		**Chairman: Prof M Ntlhe**
12:40	**Rationale for treatment of peritoneal surface malignancy (PSM)**	*Speaker :*	***Prof K van der Speeten***
13:10	**Technique for cyto-reductive surgery (CRS) and Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)**	*Speaker :*	***Prof M Deraco***
13:40	**Results of CRS and HIPEC in Colorectal PSM and Pseudomyxoma Peritonei**	*Speaker :*	***Pro: Prof K van der Speeten***
14:10	**Surgical Management of Hepatic Metastases from Colorectal Carcinoma**	*Speaker:*	***Dr M Bernon***
14:30	**Quality of Life is an important consideration when deciding on cancer treatment**	*Speaker :*	***Dr Lizette Schoeman***
14:50	**Panel discussion**	*Panellists*	***All Speaker plus Dr A Hocepied Dr J van Beljon Prof M Smith Dr R Khanyile Prof J Ramos***
15:20 – 15:50	**TEA**		
	PROPHYLACTIC SURGERY IN CANCER MANAGEMENT		***Chairman: Prof T Luvhengo***
15:50	**Prophylactic Mastectomy: Who, when, how much and what is the long-term outcome**	*Speaker :*	***Dr C Benn***
16:10	**Prophylactic Oesophagectomy Who, when, how much and what is the long-term outcome**	*Speaker :*	***Pro: Prof T Mokoena Con: Prof H vd Walt***
16:30	**Prophylactic Surgery for Multiple Endocrine Neoplasia Who, when, which glands and what is the long-term outcome**	*Speaker:*	***Dr T Rossouw***
16:50	**Role of Surgery in Management of hepatic metastasis from neuro-endocrine neoplasia (NEN)**	*Speakers:*	***Pro: Prof M Smith Con: Dr J van Beljon***
17:10	**Panel discussion**	*Panellists*	***All Speakers***
17:30	**Vote of Thanks**	*Organisers*	***Prof M Ntlhe***
GALA DINNER 18:30 For 19:00			

SATURDAY 06 OCTOBER 2012

PALLIATIVE AND ADJUNCTIVE SURGERY Chairman: Prof A Dhaffala			
08:00	**Palliative surgery options for advanced pancreatic cancer in 2012**	*Speaker :*	***Prof M Koto***
08:15	**Adjunctive surgery for disseminated gynaecologic cancer** **i). role of gynaecological surgeon** **ii). role of general surgeon**	 *Speaker :* *Speaker :*	 ***Prof L Snyman*** ***Prof T Madiba***
08:35	**Surgical options in management of cholangio-carcinoma** **i). Radical Surgery** **ii). Palliative Surgery**	 *Speaker :* *Speaker:*	 ***Prof M Smith*** ***Dr van Beljon***
08:55	**Management of Pulmonary Metastases from breast , colorectal carcinoma, melanoma or sarcoma**	*Speaker :*	***Dr A Jacobs***
09:10	**Transarterial Chemo-Embolisation for hepatic metastases from Neuro-Endocrine Neoplasia and Hepatoma**	Speakers:	***Prof T Mokoena/Dr R Khanyile/ Dr S Ahmed***
09:30	**Transarterial Radioisotope embolization therapy for hepatic metastasis of Neuro-Endocrine Neoplasia or Hepatoma**	*Speaker:*	***Prof M Sathekge***
09:40	**Results of CRS and HIPEC in peritoneal mesothelioma, ovarian and gastric PSM**	*Speaker:*	***Prof M Deraco***
10:10	**Panel Discussion**	*Panelist :*	***All speakers plus*** ***Prof J Ramos*** ***Prof K van der Speeten***

10:30 – 11:00	**BRUNCH**		
			Chairman: Prof D Kahn
11:00	**Ethical problems and issues in surgical management of cancer in HIV/AIDS patients in the HAART era** **i). General considerationsand medicolegal issues** **ii). AIDS defining neoplasia** **iii). Non-AIDS defining neoplasia** **iv). AIDS and Cultural diversity**	 *Speaker :* *Speaker:* *Speaker :* *Speaker:* *Speaker:*	 ***Dr T Rossouw*** ***Prof L Snyman/ Dr R Khanyile*** ***Prof Mokoena*** ***Dr E Osman***
11:40	**Panel discussion**	*Panel members:*	***All speakers plus*** ***Dr T Mothabeng*** ***Prof T Luvhengo*** ***TAC representative***
12:00	**Concluding remarks**	*Speaker:*	***Prof T Mokoena***

Dr Hans Jekel-Department of Surgery, Kalafong Hospital andUnitas,

1) The purpose of surgery in the treatment of breast cancer is to ensure local control. Without adequate local control cure is not possible.
2) Spread to lymphnodes takes place through lymphatic spread and not haematogenous spread.
3) Contralateral lymphnode involvement is thus N3 and not M1.
4) We do diagnose bilateral breast cancer.
5) We do diagnose breast cancer spread to lymphnodes without finding a primary.(occult primary).

Before any decision is made regarding the treatment of enlarged contralateral lymphnodes they must be evaluated properly and confirmation of malignancy by needle aspiration/biopsy is essential. After this is confirmed the contralateral breast must be evaluated to detect any possible malignancy in that breast – MRI if available.
If nothing is found in contralateral breast all possible options of treatment must be discussed with the patient. In the case that the patient qualifies for breast conservation in the ipsilateral breast , contralateral mastectomy is obviously not what the patient has in mind , but it is usually true that contralateral axillary disease is only found in advanced disease with matted nodes in the ipsilateral breast. This usually means that spread has taken place across the midline and to the contralateral breast/axilla. Doing a modified radical mastectomy on the contralateral breast will take care of microscopic disease in the contralateral breast as well as the disease in the axilla, and possibly ensure adequate local control without the need for adjuvant radiotherapy. The ipsilateral breast will possibly have to be radiated as part of adequate local control.
Most patients with advanced disease in the ipsilateral breast will receive neoadjuvant radiotherapy, but will still need mastectomy and radiotherapy in an attempt to ensure local control.
With the improvements an availability of immediate reconstructions these decisions are easier to make especially when the reconstructed breast doesn`t have to be radiated.

BILATERAL MASTECTOMY IS NOT ROUTINELY JUSTIFIED IN PATIENTS WITH BILATERAL AXILLARY LYMPHADENOPATHY AND ONLY ONE DETECTABLE PRIMARY BREAST CANCER LESION

Dr Ines Buccimazza-Breast Unit, Department of Surgery, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban

INTRODUCTION

Involvement of the contralateral axilla in breast cancer is either a manifestation of systemic disease (M1 – contralateral axillary metastasis: Stage IV) or a regional metastasis from a new occult primary (T0N1: Stage II). The uncertain laterality of the cancer responsible for these metastases complicates overall disease staging and poses a management dilemma for clinicians.

Pathological examination, in addition to clinical and radiological evaluation is essential to exclude an occult primary in the associated breast or, rarely, metastasis from another tumor outside the breast.

Contralateral axillary metastasis (CAM) from breast cancer is uncommon. It is considered as distant metastasis since the contralateral axilla is not a regional draining basin of the breast.

LYMPHATIC DRAINAGE OF THE BREAST

The lymphatic drainage of the breast is primarily to the ipsilateral axillary lymph nodes. Drainage to other areas, like the supraclavicular and internal mammary regions is less common, and occurs in up to 25% of cases. Contralateral axillary drainage is uncommon but has been shown in some lymphography and sentinel lymph node studies of the breast.

It is thought that blockage of, or damage to the usual axillary lymphatics might lead to the development of alternative routes of drainage. This can result from surgery, radiotherapy or even tumor cells in the lymphatics. Extra-axillary drainage can also occur in untreated breasts with early tumors, probably indicating a physiological alternative pathway for drainage.

CAM occurs mainly by lymphatic spread in most, if not all, patients, and not by haematogenous spread. The lymphatic channels to the contralateral axilla are thought to pass through 2 routes, one through the deep facial plexus, and the other through the superficial dermal lymphatics.

INCIDENCE

Occult primary breast cancers constitute 1% of all operable breast cancers. Around 75% of clinically occult lesions are detected by conventional breast imaging.

Contralateral axillary metastasis can either occur at the time of diagnosis of breast cancer (first presentation - synchronous CAM) or months or years later (metastatic relapse - metachronous CAM), and it can be the only site of metastasis.

The incidence reported in the literature varies according to the mode and time of detection. In studies where CAM was detected by clinical examination alone and MRI scans were not routinely used to rule out involvement of the contralateral breast, the incidence is 3.6% - 6%. These series have probably overestimated the incidence. A recent study by Morcos et al which excluded patients who had systemic metastasis at presentation in addition to CAM, but included synchronous and metachronous CAM, found an incidence of 1.9%.

CHARACTERISTICS

Patients with CAM have aggressive tumours with poor pathological features. They are generally high grade, associated with LVI, hormone receptor negative and HER-2/neu overexpressing.

Tumor stage seems to relate to the time of development of CAM with smaller tumors associated with metachronous lesions and larger tumours with synchronous lesions.

APPROACH

After the clinical assessment, securing definite pathological proof of malignant nodal involvement is imperative. An ultrasound-guided (USG) fine needle aspiration cytology revealing atypical or malignant cells warrants further pathological scrutiny.
This is obtained via an USG core needle biopsy to confirm the origin of the metastasis. Adenocarcinomas other than breast that metastasize to the axillary nodes include lung, thyroid, stomach, colon, rectum and pancreas. Apart from confirming the breast origin, a core needle biopsy also provides other important pathological information, including grade, hormone receptors and Her-2 status. A difference in grade and/or receptor status likely indicates an occult contralateral primary breast cancer, whereas concordance in the pathological information is generally in keeping with a synchronous CAM.

Where a metastatic breast cancer relapse in the contralateral axilla is suspected, a core needle biopsy is necessary to confirm this, as well as evaluate the status of the biomarkers.

Recent articles have revealed discordant biomarker results between the primary lesion and the metastatic relapse. Re-analysis of markers has prognostic and therapeutic importance.

In 24% of patients the Her-2 status can change from positive in the primary tumour to negative in the metastases. Patients with discordant Her 2 results have shorter survival than patients with concordant results, regardless of the use of targeted therapies. Similarly, the estrogen and progesterone receptor results can change between the primary site and the metastases in 16% to 40% of patients. In around 14% of patients this results in a change of management. The survival of patients with ER negative primary lesions and ER positive metastases is approximately 50% longer than that of patients who remain ER negative.

Complete examination with mammography, ultrasound and MRI scan is also important to exclude an associated occult contralateral primary breast tumor, especially in patients

with invasive lobular carcinoma or familial breast cancer. MRI can reliably identify 70% of breast cancers that have evaded detection by clinical breast examination and/ or conventional breast imaging.

TREATMENT OPTIONS

Occult breast primary

This is treated on its own merits.

Depending on whether the lesion can be identified, and hence localised sonographically or mammographically, the options include breast conservation or mastectomy, with an axillary dissection and adjuvant therapy.

CAM

As CAM is uncommon, management of these patients is not straightforward, especially with the absence of metastatic disease elsewhere. There are no clear guidelines or agreement on management. Treatment should be individualized. Options include surgery, chemotherapy and hormonal therapy.

CAM and other metastatic sites

If CAM is associated with systemic metastasis, then the treatment should be systemic.

Surgery to the axilla can be performed in some cases for local control and palliation.

CAM as only site of metastasis

In patients with CAM as the only site of spread outside the breast, therapeutic options are more controversial.

1. Contralateral axillary dissection is one option; this results in excellent axillary control with no axillary recurrences in small series. This option should be considered in patients with early-stage tumors or in patients whose axillary lymph nodes do not respond to systemic therapy. The potential for improved relapse-free survival and cure in patients who have their CAM, as well as their primary tumors eradicated is unknown. It is unlikely in patients with locally advanced disease, but possible in those with early-stage tumors.

2. Contralateral mastectomy is probably not routinely indicated. Proper workup, including breast MRI, will diagnose most cases with a contralateral primary tumor.

   Mastectomy might be considered in some cases, especially when the CAM pathology differs from the primary. Hereditary breast cancer is another possible indication for performing mastectomy.

3. The other approach to CAM is systemic therapy. This should be considered in patients with locally advanced and aggressive tumors, as there is a high likelihood that they will develop distant metastases later on. One advantage of this approach is that the response to the treatment can be monitored. The effect on survival, however, is not known.

   Response to hormonal therapy is very good, and therefore should be the first option in patients whose tumors are hormone-receptor positive. Systemic chemotherapy can be used in cases where the hormone receptors are negative or if there is no response to hormonal therapy. Trastuzumab should probably be added if there is HER-2 overexpression.

CONCLUSION

Involvement of the contralateral axilla in breast cancer, although uncommon, is occasionally encountered and poses a clinical dilemma.

A systematic approach is required to determine whether this is due to a regional metastasis from an occult breast primary, or a manifestation of systemic disease.

In the case of a synchronous contralateral primary, the breast cancer is treated on its own merits. Breast conservation is a reasonable option, provided the occult lesion can be localised.

Contralateral axillary metastasis occurs mainly in patients whose primary tumors have aggressive pathological features. The time of development of CAM seems to be related to how advanced the stage is, with locally advanced tumors developing CAM earlier. Management of these patients is controversial and should be individualized. In patients with CAM as the only site of metastasis, those presenting with locally advanced disease should probably receive systemic therapy, as the possibility of future distant metastasis is high. Hormonal therapy is the first choice in patients with hormone-receptor positive tumors and the response is excellent.

Axillary dissection offers good local control, and should be considered for patients with early-stage disease, for palliation and when there is no response to systemic therapy. Mastectomy is reserved for specific indications.

REFERENCES

1. Huston TL, Pressman PI, Moore A et al. *The presentation of contralateral axillary lymph node metastases from breast carcinoma: a clinical management dilemma*Breast J 2007 Mar-Apr; 13(2):158 - 164
2. Morcos B, Jaradat I, El-Ghanem M. *Characteristics of and therapeutic options for contralateral axillary lymph node metastasis in breast cancer* EJSO 2011; 37: 418 – 421
3. Olson JA, Morris EA, van Zee KJ et al. *Magnetic Resonance Imaging facilitates breast conservation for occult breast cancer* Ann.Surg.Oncol. 2000; 7(6): 411 - 415
4. E. Amir, et. al. J Clin Oncol 2012; 30: 587 - 592

OPPOSING ONCOLOGIC AND COSMETIC CHALLENGES FOR BREAST CONSERVING SURGERY FOR RETRO-AREOLAR PRIMARY CANCER LESION

Dr Ines Buccimazza-Breast Unit, Department of Surgery, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban

---

ONCOLOGIC AND COSMETIC CHALLENGES DO NOT ROUTINELY OPPOSE BREAST CONSERVING SURGERY IN RETRO-AREOLA PRIMARY LESIONS

INTRODUCTION

Robust level I evidence from well-conducted randomized controlled trials has shown that BCT (breast conserving surgery + adjuvant radiotherapy) is oncologically safe, and equivalent to mastectomy in terms of survival. BCT is currently considered the optimal treatment for most women with early breast cancer.
The goal of conservation therapy is to provide the patient with oncological treatment as effective as mastectomy, but with the added benefit of a good cosmetic outcome. This is achieved by complete excision of all malignant tissue with a negative resection margin, while preserving the natural shape and appearance of the breast.
It is challenging to achieve both goals of conservation therapy in the same operation. A clear surgical margin should be achieved after a single, definitive surgical procedure, and certain key factors are required to maintain a good aesthetic outcome. Failure to achieve these goals often results in mastectomy.
Improved disease-free and overall survival has resulted in increased aesthetic expectations from modern breast cancer patients. Poor BCS cosmetic outcomes, occurring in up to 25% of cases, and mastectomy remain a source of psychological morbidity, impacting on emotional and psychosexual well-being.
Not all patients with early breast cancer are suitable for BCS. Multicentricity, extensive DCIS and radiotherapy concerns are absolute contraindications to breast conservation. However, patients with central tumours either involving or close to the nipple-areola complex (NAC) are still conventionally treated with mastectomy.

CENTRAL QUADRANT LESIONS

Tumours located in the central quadrant of the breast account for 5% - 20% of breast cancers. These lesions can be entirely retro (sub)-areola or extending to within 1.5cm – 2cm beyond the areola edge. Until recently, BCT was contra-indicated in these patients because it was thought that the dual goals of BCT could not be achieved. From an oncological perspective these lesions were presumed to have a high incidence of multicentricity and multifocality. From a cosmetic perspective, the concomitant resection of the NAC with the central portion of the breast yielded unacceptable results on two fronts: loss of the NAC and loss of the central projection.
The incidence of nipple or areola infiltration with breast cancer at any site ranges from 11% - 58%. In around 58% - 82% of these cases the neoplastic involvement of the NAC cannot be recognized grossly by either clinical examination or mammography.
There is a higher likelihood of pathological infiltration of the NAC if the nipple is clinically involved - NAC involvement is suspected clinically when there is nipple retraction - and/or the primary lesion is a superficial retroareola tumour or within 2cm from the NAC. The incidence of NAC involvement in small superficial central breast tumours

without obvious clinical involvement is around 54%. It has also been shown that in 95% of involved nipples, the primary lesion is within 2.5cm of their edge.
Thus, important predictors of NAC involvement include the following:

- Tumour location
    - Tumour-areola distance of <2cm or a tumour-nipple distance of < 4-5cm are associated with a higher incidence of pathological nipple infiltration and NAC resection is safer
- Tumour size
    - ≥ T2 lesion
- Clinical evidence of involvement: NAC or adjacent skin

The high incidence of NAC involvement necessitates *en bloc* removal of the NAC with the tumor and an adequate margin. Standard breast conserving surgery (sBCS) results in a poor cosmetic outcome with a flat breast. Secondary reconstruction of these defects following radiotherapy is difficult and associated with high complication rates.
Thus, central quadrant breast tumours represent a particular challenge to achieving the dual goals of BCT: adequate margins and acceptable cosmesis. Oncoplastic surgery (OPS) is a new approach which optimises the oncological and cosmetic outcomes of breast conserving surgery in one procedure, and has expanded the role of BCT to include retro-areola lesions.

ONCOPLASTIC SURGERY

DEFINITION
OPS is the combination of oncological principles to achieve wide resection margins and the integration of the best principles of plastic surgery techniques to optimise cosmetic outcomes and minimize complications. This extends the indications for, and enhances the results of BCS by permitting wide excision without compromising breast appearance.

CLASSIFICATION
OPS techniques for are broadly classified into volume displacement and volume replacement techniques.
Volume displacement techniques are the more commonly used techniques for breast conservation. These range from simple parenchymal mobilization or re-coning (OPS level I) to more advanced reduction mammoplasty techniques (OPS level II).
The remodelling (reduction) mammoplasty is known as a therapeutic mammoplasty. Essential steps involve tumour excision (therapeutic volume reduction) followed by re-arranging the remaining breast tissue (volume displacement) to correct the defect with rotation advancement dermo-glandular flaps.
Women with medium to large breasts are ideal candidates for a therapeutic mammoplasty. The different mammoplasty techniques permit major volume excisions of 20% - 50%, or excision of small T2 lesions (< 3.5cm) in unfavourable tumour locations such as the upper inner or central quadrant. The volume of tissue excised requires that a contralateral symmetrizing procedure is performed to achieve symmetry.
Volume replacement techniques are commonly associated with mastectomy and total reconstruction. They are occasionally used in breast conservation to reconstruct the central quadrantectomy defect with myocutaneous (latissimus dorsi) or local fasciocutaneous flaps (intercostal artery perforator-based). The procedures are long, associated with considerable morbidity and result in additional scarring in the back or

lateral chest. However, they may be of great value in large central masses (> 3.5cm) when tumour resection removes approximately one-third of the breast volume. These techniques will not be discussed in this document.

GENERAL CONSIDERATIONS

Despite the numerous advantages of oncoplastic surgery there are particular vagaries to consider.
Not all patients are candidates for a therapeutic mammoplasty. Patients with very small breasts (A-cup bra size) are unsuitable for this approach, and are best served with a mastectomy and immediate breast reconstruction.
The operation time for a therapeutic mammoplasty is longer, averaging around 2 hours, and the procedure requires expertise in both plastic and oncologic breast surgery techniques. If a suitably trained surgeon is unavailable, scheduling can be a logistical challenge.
All OPS procedures commence with pre-operative marking of the patient in the standing or sitting position prior to induction of anesthesia. Thereafter both breasts are draped into the operative field to facilitate comparison during surgery. The operating room table should permit transitioning the patient between the supine and upright position for optimal re-shaping and symmetry.

COUNSELLING

OPS procedures result in a high level of patient satisfaction with respect to final breast shape, and often avoid the need for a mastectomy.
However, there are caveats associated with the procedures.

OPS may result in longer and multiple scars. A therapeutic mammoplasty is associated with volume asymmetry compared with the contralateral breast, requiring symmetrisation. This is usually performed immediately at the time of the index operation, but can be performed as a second-stage procedure if desired by the patient.

BREAST CONSERVATION TECHNIQUES FOR CENTRAL QUADRANT LESIONS

Patients with central quadrant breast cancers are now considered suitable candidates for BCT. The alternatives to mastectomy for these lesions include a number of therapeutic mammoplasty approaches.
In all cases, excision of the NAC and skin directly over the tumour allows re-shaping without extensive glandular mobilization. Full-thickness excision of the gland down to and including the pectoralis fascia ensures clear anterior and posterior margins. Prior to closing the cavity, metal clips are placed along the edges of the tumour bed to guide future radiotherapy.

Small series have reported central quadrantectomy with NAC preservation and volume displacement where the NAC was not clinically involved. However, these were associated with a positive resection margin (8% of cases), local recurrence (4% of cases) and NAC distortion in most cases.

En bloc removal of the NAC with the tumour results in a flat breast and poor cosmetic outcome if no therapeutic mammoplasty techniques are employed.

Technique 1: **Modified inverted T-scar mammoplasty (NAC resection)**

The technique is similar to the superior pedicle mammoplasty, which results in inverted T and peri-areola scars as seen in most cosmetic reduction mammoplasties. The only modification for central quadrant lesions is that the two vertical incisions encompass the NAC which is removed with the tumour.

Unlike the superior pedicle mammoplasty, the area surrounding the NAC is not de-epithelialized as the NAC is sacrificed and included in the specimen. Thus there is no dermo-glandular pedicle. The inframammary incision is then completed, followed by wide undermining of the breast tissue off the pectoralis fascia. The undermining starts inferiorly and then proceeds superiorly to beyond the sacrificed NAC, while encompassing the medial and lateral aspects of the breast. The tumor and NAC is removed *en bloc* with a large margin of normal breast tissue and overlying skin, after which the breast is reshaped by re-approximation of the medial and lateral glandular columns towards the midline to fill in the defect.

The NAC can be reconstructed during the same procedure, but is usually performed after completion of radiotherapy.

Modification*:*Modified Lejour (vertical scar mammoplasty) with NAC excision

One possible modification to this technique is the vertical-scar mammoplasty described by Lejour. The site and volume of excision are identical to
the inverted T-scar described above, but this approach avoids the submammary scar.

Technique 2: **Grisotti technique**
Grisotti combined two reduction mammoplasty techniques exclusively used for cosmetic breast surgery in the past (Strombeck and Regnault B-flap mammoplasty), to reconstruct the central quadrantectomy defect after sacrifice of the NAC. This oncoplastic technique offers the advantage of allowing for immediate NAC reconstruction through preservation of a skin island on an advancement flap. It has been validated as a technique that yields a high level of cosmetic satisfaction with minimal complications.
The procedure commences with a full-thickness glandular excision of the central quadrant including the NAC, down to, and including, the pectoralis major fascia. The resection should include a circumferential macroscopic margin of at least 1cm of normal breast tissue. After orientation of the specimen, intra-operative margin assessment is advisable to ensure clear margins prior to defect reconstruction. Involved margins are promptly re-excised and if a second attempt still yields involved margins the procedure is converted to a mastectomy.
The defect is reconstructed by advancing a de-epithelialized infero-lateral dermo-glandular flap into the cavity. It is prudent to delay de-epithelialization until intra-operative confirmation of clear margins is obtained. A disc of skin at the upper end of the flap is left intact for the NAC reconstruction. The deep portion of the flap is sutured to the deep aspect of the breast defect. This is followed by closure of the circular areolar defect around the skin disc in two layers; then, in a similar manner, the medial breast pillar to the lateral edge of the flap thus completely covering the de-epithelialized surface of the flap.

The NAC reconstruction is performed by dermal tattooing of the areola and the nipple refashioned via a banner flap. Several authors have reported patient refusal to complete the NAC reconstruction. This refusal is across the spectrum from conservative societies to more enlightened parts of Europe. The authors independently concluded that simple preservation of the breast mound to maintain the breast contour is more essential to most women than the NAC reconstruction.

COMPLICATIONS OF ONCOPLASTIC SURGERY

Surgeons embarking on volume displacement OPS techniques must be cognisant of the possible complications.

A systematic review of all therapeutic mammoplasty studies revealed all-type complication rates ranging from 10 % - 90%. With particular reference to central quadrant excisions, the surgical complication rate is around 13% and is largely due to flap necrosis (superficial epidermolysis more common than full thickness necrosis). Less frequent complications include surgical site infection and wound collections (hematoma, seroma)

VALIDATION AND SAFETY OF ONCOPLASTIC SURGERY

The application of aesthetic techniques for therapeutic purposes must never compromise the main objective of breast cancer surgery, namely clear margins with good local disease control.
There is growing evidence through prospective trials that OPS techniques offer patients safe and effective oncological outcomes.

LOCAL FAILURE AND OVERALL SURVIVAL RATES

The first studies to demonstrate the oncologic safety of the procedure were by Cothier-Savey (1996) and Clough (2003), and demonstrated 5 year local recurrence rates of 9.4% and 8.5%, and overall 5 year survival rates of 86% and 95.7% respectively.
More recently Rietjens et al (2007) reported a 3% ipsilateral recurrence rate and 92% survival rate after a follow up of 74 months (> 6 years).
In a recent systematic review of therapeutic mammoplasties the reported local recurrence rate was around 7%, but the duration of follow-up varied widely. The same review reported distant metastases and mortality rates of 14% and 10% respectively after a median follow-up of 4 years.
A small study reporting exclusively on the safety of OPS for central quadrant tumours revealed a 4.3% local recurrence and distant metastatic relapse rate at 18 months follow up.

ADJUVANT THERAPY

OPS techniques for tumours located in the central quadrant do not delay the onset of adjuvant treatment.

RADIOGRAPHIC SURVEILLANCE

The glandular re-shaping following central quadrantectomy does not affect clinical or radiographic follow up and continued screening.

CONCLUSION

The increasing demand for breast conservation in patients with early breast cancer has driven the development of techniques to expand the indications for breast conservation while maintaining the twin goals of oncologic safety and a pleasing aesthetic appearance.
Retro-areola breast tumours have posed a particular challenge in this respect. However, the advent of oncoplastic surgery has made it possible for patients with tumours in the central quadrant to be considered for breast conservation. In particular, volume displacement techniques have been shown to be oncologically safe and have resulted in satisfactory cosmetic outcomes.

REFERENCES

1. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. "Improving Breast Cancer Surgery: A Classification and Quadrant per Quadrant Atlas for Oncoplastic Surgery" *Annals of Surgical Oncology* 2010; 17(5): 1375 – 1391
2. Naguib SF. :Oncoplastic Resection of Retroareola Breast Cancer: Central Quadrantectomy and Reconstruction by Local Skin-Glandular Flap" *Journal of the Egyptian Nat. Cancer Inst.* 2006; 18(4): 334 – 347
3. Clough KB, Lewis JS, Couturaud B, Fitoussi A, Nos C, Falcou MC. "Oncoplastic Techniques allow extensive resections for breast-conserving therapy of breast carcinomas" *Annals of Surgery* 2003; 237(1): 26 – 34
4. Rietjens M, Urban CA, Rey PC, Mazzarol G et al. *Breast* 2007; 16(4): 387 - 395
5. McIntosh J, O'Donoghue JM. "Therapeutic mammoplasty – A systematic review of the evidence" *EJSO* 2012; 38: 196 – 202

Dr Carol Benn-Departmentof Surgery, University of Witwatersrand (Wits)

Introduction

The surgical treatment of breast cancer has evolved from radical mastectomy with routine removal of the nipple-areolar complex (NAC) to breast conservative therapy with preservation of the breast and nipple areolar complex.
Breast conservation with radiation therapy has now become the standard surgical management for patients with stage 1 and 2 breast cancer in the 21st century. This dramatic and revolutionary change from mastectomy is well supported by level 1 research data showing that this method has resulted in surgery with less morbidity and no change in survival.
The essence of breast conservation is a satisfactory cosmetic result, ensuring an almost normal breast appearance while adhering to standard oncological principles. Poor cosmetic results are seen in 20% to 30% of patients. These are due to poor surgical technique, choice of procedure and late radiation changes. Deformed breasts –a source of distress to the patient -are difficult to assess clinically and radiologically and hence recurrences cannot be reliably detected.

Chasing the nirvana of the perfect breast reconstruction results in conflict between maintaining surgical oncological principles while chasing more aesthetically pleasing and possibly better functioning reconstructed breasts

Approximately 5-20% of breast cancers are located centrally, and these tumours are traditionally treated with a mastectomy.

The high incidence of nipple areolar complex involvement seen with central tumours, often necessitates the resection of the nipple areolar complex within the specimen to ensure an adequate safety margin, and can if not closed with the use of oncoplastic techniques result in significant breast deformity

Oncological Safety Net

Looking at retrospective studies on patients undergoing SSM for invasive cancer or DCIS, the nipple is affected by tumour cells in 5%-10% of cases

a. Tumour Biology

Certain breast carcinomas should be treated with a mastectomy, as ability to determine underlying residual disease may be tricky
Carcinomas safer to treat with a mastectomy:

1. Lobular Carcinomas
2. Pagets disease
3. Multicentric tumours
4. Extensive intraductal component (DCIS)
5. Inflammatory carcinomas

Locally advanced central tumours, which have had a good response to primary chemotherapy, are not contraindications for central breast excisions and reconstruction

The EORTC 10801 with 5569 patients with stage 1 or 2 breast cancer showed no impact on survival when practicing local excision on tumours more than 5 cm.

b. Radiology

Careful patient selection and preoperative planning are essential components to the success of any oncoplastic procedure and critical particularly when used for retroareolar tumours.

Translational radiology is the use of mammogram, ultrasound, MRI scanning and now breast tomosynthesis to gain as close to a 3D idea of position of the tumour in the breast, size of the lesion and extent of intraduct component prior to planning oncoplastic procedures

c. Breast

Not dissimilar to property sales, location and size are critical when planning ability to safely perform breast conservation and immediate reconstruction.

Breast and tumour size are closely related, the larger the tumour, the larger the breast should be when performing certain oncoplastic procedures.

Depth of the tumour to the nipple areolar complex should also be assessed, and a discussion with patient about nipple areolar complex loss probabilities

The density of the breast tissue and breast volume left is also critical in determining aesthetic results.

The rule of excising more that 5% of volume requiring minor oncoplastic rotational flaps and removal of 20% of the volume requiring trained oncoplastic procedures is critical when dealing with central lesions

d. **Margins**

The main determinants of local recurrence in breast conserving surgery are the following; residual tumour, positive margins (R1 and R2), residual malignant calcifications on mammogram , extensive intraduct component with positive margins, lymphatic vessel invasion, vascular invasion , high proliferative rate and young age less than 35 year. It is accepted that insufficient margins are related to local recurrence. The question as to what the required margin should be macroscopically and microscopically does not have consensus... While some authors advocate a margin of 10 mm, others boldly state that no tumour at the inked margins is sufficient .The suggested macroscopic margins requires a 1cm clear margin (lumpectomy), while a quadrantectomy requires a 3cm margin.

In our unit a 10mm margin is mandatory and intraoperative pathology determines clear margins

e. Psychology and patient factors

Issues around cancer recurrence with breast conservation, loss of nipple areolar complex, radiation complications, future radiological follow-up and patient anxiety all play a role in determining choice of procedure and reconstruction. All options highlighting the advantages and disadvantages of each procedure and the technical challenges should be discussed with the patient

General patient factors, medical and social (diabetes, obesity and smoking, and prosthesis) as well as relative contra-indications for radiation should be assessed prior to offering any procedure

Chasing Cosmesis

Oncoplastic procedures are divided into volume displacement (variations on breast reduction patterns), and volume replacement (the use of local or regional flaps)

The discussion around tumour and margin excision (mass and volume lost) and expected breast size should be discussed with patients prior to procedure choice

A good oncoplastic team has the ability to change techniques depending on amount of tissue and where that tissue is removed from, once margin assessment is complete

General Principles

1. Discussion in oncoplastic , clinical radiology meetings prior to procedure
2. Pre-operative skin markings denoting technique most likely to be used for that parenchymal excision
3. Evaluation of the most likely technique (volume displacement or replacement) to be used
4. Risk to nipple areolar complex, and best adaptation of the central breast mound
5. Need for opposite breast symmetrisation, and selection of incisions, and techniques and scar placements for the opposite side

1. Volume displacement techniques

a. Nipple Areolar Loss

Central tumour excision with expected nipple areolar complex loss is an easier procedure, as critical assessment of nipple areolar complex blood supply is unnecessary.

Infero-lateral based pedicle flaps are commonly used with wise pattern breast reduction based incisions

The Grisotti technique is simple and offers excellent long-term cosmetic results. A circular disc is drawn on the skin usually below the nipple areolar complex and this is used as the neo-areola.

Variation on this technique has resulted in the neo areola disc being drawn above the nipple areolar complex, as long as below the accepted nipple areolar complex distance is sited at between 17-23cm from the sternal notch

Care should be taken to avoid devascularisation of the parenchymal tissue below the neo-areola

An L shaped pattern breast reduction may also be used with no neo-areola disc, should insufficient residual skin be available for a disc

b. Retaining Nipple Areola

Tumours that are located deep to the nipple areolar complex, may if intraoperative margins are clear result in retention of the nipple areolar complex

Again care to ensure blood supply to the nipple areolar complex is retained is essential in performing this procedure

2. Volume replacement techniques

In women, who prefer breast conservation surgery, but whose tumour to breast ratio prevents a volume displacement technique, the use of loco-regional flaps may be employed for central lesions.

Flap options include thoraco-epigastric flaps for central and medial tumours, LiCAP and thoracodorsal flaps for central and lateral tumours

The latissimus dorsi flap provides a useful workhorse for all central defects, and a skin disc can be placed at the time of positioning the latissimus flap

Essential when offering flap surgery is to ensure good intra-operative pathology

The Nipple

Reconstruction of nipple areolar complex can be performed at the same procedure or at a later stage

Delayed reconstruction is generally safer, and should be performed 6 months post radiation

Conclusions

Central breast carcinomas are no longer required to be treated by mastectomy, and the use of a variety of oncoplastic techniques are available today to ensure a satisfactory cosmetic outcome while ensuring minimum complications and good long term oncological safety.

Prof Jose Ramos-University of the WitwatersrandDonald Gordon Medical Centre

Introduction

Resection for malignant tumours has become an established and important tool in the management of patients with either primary or metastatic tumours affecting the liver. In the last two decades, a better understanding of hepatic anatomy and pathophysiology, as well as increasing expertise in liver resection in centres of excellence has made hepatic resection safe with acceptable morbidity and mortality rates. The emergence of multimodality treatment has also aided in clarifying and increasing the role of resection of liver tumours. Better understanding of tumour biology and natural history has helped to predict the potential benefit of liver resection in patients who often have widespread disease.
Limitations of hepatic resection have included size of tumours, extent of disease, number of tumours in the liver, location of the tumour/s in the liver, and the state of the liver. Previously, liver resection was limited to a relatively few selected patients because of these limitations. In order to increase the number of patients who are eligible for resection, various strategies have emerged to increase resection rates. **Downstaging** of the tumours can be achieved by systemic chemotherapy, trans-arterial chemoembolisation (TACE), and trans-arterial radioembolisation (TARE), making it possible to successfully resect previously irresectable tumours. Limitations in remnant liver volume can be addressed by pre-operative **portal vein embolisation**, making it possible to perform more extended hepatic resections with lesser risk of post-resection liver insufficiency. **Combinationof liver resection and ablation** by either radiofrequency ablation (RFA) or microwave ablation (MWA) may make it possible to completely address the existing liver tumours. **Staged hepatic resection** may enable the complete resection of all liver tumours

Requirements for successful liver resection

- Correct indication for resection
- Assessment by a multidisciplinary team
- Patient is fit for major surgery
- Resection performed by suitably trained HPB surgeon in a centre of excellence
- Ability to achieve complete resection
- Healthy liver amenable to safe resection
- Adequate remnant liver portal venous, hepatic arterial and biliary inflow, and hepatic venous outflow

Rationale for liver resection in metastatic malignancy

1) Resection with curative intent

This is by far the commonest indication and may be performed as a single or staged procedure, provided that the ultimate goal is for a complete resection making it possible to offer the patient a potential cure, or at least offer the patient prolonged survival.
As ultimate cure is the objective, it is necessary that the primary malignancy has been, or will be, completely removed. Also, it is implied that no extrahepatic metastatic

disease is present or that if present has either been resected, or is to be resected after the hepatic tumours have been treated.

2) Resection for palliation

This implies a less than complete eradication of liver metastases and is an uncommon indication except where the patient has liver metastases from functional neuroendocrine malignancies and where hormone production by the metastases is adversely affecting the patients quality of life. Typical examples would be patients with carcinoid syndrome or metastatic insulinoma. Resection for control of pain is very seldom, if ever, indicated and other modalities to control pain are invariably more appropriate.

Indications for resection of liver metastases

The liver is a common site for metastatic malignancy and up to 40% of patients dying of their malignancy will be found to harbour liver metastases in autopsy series. The majority of these patients will however also have metastases to other sites. Metastatic disease confined to the liver is thus uncommon, depending on the type of underlying malignancy. In the setting of metastatic colorectal cancer, only 20-25% will have isolated liver metastases. With most other primary malignancies, even fewer patients would have metastatic disease confined to the liver. Thus relatively few patients with metastatic malignancy would be eligible for hepatic metastasectomy with curative intent.

In the last few decades, the increasing safety and experience with liver resection has led to a progressive expansion in the indications for liver resection, including resection of metastatic malignancy. Although the value of hepatic metastasectomy has never been evaluated in a prospective randomised trial, it has become apparent that the ability to completely resect metastases confined to the liver appears to confer a significant survival benefit to the patient when compared to historical or case-matched controls. Prolonged survival and even cure has now become possible with certain types of primary malignancies which have metastasised to the liver. This represents a paradigm shift in the approach to metastatic malignancy, the prevailing view being that metastatic malignancy was incurable.

In the setting of hepatic resection of metastases, the most common indications for resection have been for colorectal cancer (CRCLM) and, less commonly, neuroendocrine metastases (NET). The survival (or palliative) benefit of metastasectomy in these two types of malignancy is now well established with 5-year survival rates of between 30% and 60%, and 10-year survivals of up to 30% being typically reported for metastatic colorectal cancer. Indications and requirements for liver resection in CRCLM and NET's are now well understood.

The apparent success of hepatic metastasectomy in the above tumours has led to resection being extended to other malignancies which have metastasised solely to the liver, including breast, melanoma, renal, gynaecological, soft tissue tumours and others. Experience with these is however quite limited and all of the available data is derived from small historical series and collections of cases. These tumours have typically been grouped together as non-colorectal non-neuroendocrine liver metastases (NCRNNLM) as numbers for each individual malignancy are relatively small.

As happened in CRCLM, the indications for resection of hepatic metastases from other malignancies have largely evolved from accumulating uncontrolled data of outcomes following metastasectomy compared to historical or case-matched controls. At present

however, despite the lack of controlled trials, enough data has emerged to provide some clarity on the role of metastasectomy for NCCNNLM.

Multimodal therapy of metastatic malignancy

Numerous tools are now used in the management of metastatic malignancy including:

- Chemotherapy
- Hormonal therapy
- Targeted and biological therapy
- Radiofrequency (RFA) and Microwave (MWA) Ablation
- Radiotherapy
- Angiographic embolisation
- Surgery

With so many therapeutic options available, it is clear that the management of metastatic malignancy should be carried out in a **multi-disciplinary environment** with all relevant specialties being involved in the decision-making process to offer the patient the best possible outcome. Ideally these patients should be managed in high-volume centres of excellence where access to all possible therapies is available. This may be a challenge for resource-limited countries but is still the goal that should be pursued. Having provided some perspective on the overall role for surgical resection of hepatic metastases, it is now possible to critically review the role of hepatic resection for breast, melanoma and sarcoma metastases.

Breast carcinoma metastases

About 40% - 50% of patients with breast cancer will go on to develop metastatic disease (Stage IV), with 25-50% of these patients having liver metastases. Liver metastases are present in about 15% of patients with newly diagnosed metastatic breast cancer. Only about 12% - 15% of patients with metastatic breast cancer will however have metastases primarily in the liver and only 5% will be isolated to the liver, a very small proportion.

Overall prognosis for metastatic breast cancer is relatively poor with a historical median survival rate of 4-14 months using standard chemotherapy. With the availability of modern chemotherapy, targeted therapy and hormonal blockade, 21% - 25% 5-year survival and median survival of 24-33 months can be expected.

With the encouraging results obtained in resection of colorectal and neuroendocrine metastases to the liver, patients with isolated breast cancer liver metastases (BCLM) have been considered for and offered liver resection. Since 2000, there have been 19 publications reporting on the results of resection of BCLM. These series are largely retrospective, analysing the outcome of patients undergoing resection BCLM as a subgroup of overall liver resection for metastatic malignancy. The number of patients actually resected ranged from 10-85, with about 80% of patients undergoing exploration being resected. Morbidity rates were 0% - 44% and mortality rates were 0% - 6%. After hepatectomy, overall survival was 15-74 months (median 40 months) and 5-year survival was 21% - 80% (median 40%).

Multiple clinicopathological prognostic factors have been evaluated to determine which parameters could predict the outcome following resection of BCLM. The data is conflicting, with inconsistent results being reported in different series. The following

factors may however affect prognosis following hepatic resection of metastatic breast cancer although these are debatable as not all series are consistent:

Favourable prognostic factors:

- Older age
- Interval from primary breast cancer > 1 year
- Oestrogen receptor positive tumour
- R-0 resection
- Favourable response to systemic chemotherapy

Negative prognostic factors

- Positive resection margin
- Extrahepatic disease
- Hormone refractory disease
- Progressive disease prior to resection

Based on the reported survival data, it would appear that successful resection of BCLM is a worthwhile management option in patients with this disease. It must however be stressed that this data is uncontrolled and resections have been carried out in highly selected patients. There is also a high risk of bias in many of these reports. Properly controlled prospective trials are required in patients with BCLM to critically assess the role of hepatic resection of BCLM. There is however sufficient justification to include surgical resection of BCLM as a treatment option in properly selected patients where all treatment options have been assessed by a multi-disciplinary team.
The role of ablation of BCLM is unclear. As in data from colorectal liver metastases, there are however several reports of successful outcomes following radio-frequency ablation (RFA) with mean overall survival of 30-60 months and 5-year survival of 27% - 41%. Ablation may thus be considered a reasonable therapeutic option in BCLM and similar outcomes to resection may be achieved.
Some small studies have reported favourable outcomes from resection of hepatic and extrahepatic breast cancer metastases, provided that all known metastases can be completely resected. Careful patient selection is however mandatory.

Melanoma hepatic metastases

Almost 70 000 cases of malignant melanoma (MM) are reported in the USA annually. Of these, about 95% are cutaneous and less than 5% ocular. The metastatic pattern of these two types is different with 95% of patients with metastatic ocular melanoma developing liver metastases, while only 10% - 20% of patients with metastatic cutaneous melanoma developing liver metastases. Large studies of patients with ocular melanoma have reported that liver metastases develop in 13% - 21% of cases. It is interesting that the liver is the sole site of metastases in 60% - 80% of cases. There is typically quite a delay between the diagnosis of the primary ocular melanoma and the appearance of liver metastases, the latency often being many years. Typically, multiple liver metastases are present and overall prognosis is poor in these patients with a life expectancy of 6-9 months and a median survival of 4 to 6 months.
As is the case in BCLM, no prospective data exists to determine the role of hepatic resection in melanoma liver metastases (MLM). Traditional therapy for stage IV MM has

included interferon, immunotherapy and chemotherapy with drugs such as dacarbazine, temozolomide, interleukin-2, paclitaxel, cisplatin, and carboplatin. The benefits of

systemic chemotherapy are however limited with response rates below 20%. Newer targeted agents such as vemurafenib and ipilimumab have shown some promising results and may improve the overall survival of these patients.
Resection of MLM has been reported in various studies, usually as part of series of NCNNLM, the numbers being relatively small. Putting the role of hepatic resection for MLM into perspective, only 34 (2%) of 1750 patients with melanoma liver metastases at the John Wayne Cancer Institute were considered candidates for resection, and only 24 actually underwent resection. The median overall survival for the resected patients was 38 months and 4 months in the 10 patients who underwent exploration alone. In Adams series, 44 patients with cutaneous MLM underwent resection with an overall 5-year survival of 22%.
Larger series of hepatectomy for ocular MLM have been reported, the largest being by Mariani et al in which 255 patients were resected. Of these 30% had R0, 9% had R1 and 61% had R2 resections. Median survival was 27, 17 and 11 months respectively. Median survival in those patients not resected was 8 months. In a smaller series by Rivoire et al of 54 patients, 28 were resected, 14 having R0 and 14 having R1 or R2 resection. Median survival was low at 16 and 14 months, the median survival for those not resected being 11 months. In the series by Frenkel at al, 35 patients were resected, the median survival in the R0 group being 55 months.
Improved outcomes appear to occur in the following groups:

- R0 resection
- Age < 70
- Number of metastases < 4
- Disease-free interval from primary tumour diagnosis > 24 months

While resection of MLM appears to be of benefit in patients whose disease can be entirely resected with clear margins, surgery alone is likely to have a limited role in the overall management of metastatic MM. It should however be considered in those selected patients with resectable disease and predicted favourable outcome.

Sarcoma liver metastases

Data on resection of sarcoma liver metastases (SLM) is limited. While up to 25% of pateints with sarcomas will develop liver metastases, they are rare in sarcomas arising from the extremities and trunk. Retroperitoneal and visceral sarcomas develop liver metastases in 16% and 62% respectively. Seven series have been published, dealing mainly with GIST and leiomyosarcomas, with patient numbers between 10 and 66. Median overall survival of 30-58 months and 5-year survival of 27% - 49% are reported, however median disease-free survival is only 14-32 months.
The survival rates are however confounded by the CD117 (c-kit) positive patients who would be expected to respond to imatinib or other tyrosine kinase inhibition. In a small series by Chua et al, CD117-positive patients had an 80% 5-year survival while those who were CD117-negative had a 50% 5-year survival. In another series, CD117-negative patients had a 33% 5-year survival.
There are also reports of RFA and chemoembolisation of sarcoma liver metastases with fairly good results.

It may thus be reasonable to consider resection of selected patients with SLM, particularly if their tumours are CD117-positive. Surgery will however have a limited role in this disease.

Summary

Despite the lack of controlled randomised trials, there is accumulating evidence that resection of isolated metastases from breast carcinoma, malignant melanoma, and sarcoma may confer some survival advantage to properly selected patients. Prolonged survival when compared to historical or unresected patients is regularly reported. These metastatic malignancies are also however usually treated with other modalities such as chemotherapy, immunotherapy, radiotherapy, targeted therapy, ablation and embolisation, often in combination. This may confound the data on actual success of resection. Resection must therefore be seen as a part of the multimodal therapy of metastatic malignancy. Proper patient selection is thus vital and management decisions should take place in a multi-disciplinary environment in order to rationalise treatment and achieve the most favourable outcome.
The following treatment algorithm can be considered.

When is neo-adjuvant Chemo required?

- Locally advanced breast ca:
  - Breast conservative surgery is intended but not possible
  - Mastectomy is intended but not possible
- Early information on tumor response
- Reduce mortality from breast ca

Useful features

- Age
- ER/PR/HER 2 status
- Tumour grade 1 – 3
- Ki 67

ANTHRACYCLINE BASED CHEMO

- Backbone of breast ca treatment for many years
- Which pts: - younger pts
  - normal heart(EF% >/=55)
  - luminal B
  - triple negative
  - HER2 +
  - co-morbidities

COMBINATION

- FAC – MD Anderson reported 10 yr results in 1989
  - 1% cardiotoxicity
  - 62% survival- stg 2
  - 40% survival – stg 3
  - this was confirmed as good adjuvant treatment
  - It is also used in neoadjuvant settings

NEOADJUVANT FAC/FEC

- First used in 1970s in a multimodality treatment
- Primary aim was to down-size T3/4 tumor, making it operable
- Recently, it is used for both cosmetic and survival benefit
- Any chemotherapy that is used in adjuvant setting can be used in Neoadjuvant setting
- AC: Fisher at el(NSABP B-18), in 1998 showed same benefit when AC was used as either neoadjuvant or adjuvant
  - Primary operable breast ca
  - Conclusion: pre-operative AC is as effective as post-operative AC
  - More lumpectomies are done
  - Response correlates with outcomes

New Generation

- AC –T: Sparano at el (ECOG), in 2008 published results showing better outcome of wkly paclitaxel compared to taxotere in adjuvant settings
- Other studies have shown equivalent outcome
- Currently, any pt who is a high risk of relapse is given AC – T(P/T) in Adjuvant/neoadjuvant setting.

Anthracycline based

- CMF: Anthracycline based chemo have been shown to be better than CMF
  - Should be used in Pts with contra-indications for Anthracyclines
- TC: Doxetaxel/Carboplatin
  - TNBC
  - HER2 + in Combination with Trastuzumab
  - ER/PR neg

Trastuzumab(herceptin):

- HER 2+ pts
- Combined with AC – TH, TCH
- Cardiac monitoring mandatory
- Avoid in pts with EF% < 55 or in pts with decrease of EF by >10 – 15%
- Duration – 1 yr

Endocrine therapy:

- Pts with ER/PR +ve breast ca
- Aromatase inhibotors are recommended in postmenopausal pts
- Tamoxifen in premenopausal pts
- HER 2 neg

Summary

- All pts with locally advanced breast ca can benefit from neoadjuvant chemo
- Stage < II has not proven to benefit from noeadjuvant chemo
- Herceptin and endocrine therapy should be used in HER 2+ve and ER/PR +ve pts respectively
- Neoadjuvant chemotherapy is the same as adjuvant chemo.
- Neoadjuvant chemo: part of it can be given pre-op and the other part post-op
- pCR correlate with DFS and OS

References

- To be added later

WHAT IS THE JUSTIFICATION FOR THE RETURN OF RADICAL SURGERY FOR ADVANCED BREAST CANCER?

Dr Hans Jekel-Department of Surgery, Kalafong Hospital and Unitas,

Advanced breast cancer has always been deemed to be incurable and was usually seen as being irresectable. It is also true that patients with advanced cancer of the breast will probably have metastatic disease – even if not immediately detectable. These patients were referred for chemotherapy and radiotherapy to control local disease until the inevitable demise of the patient occurs.

With the development of Neo-adjuvant chemotherapy as well as Breast sparing surgery these ideas have to be revisited.

Neo-adjuvant chemotherapy has shown that previously irresectable disease can now possibly be made resectable . In some cases this meant a complete pathological response to chemotherapy but usually viable cancerous tissue remained , even if not clinically detectable. The possibility of cure improves dramatically with proper local control. Local control achieved by radiotherapy depends on tumor bulk with an exponential decrease in control with an increase in bulk. Thus local control must include surgery.

Breast conserving surgery has highlighted the role of radiotherapy in conjunction with surgery for local control of breast cancer. Numerous trials on radiotherapy have shown that distant disease is much less when proper local control is achieved.

The treatment of advanced breast cancer MUST include Chemotherapy, Surgery and Radiotherapy – and usually in that order.

The aim of surgery is to achieve local control and thus more radical surgery is indicated. If surgery is intended as palliation, only that will be achieved.

Radical surgery is not indicated in the patient with proven metastatic disease UNLESS it is only bony metastatic disease, as these patients usually have a relatively long life expectancy.

Radical surgery may from time to time include reconstructive surgery – and not necessarily only to reconstruct a breast, but also to close large chest wall defects. These patients must however be chosen carefully and counciled extensively and the planning of post surgical radiotherapy must also be considered.

WHAT IS THE JUSTIFICATION OF THE RETURN OF RADICAL SURGERY FOR ADVANCED BREAST CANCER?

Dr Carol Benn-Department of Surgery, University of Witwatersrand (Wits)

INTRODUCTION

The importance of systematic nature of breast cancer was recognized as early as Hypocrates (400 BC), who noted that many patients died quickly even when their primary cancers were excised, and Galen (100 AD) whose humoral theory specifically acknowledged the systematic nature of the disease.

In the 1940's Haagenson and Stout described criteria for operability and recognized that cancers with certain features could not be cured by even the most radical surgery. This resulted in the use of "salvage "chemotherapy for inflammatory and other locally advanced irresectable breast carcinomas. This resulted in the use of chemotherapy prior to surgery.

Locally advanced breast cancers contribute to about 10-20% of newly diagnosed worldwide

Unfortunately in South Africa as in many developing countries 60% of tumours are classified as locally advanced

Locally advanced cancers have widely different clinical and biological characteristics

Preoperative, neoadjuvant or primary systematic therapy (PST) refers to the administration of chemotherapy before loco regional treatment with surgery and/or irradiation.

The role of primary chemotherapy for breast cancer has expanded over the past two decades. Primary chemotherapy is the gold standard for locally advanced breast cancer, initially used for inoperable and inflammatory breast cancer and is now being used for operable stage 3 and stage 2 breast cancers that desire breast conserving surgery. .

DEFINITIONS

For the purpose of this chapter advanced breast cancer will be divided into

1. Locally advanced breast cancers: Large primary tumours and /or extensive regional lymph node involvement without evidence of distant metastases that don't respond to primary chemotherapy regimes
2. Large primary tumours and or extensive regional lymph node involvement with evidence of distant metastases that do respond to primary chemotherapy

a. Bone metastases only
b. Visceral metastases

Some patients have a history of rapid growing tumours and others of indolent tumour growth; this and the biology of the tumour are of critical importance

INFORMATION REQUIRED PRIOR TO STARTING THE TRIP

Ideally the initial assessment of the patient should be in a multi-disciplinary unit

Triple assessment is critical, with detailed attention to the following on:

1. History and examination: History of bone pain or headaches should be documented. Accurate sizing of the tumour should be documented, ideally photo-documentation can ensure accurate response to treatment

2. Radiology: bilateral mammogram and ultrasound of the breast and draining lymphatics (axillary, supraclavicular, and opposite axilla) will help define the

3. Extent of involvement within the breast and the nodal chains, the presence of additional tumor foci within the same breast or the contralateral breast, and the extension of the tumor to deeper structures.
4. Pathology: obtained by core needle biopsy and never surgical biopsy. Core allows for assessment of tumour grade, hormone receptors, other biomarkers, Ki 67, Her 2 neu
5. Metastatic workup: distant metastatic disease is documented in 20% of asymptomatic patients. Bio-chemical tests including liver and renal function and calcium levels. CT chest and abdomen, or Chest Xray and abdominal sonar should be performed, as well as a bone scan.

   The importance of an accurate initial assessment of the extent of primary tumor burden cannot be emphasized enough as the efficacy of subsequent local treatment will depend mostly on this initial assessment.

THE ROAD NOW LESS TRAVELLED : THE ARGUMENT FOR NO UPFRONT SURGERY

When previously looking at the natural history of patients with locally advanced breast cancer the following is noted:

1. For all types of LABC, irrespective of whether operable or not, the majority of patients developed distant metastases within 24months of diagnosis
2. High rates of loco-regional failure was documented again irrespective of whether surgery and or radiation was offered (surgery alone=60% local recurrence)
3. Loco-regional recurrences varied from 25-72%
4. Preoperative or postoperative radiation therapy improved loco-regional control rates but did not alter survival rates
5. Local control without systemic therapy results in a less than 20% 10 year survival

PRIMARY CHEMOTHERAPY UNPACKED

The biologic rationale of using primary chemotherapy is based on the observation in animal tumour models that there is accelerated metastatic growth after primary tumour resection. Observations of enhanced survival after administration of chemotherapy in the adjuvant setting suggest that, by giving chemotherapy as a primary treatment, this might minimize the emergence of chemoresistant clones and, thus reduce or eradicate metastatic disease.

Further reasons for the use of preoperative chemotherapy are based on its potential clinical benefits, such as increasing tumour resectability by reducing the size of the primary tumour, improving local control of disease, and allowing breast-conserving surgery to be undertaken

More than 70% of patients achieve a good clinical response with 10-25% of them achieving a complete pathological response

WHAT DRUGS FOR WHO AND WHEN

Prior to selecting the initial cocktail for use in advanced breast cancers,the following points should be noted

1. Physical Health of the patient, particularly cardiac status
2. Biological and physiological age of the patient
3. Not placing all your cards on the table (in metastatic disease setting, pacing which chemotherapies when is critical

4. CMF is not very effective for shrinking tumours and is better used in the adjuvant setting
5. Lobular carcinomas are more endocrine sensitive that chemo sensitive (although we have excellent results in our unit with weekly taxol for lobular carcinomas in terms of clinical and pathological response)

Common regimens used in the neo-adjuvant setting are as follows:

1. CAF
2. AC/T
3. TAC
4. EC/CEF
5. TC
6. TCH

C= cyclophosphamide; A= Adriamycin, F= fluorouracil , T=taxane (either taxol or taxotere)
TCH=taxotere, carboplatin and Herceptin

In advanced breast cancers that do not respond to traditional chemotherapy regimens, other drugs may be used in the second line node-adjuvant setting:

1. Cisplatin
2. Vinorelbine
3. Capecitabine
4. Doxil
5. Gemzar
6. Mitoxantrone
7. Ixabepilone
8. Abraxane

The drugs above are mentioned not to impress, bore or confound but merely to emphasis, that not unlike antibiotics developed for bacterial resistance the list is ever increasing and prior to accepting primary chemotherapy defect, and offering a salvage operation. Careful discussion as to the heroic and sometimes foolish outcomes must be born in mind

TARGET THERAPIES ADD TO THE WEAPONRY

In recent years the identification of signalling pathways and genetic alterations has lead to the clinical development of a number of successful molecular targeted therapeutic agents. The most well known being Herceptin and similar active agents that have changed the natural history of Her2 amplified breast cancers. There are numerous other targets under investigation, the most exciting is everolimus and the Bollero trials
Combination approaches that act on secondary mutations and compensatory pathways in resistant tumours will play a role in both local and metastatic control,
The following review is well recommended for reading pleasure:

1. JCI: Targeted therapies for breast cancer: Michaela.J. Higgins and Jose Baselga; Oct 3 2011

THE EFFECT OF ADVANCED BREAST CANCER ON QUALITY OF LIFE

The physical issues of pain, odour and loss of function must be carefully considered when deciding on treating or withholding treatment in these women
Psychological support, both through therapy and medication (anti-depressants, and anxiolytics) play an important role
For many patients failure to respond to primary chemotherapy or the development of metastatic disease is more devastating than the original cancer diagnosis
Dealing with issues around fear of dying, including practical issues for the family should be addressed by a health care provider in the multi-disciplinary team

In view of the vast improvements made in oncological care and the effect of advanced breast cancer on patient morale , surgery is a double edged sword
There is most definitely a place for surgery in patients with advanced breast cancer, the question is when?
There is no doubt that when it comes to surgery, the analogy of the titanic and the iceberg holds
Imagine your patient with advanced breast cancer is the titanic, and the cancer is the iceberg.
Surgery upfront prior to chemotherapy is like chopping off the top of the iceberg, daft as the ship is still going down (quickly)
Chemotherapy upfront, followed by surgery (timed when appropriate, see below), although the ship is still going to sink, this may be a more dignified exit approach and akin to the band playing while a few brave souls continue dancing….and who knows some may reach a life boat

GUIDELINES:

1. Leaving macroscopic tumour behind, is not a surgical victory
2. Operating in the presence of active, aggressive visceral disease is pointless
3. Patients who have had a good response to primary chemotherapy who still have large tumour volumes, should be reassessed in the MDM, with particular attention being paid to:

a. Radiological assessment of extent of axillary nodal disease
b. Photo-documentation of extent of tumour discussed with onco-plastic team
c. Documentation of metastatic disease at time of finishing primary chemotherapy
d. Options of palliative radiation therapy
e. Value of second line chemotherapy
f. Psychological profile of the patient at the current time.

CONCLUSION
Surgery does play a role in the management of advanced breast cancer. Although It may not be the star of the show (leading lady) , surgery is definitely not completely in the wings.

DOES NEO-ADJUVANT TREATMENT REALLY DOWN STAGE BREAST CANCER- WHAT IS THE EVIDENCE?

Dr Richard Khanyile-Department of Oncology, University of Pretoria

Kuerer et al published in 1999 outcomes of pts with pathological complete response after neoadjuvant chemotherapy.

- 377 pts – enrolled prospectively for 2 neoadj trials between 1989- 1996
- FAC(infusional) was used in both trials
- LABC was defined as stage >/= IIA according to AJCC 1998

Lymph node mets were confirmed by FNA

- metallic marker were used for responding pts after 1- 2 cycles of chemo for subsequent intraoperative localization
- after 4 cycles of chemo – 103 pts done segmental mastectomy with ALND and 253 pts received modified radical mastectomy

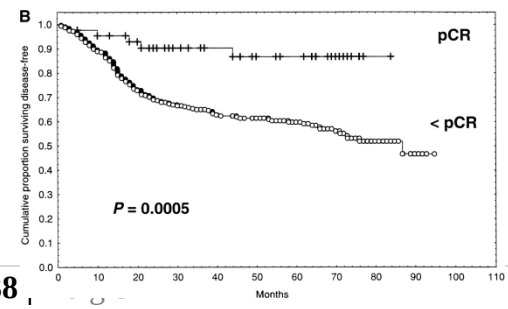
Non**-responders received RT**

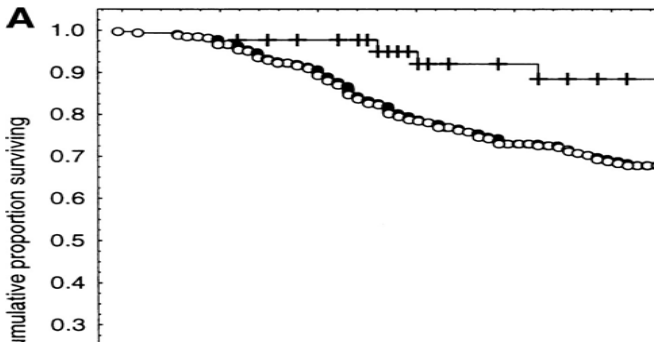
Results: - 12%(n-43) had pCR(13% ER +ve)
- 203 pts incomplete responders(49% ER+ve)
- Smaller tumors(T0-2), 21%, more likely to have pCR than T3/4, 7%.

- **Non-responders received RT**
- **Results: - 12%(n-43) had pCR(13% ER +ve)**
  - 203 pts incomplete responders(49% ER+ve)
  - Smaller tumors(T0-2), 21%, more likely to have pCR than T3/4, 7%.

- **58 mnths of follow up:**
  - 2 (5%) local recurrences in pCR pts vs 30(9%) local recurrences in incomplete responders
  - 12% distant recurrences in pCR pts vs 37% in incomplete responders(p=0,01

5 yr survival outcomes





82% 5 yr OS in pt with segmental mastectomy plus ALND vs 66% in modified radical mastectomy

- 73% 5 yr DFS in pts with segmental mastectomy vs 57% in modified radical mastectomy

- Neoadjuvant chemo identifies minimal responders
- the data indicate that the complete histologic elimination of invasive disease from the breast, the axillary lymph nodes, or both after neoadjuvant chemotherapy confers a survival advantage

NSABP B-18

- 1523 pts
- AC pre-op vs AC post-op
- No significant differences in DFS, OS

TAC

- Gepartrio group presented preliminary findings at 26th San Antonio Breast Cancer Symposium on Neoadjuvant TAC

- 51% CCR with 23% pCR in responders

NSABP B-27

- AC – T pre op vs AC preop vs AC preop + post op T(docetaxel)

- 2411 pts

- Increase in pCR- 26,1% in preop AC – T vs 14,3% in preop AC and postop T
- No increase in DFS or OS

PROACT TRIAL

- 451 Postmenopausal women
- Anastrozole vs TMX – given for 3 mnths
- Showed no differences in response rate
- Anastrazole had more BCS than TMX

IMPACT TRIAL

- 330 Postmenopausal women
- Letrozole vs TMX vs combination of the two
- Same response rate in 3 mnths

Anastrazole had better BCS

References

- To be added later

MANAGEMENT OF METASTATIC SQUAMOUS CELL CARCINOMA CERVICAL LYMPHADENOPATHY WITH "OCCULT" PRIMARY: HOW HARD SHOULD "OCCULT" PRIMARY BE SOUGHT.

Prof Jan Pretorius-Department of Surgery, University of Pretoria

Carcinoma of Unknown Primary Origin (CUP) in the Head and Neck Region, with Metastatic Cervical Lymph Node Metastases

When clinicians are unable to determine the origin of a metastatic malignant lesion after thorough clinical examination and appropriate special investigations, the cancer is said to originate from an unknown primary origin.

Carcinomas of unknown primary (occult) origin (CUP) are the 7th most common malignancy. No primary site can be identified in 3 - 5% of patients diagnosed with metastatic cancer. The most common sites for CUP's to metastasise to are the lung, lymph nodes, liver and bone. CUP lesions may represent a class of tumours with a greater propensity to disseminate early. In approximately 15 - 25% of cases, the primary site cannot be identified even at post-mortem examination. As the disease is diagnosed at a metastatic stage the prognosis is usually poor. In general, the mean survival time is about 3 - 4 months with less than 25% alive at 1 year and less than 10% at 5 years.

Presentation with metastatic cervical lymphadenopathy is not uncommon for patients with SCC of the head and neck. In head and neck oncology, about 10% of cases with squamous cell cancer (SCC) will present with palpable metastatic cervical lymph nodes but with no obvious primary tumour. Annually, between 1 - 3% of new cases of SCC in the head and neck region, may present as CUP lesions. Although squamous cell cancer is the most likely histological finding (90%), in patients with cervical metastatic lymphadenopathy, adenocarcinoma or melanoma or even anaplastic tumours may also be found.

Carcinoma of unknown primary origin of the head and neck region differ from CUP's in the rest of the body in some important aspects. Of metastatic lymph nodes in the neck, 15% will be from a primary below the clavicles. These lymph nodes usually present in the supraclavicular or lower part of the internal jugular chain and have a bleak prognosis and are usually adenocarcinoma. Isolated supraclavicular lymphadenopathy, including those of SCC origin, almost always originates from the skin or beneath the clavicles (ie lung, breast, colon, prostate, esophagus, cervix, ureteral and lymphoma primaries) With adenocarcinoma located in nodes in the upper neck, one must exclude a salivary gland, thyroid or parathyroid primary tumour. Patients with enlarged lymph nodes in the upper and mid neck have a good prognosis when treated aggressively compared with patients with enlarged lymph nodes in the lower neck. The majority have either SCC or poorly differentiated carcinoma.

The management of unknown primary true head and neck SCC is directed at cure for most patients who present with cervical lymphadenopathy, as this represents a locoregional but not distantly metastatic condition for most patients. This is in sharp distinction to CUP's presenting with distant metastases originating from below the clavicles that are generally incurable and associated with brief longevity unless it is a chemotherapy curable tumour.

Opinions are divergent concerning the value and extent of evaluation that should be performed to determine the primary tumour in patients presenting with CUP. While this

may be pragmatic for patients with CUP from sites below the clavicles, CUP arising from head and neck sites have a better prognosis and comprehensive evaluation should be performed.
Normally, when the primary site of the carcinoma is known, clinicians are able to administer focused therapy to the primary site as well as the cervical lymphadenopathy. It is suggested that mucosal irradiation significantly reduces the risk of primary site failure and also lowers the risk of second primary cancers developing subsequently. The problem with CUP lesions then is that clinicians are obligated to treat the entire pharyngeal axis and larynx to cover the possible origins of the metastatic carcinoma. The occult primary treatment regimen results in a significant increase in morbidity, predominantly due to radiation and chemotherapy.

A thorough and detailed evaluation to identify a primary tumour, is therefore essential to treat head and neck CUP lesions optimally. This evaluation includes a comprehensive history and extensive physical examination, imaging and panendoscopy.

The history should include exposure to any etiological factors or carcinogens of which alcohol and tobacco products are most important. Occupational hazards (chemicals, metals) and the country of origin (regions in China and North Africa with increased incidence of nasopharyngeal tumours) may be of help. Previous malignancies, including skin cancers may reveal important clues. Many patients, especially the elderly with along dermatologic history, will fail to mention the small growth that had been removed. Furthermore one should attempt to find any symptoms of the head and neck that could indicate a site of origin such as pain, trismus, odynophagia, dysphagia, haemoptysis or hoarseness, epistaxis, nasal congestion or aspiration. The typical presentation of a head and neck CUP is a complaint of a painless neck mass present for weeks to months.

The physical examination should encompass a thorough examination of the total head and neck region including the skin for new cutaneous malignancies as well as scars that may have resulted from recent dermatological surgery for a cutaneous neoplasm. Even examination of the cranial nerves is important to reveal the site and extent of an occult primary. Inspection and manual palpation of all anatomical structures and sites are essential – scalp,skin, ears, nose and nasal vestibules, salivary glands, oral cavity, oropharynx, nasopharynx, hypopharynx and larynx. Submucosal lesions can only be detected by palpation. Oropharyngeal tumours can be very difficult to identify since small tumours arising here are often concealed in normal appearing lymphoid tissue. Examination under anaesthesia (EUA) is useful. Especially the tonsils and base of the tongue should be palpated for irregular firmness or ease of bleeding. High-yield anatomical sites for CUP lesions are the nasopharynx, tonsils, pyriform sinus, hypopharynx, postcricoid area and the base of the tongue – biopsy samples should be obtained from these and any other suspicious areas, guided by direct inspection and palpation.

All zones of the neck should be palpated thoroughly to find additional lymphadenopathy or masses. Determine the size of the neck mass, fixation to skin or deep structures, the location to vital structures and bilaterality of nodes. If the neck mass is unilateral, the primary lesion should be sought in ipsilateral mucosal or cutaneous sites (eg tonsil,

scalp). If the neck mass is bilateral, the occult primary is likely from a midline structure (eg base of tongue, nasopharynx) Knowledge of various lymphatic drainage patterns and the levels of the lymph nodes in the neck with most common metastatic disease

presentation helps the clinician tailor the search for the unknown primary. For example level III or the middle jugular nodes typically drains disease fom the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx.

Computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast should be performed first for head and neck CUP lesions. If a primary tumour could not be identified, positron emission tomography with fluoro-deoxyglucose (FDG-PET) or integrated PET/CT is useful prior to panendoscopy. In some studies PET detected approximately 25% of tumours that were not identified during workup that did not include PET. Integrated PET/CT imaging appears to be more sensitive than PET alone in identifying the primary site. PET or integrated PET/CT should be performed before panendoscopy in order to guide biopsies and to avoid false positive FDG avidity from tissue manipulated during endoscopy.
Flexible fiberoptic laryngoscopy is essential to evaluate the sinuses and nasal cavity, the nasopharynx, the base of tongue, hypopharynx and the larynx. In addition direct laryngoscopy under anaesthesia is best to evaluate the oral cavity, oropharynx, hypopharynx and larynx and to perform directed biopsies of the high yield sites and all areas of clinical suspicion including mucosal irregularities, ease of bleeding or those suspicious on imaging. Bilateral tonsillectomy is recommended by many. Concurrent nasopharyngoscopy and esophagoscopy completes panendoscopy.

Even with an extensive evaluation, a primary tumour can often not be found. Fortunately, newer diagnostic procedures show potential in aiding the identification of the primary tumour:

1. In fine needle aspiration biopsy from a pathological lymph node: a) Human papillomavirus – more than 50% of oropharyngeal SCC are HPV positive vs only a small percentage of tumours from non-oropharynx head and neck sites. Immunohistochemical analysis of p16 is a valuable biomarker to identify tumours associated with HPV infection.

   b)EpsteinBarr virus is a sensitive marker for the presence of nasopharyngeal carcinoma using polymerase chain reaction analysis (PCR). Because of the relative high frequency of HPV and EBV negative tumours, a negative result cannot exclude oropharyngeal or nasopharyngeal primary tumours.

2. Time-resolved laser-induced fluorescence spectroscopy is a promising noninvasive diagnostic technique to discriminate between normal and malignant tissue.

3. Immunohistochemical analysis: for example studies that evaluate staining for keratins, leukocyte common antigen and S-100 a neuroectodermal antigen expressed in melanomas.

4. Gene expression profiling using an immunohistochemical panel may allow identification of a potential site of origin in patients with adenocarcinoma of unknown origin.

5. Electron microscopic analysis can sometimes aid in the diagnosis of CUP. In particular, the presence of desmosomes and bundles of tonofilaments are characteristic of SCC.

The pathologist has a central role in the evaluation of CUP, using all of the above, but also closely relating to the oncologist and primary physician. The complexity of the pathologic evaluation tends to be inversely related to the degree of differentiation of the tumour.
If a primary tumour cannot be identified in the head and neck region, aggressive local therapy is indicated. This may involve any of the following, although the optimal treatment of these patients is uncertain.

1. Radical radiation therapy with curative intent to the neck and possible site of origin
2. Preoperative radiation therapy followed by radical neck dissection
3. Radical neck dissection
4. Radical neck dissection followed by radiation to possible sites of origin.

Five year survival rates as high as 30 – 50% have been achieved with this approach. Concurrent chemoradiotherapy is suggested to be more effective in this situation. Patients with metastatic cervical nodes from SCC from CUP have an overall survival comparable to that of patients with a known primary.
Achieving locoregional control in patients with head and neck SCC of unknown primary has two components: controlling the disease in the neck and ensuring that a primary cancer does not develop (primary emergence). The most important factor influencing prognosis seems to be the clinical stage at diagnosis. Single modality treatment in these cases has selected application. Combination therapy is chosen to contain the risk of neck recurrence and emergence of primary tumours.

Lacking randomized controlled trials, it is recommend that the following guidelines be followed:

1. Patients with N1 and N2a disease without extracapsular extension:
    a. Single modality radiation therapy with IMRT technique to spare the mucosa
    b. Formal neck dissection for appropriately selected cases
2. For stage 2b or higher neck disease and extracapsular extension:
    a. Concurrent chemoradiation with IMRT technique
    b. Surgery is reserved for persistent or recurrent disease following radiation-based treatment.
    c. Formal neck dissection with postoperative radiation therapy (with or without chemotherapy) is a second option
3. Radiation therapy, with or without chemotherapy, to putative mucosal sites of primary tumour is important to minimize primary emergence.

Bibliography.

1. 2012 UpToDate www.uptodate.com Head and neck squamous carcinoma of unknown primary
2. Arch Otolaryngol Head Neck Surg 2009;135(10):1024-1029
3. http://emedicine.medscape.com/article/280505-treatment

MANAGEMENT OF METASTATIC SQUAMOUS CELL CARCINOMA CERVICAL LYMPHADENOPATHY WITH "OCCULT" PRIMARY: ROLE OF SURGERY IN SUCH PATIENT MANAGEMENT

Dr Gary Fetter-Waterfall City Hospital, Johannesburg

Occult squamous cell cancer with positive cervical lymph node metastases is fortunately a rare phenomenon. When it does occur, it is the non-identification of the occult primary tumour that remains a clinical challenge. By definition any primary tumour detected during treatment no longer qualifies as an occult primary.

More than 80% of occult primary cancers are most likely to arise in the head and neck region with a minority of the primary cancers occurring below the level of the clavicles. Supraclavicular lymphadenopathy, particularly on the right, is more likely to arise from a source below the level of the clavicles.

Although occult disease has an ominous outcome, a significant number of patients achieve substantially good outcomes with appropriate surgery and radiotherapy approaches. Patients with this condition should always be offered potentially curative treatment.

Many studies show variable outcomes due to relatively small number of patients who make up this group. Three year disease free survival after surgery alone or combination therapy range from 40 – 50% in patients with N1 disease, 38% and 26% for N2 and N3 disease respectively. In patients where the primary lesion is diagnosed after initial treatment was completed generally have a worse prognosis (two fold).

Patients should be evaluated as follows prior to any treatment:

1. Surgical or fine needle aspiration biopsy of a lymph node.
2. Direct nasopharyngoscopy, laryngoscopy, bronchoscopy, oesophagoscopy with biopsies of any suspicious areas.
3. Random biopsies should be taken of nasopharynx, base of tongue, tonsil, piriform sinus on the side of the cervical lymphadenopathy.
4. CT scans and/or PET CT scans.
5. MRI scan.

If no primary is found then the management should be planned around what is best for the individual patient.

One has to understand that most treated patients with progressing, recurring or relapsing disease is poor, regardless of the type of tumour or primary treatment modalities. The long-term complications and side effects of chemoradiotherapy are also significant regarding the quality of life that these patients experience after such broad field "blind" treatment to the area of the suspected occult primary tumour. Regression of the primary cancer can occur in many instances and therefore one has to ask the question whether blind treatment for an unknown primary cancer is warranted; particularly in view of the long-term irreversible complications.

I personally recommend, after a very extensive and thorough failed search for the primary cancer, that an appropriate modified or radical neck dissection on the affected side of the neck should be performed and to reserve further treatment, including chemoradiotherapy, for possible recurrent or persistent disease. Once a patient has received all forms of therapy at the initial time of treatment and gets recurrent or persistent disease, only further surgery is available to the patient with very poor long-

term results in that instance. In that time, from initial treatment to recurrent disease being documented, hopefully the primary cancer will become clinically obvious, where

more specific and directed therapy can then be given to that type of cancer with less severe long-term side effects one gets with “broad field” therapy.
On-going prospective randomised trials will be required to answer which approach will be best in the long-term for this group of patients but many will argue for their specific type of approach based on the available evidence.

MELANOMA AND THE MANAGEMENT OF LYMPH NODES

1) DOES THE TIMING OF LYMPH NODE DISSECTIONS ALTER SURVIVAL?

One of the fundamental questions of Oncology remains whether there is a therapeutic benefit in the early detection and management of occult metastatic disease. Does improved staging translates into improved survival? Does early lymphadenectomy for occult metastasis have a survival advantage over therapeutic lymphadenectomy (ThLND) for clinically overt metastasis?
The sequential spread theory of Halsted would like us to believe that cancer spreads in a controlled predictive way, which lends itself to successful cancer surgery.
The theory of Fischer challenges that of Halsted with the concept that cancer metastasizes in an uncontrolled, multidirectional way, resulting in a systemic disease from the onset. Or as translated by Blake Cady: "Lymph nodes are only indicators but not governors of survival"

2) IS THE TIME SPAN BETWEEN OCCULT AND CLINICALLY EVIDENT METASTATIC DISEASE (16 MONTHS) REALLY IMPORTANT FROM A SURVIVAL POINT OF VIEW?

3) DID THE HISTORICAL ELECTIVE LYMPH NODE DISSECTIONS (ELND'S) IMPROVE SURVIVAL?

ELND relies on a calculated decision on firstly which melanomas are prone to metastasize and secondly which lymph node basin would be affected first.
The accepted concept was, and still is, that patients with intermediate thickness melanoma (1-4 mm) have an increased risk of nodal disease without a high risk of distant disease. The hypothesis is that both thinner and thicker melanomas can be excluded from ELND, because thin tumours (<1mm) would have a low risk of metastases at any site and that patients with thick melanomas (> 4 mm) had a high risk of both regional and distant metastases.
The prediction of the possible affected basin was made purely on anatomical considerations
Yes, ELND did improve survival, but only marginally so. Intermediate thickness melanoma: WLE (Wide Local EXCISION) vs. WLE + ELND, DFS (Disease free survival) at 5 years was 51,3% vs. 61,7% respectively, p=0,09

4) WHAT IS A SLN?

The sentinel node is the first node that receives lymph from a primary neoplasm. The drainage pattern is determined by the anatomical site of the primary as well as by variations in lymphatic anatomy. It is estimated that the discordancy between lymphoscintigraphic and clinically defined nodal nodal basins is 5% for lower extremity melanoma, 14% for upper extremity melanoma, 25% for truncal melanoma and 48% for head and neck melanoma.

5) WHICH ARE THE DRAINAGE SITES ON THE TORSO?

The head and neck and truncal melanomas are less predictive in terms of lymphatic drainage. In addition drainage may be to more than one site.
2 Lines determine the direction of draining in truncal melanomas:
Midline anterior and posterior
Sappey's line (umbilicus to iliac crest to L2 to umbilicus)
These 2 lines form 8 quadrants
The Sydney Melanoma Unit has developed computer programmes with three dimensional maps that predict the drainage sites of melanoma very accurately. They pointed out that Sappey's line is not effective in predicting lymphatic drainage.

6) THE TECHNIQUE OF SLNB?

The lymphoscintigram should preferably be scheduled on the day of the operation. Multiple intradermal injections of Tc-99 sulphur colloid (total dose of 1 mCi) are made at the perimeter of the biopsy scar. Tc-99 sulphur colloid has been shown to concentrate in the regional lymph node basin within at least 3-6 hours and can be detected in the SLN for up to 7 hours without significant leakage to adjacent nodes. All regional node bearing areas are scanned under the gamma camera and the sites of uptake are marked (on the lymphoscintigram and on the patient's skin). In the operating room 2-4 ml of a dye (e.g. isosulfan blue, patent blue or methylene blue)) is injected intra-dermally at the biopsy scar. On average, the SLN will be visible within 5-15 minutes after injection. An incision is made over the pre-operatively identified area and the dissection is performed until a blue node is visualized, which is removed. Using a combination of inspection and the gamma probe, the wound is examined for more blue and or hot nodes. To decrease the miss rate, all SLN's with more than 10% of the ex-vivo radioactivity of the "hottest" SLN should be removed. In 16% the positive SLN was found to have a lower radioactive count than the "hottest" SLN, which was negative.

7) HOW SUCCESSFUL IS THE HUNT FOR (AFFECTED) SENTINEL NODES?

*Clinical examination is not sensitive. More than 25% of patients with a clinically negative lymph node examination have microscopic nodal disease.
*Preoperative Ultrasound and FNAC followed by lymphoscintigraphy and SLNB yield a detection rate of 100% for micrometastases. Lymphoscintigraphy, combined with SPECT CT, is equally effective.
*The SLN could be identified in 95% of attempted cases. The drainage basins frequently are uncommon and or multiple sites. In 80% of cases the SLN is both blue and hot. Radioactive localization of SLN is more sensitive than the blue dye method.

8) Can we predict if a SLN is going to be positive?

*Statistically significant predictors of for positive SLN are:
-Increasing Breslow thickness:
<1mm: 3% SLN +
1-2mm: 13% SLN +
2-3 mm: 22% SLN +
>4mm: 35-65% SLN +

-the extent of tumour lymphangiogenesis
-lymphovascular invasion
-ulceration
-absence of regression
-younger age
-tumour location on the trunk

9. HOW IS THE SLN EVALUATED FOR METASTATIC DISEASE?

9.1 Intra-operative evaluation of SLN''s is done by:
*Frozen section
* Imprint cytology (node is bisected and imprinted)
*RIHC (Rapid Immunohistochemistry) provides an answer in 30 minutes
9.2 A detailed pathologic analysis of the SLNB will detect micrometastases that could be missed by standard techniques (2mm slices, embedded in paraffin blocks and 10 sections from each block).
9.3 Immunohistochemistry (IHC) for S100 and HMB45
9.4 Recent advances: PCR is a molecular biological technique that can detect a single metastatic cell in 10^7 normal cells. Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) thus is more sensitive for the detection of submicroscopic melanoma than histology or IHC. RT-PCR upstaged 30% of histological negative SLNB's.

10. WHAT IS THE NEGATIVE PREDICTIVE VALUE OF SLNB?
If the SLNB is negative or micrometastatic (<0,1mm tumour), the lymph node basin is truly negative in 95% of patients.

11. WHAT IS THE POSITIVE PREDICTIVE VALUE OF SLNB?
If the SLNB is positive, 20% of patients have other positive lymph nodes in the basin. This increases with the diameter of the tumour in the SLNB, the density of the dendritic leucocytes in the paracortex as well as with the poor prognostic factors of the primary. A score has been developed to predict the status of the Non-SLN in SLNB positive patients (S1, S2 or S3).

12. AFTER THE SLN HAS BEEN IDENTIFIED AND ANALYSED, SHOULD A COMPLETION LYMPH NODE DISSECTION (CLND) BE PERFORMED?
*If the SLN is positive, a CLND is recommended in the affected basin.
*If the SLN is negative or technically inconclusive:
Several classification criteria have been proposed to identify patients with positive SLNB but without a risk for additional positive nodes. Patients with very limited tumour burden in the SLN (<0.1mm) are probably unlikely to benefit from a CLND. Tumour thickness, ulceration, angiolymphatic invasion and mitotic index are significant prognostic parameters for positive CLND status and might be considered in the decision to perform CLND.

13. ANY FALSE NEGATIVE SLN?
The risk of nodal recurrence after a negative SLNB IS <5%.
*Nodes obliterated by tumour may not take up blue dye or radioisotope.

14. ANY FALSE POSITIVE SLN?

IHC may inadvertently report false positive SLNB due to phagocytic cells containing melanocyte antigens

15. MORE THAN ONE SENTINEL NODE?

* More than one sentinel node is almost the rule: average number of SLN per basin is 1,8.

*More than one basin: patients with a melanoma around the waist (180 mm above or below the umbilicus) will have a 17,7% probability of dual drainage to the axilla and groin.

.

16. IS THERE AN ONCOLOGICAL DOWN SIDE TO LYMPH NODE DISSECTION?

Regional immunity is probably affected. An analysis of cytokine profiles of negative SLN indicates that soluble tumour antigen draining to these nodes result in increased production of GM-CSF, IFN-gamma and IL-2 in these nodes. This benefit disappears in positive SLN.

17. WHAT IS THE PROGNOSTIC VALUE OF NEGATIVE SLN'S IN TERMS OF DFS?

*5 year DFS survival in thin melanomas and negative SLNB's: 85,3%

*5 year DFS survival in thick (4mm) melanomas and negative SLNB's: 47%

18. WHAT IS THE PROGNOSTIC VALUE OF POSITIVE SLN'S IN TERMS OF DFS?

Three histopathological parameters of positive SLNB's predict a poor prognosis: tumour burden, tumour penetrative depth >2mm and infiltration of the SLN capsule.

19. POSSIBLE CONTRA-INDICATIONS FOR SLNB?

19.1.1 Where previous surgery (e.g. skin flaps) has resulted in disruptions of the lymphatic vessels.

19.1.2 A melanoma thickness of less than 1mm without additional risk factors such as a previous shave biopsy, angiogenesis etc.

19.1.3 Desmoplastic melanoma. Unconfirmed studies show a 1-2% incidence of positive SLNB even in thick desmoplastic melanomas.

THE MILLION DOLLAR QUESTION: DOES THE TIMING OF LYMPHADENECTOMY IMPACT ON SURVIVAL? IS THERE A SURVIVAL BENEFIT IN EARLY LYMPHADENECTOMY (SLNB+/-CLND) VERSUS THLND (WAIT AND SEE)?

YES, but a qualified yes. A meta-analysis of 6 studies (n=2633) indicated that there is a significant lower risk of death for patients who underwent SLNB+/-CLND compared to patients who underwent ThLND (CI 1.28-2.00; p< .0001). The median survival was 119 months for the SLNB+/-CLND group vs. 62 months for the ThLND group. The qualified yes is because these 6 studies were (published) retrospective series and not RCT's.

SELECTED REFERENCES

1. Sandro Pasquali, MD; Simone Mocellin, MD, PhD; Campana, MD, et al. Early (Sentinel lymph node biopsy-guided) versus delayed lymphadenectomy in melanoma patients with lymph node metastases. Cancer, March 1, 2010: 1201-1209.

2. Simone Mocellin, Dave S.B. Hoon, Pierluigi Pilati, et al. Sentinel lymph node molecular ultrastaging in patients with melanoma: A Systematic Review and Meta-Analysis of prognosis. Clinical Oncology J. 2007;25: 1588-1595.
3. Matias E. Valsecchi, Damian Silbermins, Nicole de Rosa, et al. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: A Meta-analysis. Clinical Oncology J. 2011;29: 1469-1487.
4. Cochran AJ, Wen DR, Huang RR, et al. Modern pathology: Prediction of metastatic melanoma in nonsentinel nodes and clinical outcome based on the primary melanoma and the sentinel node. Modern Pathology: An official journal of the United States and Canadian Academy of Pathology, July 2004: 747-55.
5. Satzger I, Volker B, Al Ghasal M, et al. Prognostic significance of histopathological parameters in sentinel nodes of melanoma patients. Histopathology, May 2007: 764-72.
6. Eudy GE, Carlson GW, Murray DR, et al. Rapid immunohistochemistry of sentinellymph nodes for metastatic melanoma. Human Pathology, August 2003: 797-802.
7. De Giorgi V, Leporatti G, Massi D, et al. Outcome of patients with melanoma and histologically negative sentinel lymph nodes: one institution's experience. Oncology, 2007: 401-6.
8. Wong SL, Morton DL, Thompson JF, et al. Melanoma patients with positive sentinel nodes who did not undergo completion lymphadenectomy: a multi-institutional study. Ann Surg Oncology, June 2006: 809-16.
9. Soo V, Shen P, Pichardo R, et al. Intraoperative evaluation of sentinel lymph nodes for metastatic melanoma by imprint cytology. Ann of Surg. Oncology, May 2007: 1612-7.
10. Gradilone A, Ribuffo D, Silvestri I, et al. Detection of melanoma cells in sentinel lymphnodes by reverse transcriptase-polymerase chain reaction: prognostic significance. Ann of Surg. Oncology, Nov 2004: 983-7.
11. Leong SP, Peng M, Zhou YM, et al. Cytokine profiles of sentinel lymph nodes draining the primary melanoma. Ann of Surg. Oncology, Jan-Feb 2002: 82-7.
12. Kunte C, Geimer T, Baumert J, et al. Analysis of predictive factors for the outcome of complete lymph node dissection in melanoma patients with metastatic sentinel lymph nodes. J Am Acad of Dermatology, April 2011; 655-62.
13. Stoffels I, Dissemond J, Poeppel T, et al. Advantages of preoperative ultrasound inconjunction with lymphoscintigraphy in detecting malignant melanoma metastases in sentinel lymp nodes: a retrospective analysis in 221 patients with malignant melanoma AJJCC Stages I and II. J Eur Acad Dermatol Venereol, Jan 2012: 79-85.

Usual sites: distant skin, subcutaneous
nodules, L/nodes
Lung/liver/other visceral
organs/brain

Prognosis

- Very poor
- Median survival 6 – 9 mnths with lung/ L/node/ skin only may be up to 15 mnths
- Surgical treatment should always be considered

Chemotherapy

- Melanoma is generally resistant to chemotherapy
- Dacarbazine - is FDA approved
  - Response rate of 7% but other clinical trial have reported higher RR of up to 15%
  - OS - 8 mnths

IMMUNOTHERAPY

- Interleukin-2: - FDA approved
  - RR of 6 – 9%
  - Atkins et al, in 199 published in JCO – HD IL-2 data
    - 720 000iu/kg iv bolus
    - OOR - 15,5%
    - Brain mets were Excluded

- Durability of CR is the hallmark of IL-2 therapy
- 80% of complete responders are likely cured
- Toxicity: very toxic –e.g capillary leak syndrome
- Need ICU

IPILUMAMAB: FDA APPROVED
Anti-CTLA-4 Monoclonal antibody
ORR 10 – 15%
Disease control rate of 30%
Toxicity is manageable
Induce long-term responses in minority of pts

VEMURAFENIB: TKI, BRAF INHIBITOR
BRAF activating mutation is found in approx 40-60% of melanoma pts

Response is seen within 2 wks but PD of disease is notice at 6 months

VEMURAFENIB: IMPORTANT MUTATION IS V600E

COMBINATION CHEMOTHERAPY

- Only in Clinical trials
- None has shown better results

IMMUNOTHERAPY PLUS TARGETED THERAPIES?

REFERENCES

- To be added later

THE ROLE OF SURGERY

Despite major advances in the primary treatment of squamous head and neck cancer with chemoradiotherapy, the oncologists, reluctantly at times, will concur that primary surgery remains the gold standard of treatment for most of these types of cancers. Surgery can only realistically be performed in these patients if adequate quality of life and functionality can be preserved after major resection and reconstructive procedures. The larger the resection required, the more need for complex pedicled or free flaps are needed to repair the defect created. Free flaps have a high failure rate in inexperienced hands and therefore the head and neck surgeon has to take this into consideration before embarking on a major debilitating procedure.

Unfortunately, 2/3 patients presenting with squamous cell cancer of the head and neck are Stage III or IV cancers. Five year overall survival for Stage three cancers is about 30 – 40% and Stage IV cancer below 20%. Twenty percent of these patients will develop distant metastases.

Not only are these advanced cancers but most patients are of poor general health with most having a significant smoking and alcohol history. These relatively malnourished and unhealthy patients have a much higher surgical morbidity and mortality risk. Unfortunately the aggressive nature of these cancers does not permit time to get many of these patients fit for major surgery and many have to be declined for primary surgery and even chemoradiotherapy on this basis.

These cases have to be assessed by a multidisciplinary team; not just the surgeon and oncologists, but the physician, dietician and anaesthetist as well. Certain cancers respond exceptionally well to primary chemoradiotherapy, particularly nasopharyngeal, tonsillar some of the oro- and hypo-pharyngeal cancers. Where possible the rest should be treated by primary surgery, where the patient is deemed fit enough to undergo such a major procedure. Even though the surgical resection margins may be “clear” on final pathology, good prospective data has shown better disease free survival and overall survival benefit with adjuvant chemoradiotherapy.

There are still some supporters, particularly in the surgical fraternity, who will subdivide the surgical group into high risk and low risk of recurrence; submitting only the high risk group for immediate post-operative adjuvant therapy. The rationale for this decision is a valid one. Once radiotherapy has been given it is very rare that one can give it again when a recurrence occurs. Likewise, salvage surgery on its’ own is unlikely to be successful and in that scenario one would like to have effective adjuvant therapy available as a second line of treatment. Even though surgery only is done in these low risk groups and there is a slightly higher risk of recurrence without adjuvant therapy, one now has the option of re-operating on the patient and then giving post-operative chemoradiotherapy, as clear good margins in this group of patients is hardly ever achieved second time round.

Head and neck cancers represents a collection of diseases with a diverse subset of squamous cell cancer groups, with each behaving differently. This makes individual treatment complex as it is not just about the stage of the cancer that one has to consider, but patient factors, pathological response and behaviour, tumour biology, prognosis and effect on quality of life as well. Functional outcome of the patient is to be debated by the team before treatment is instituted, without compromising disease free or overall survival significantly.

THE ROLE OF RADIOTHERAPY

The management of Stage III and IV Head and neck tumours has undergone dramatic changes over the past decades.

It did not take long for the discovery of X-Rays by Roentgen in 1895, and subsequently the discovery of Radium by Marie Currie in 1898, to be applied to the management of patients with cancer.

In the early 1920's, cancer of the larynx, for example, was managed with radiation only. Surgery was limited to the small "intrinsic" tumours.

At that time, radiation was more 'trial and error', and due to concerns about toxicities and with the improvement and refinement of surgical techniques in the 1940's, the pendulum swung towards the surgical management of head and neck tumours.

In the 1970's, it become standard practice to offer postoperative radiotherapy when indicated following surgery.

RTOG 7303 confirmed that postoperative was preferable to preoperative radiotherapy. Studies have also mentioned the poor outcomes that are associated with radiotherapy delay and prolongation of overall treatment time. Radiation should ideally start within six weeks following surgery.

The landmark trial from the Veterans Laryngeal group published in 1991 confirmed a role for chemotherapy combined with radiotherapy in organ preservation.
64 % of patients with larynx cancer assigned to induction chemotherapy had their larynx preserved.

Recent developments in Radiotherapy such as IMRT offer us an opportunity to limit the dose to critical and normal structures as well as to give a concomitant boost to the tumour bed, limiting the overall treatment time which in terms of radiobiological effects should be beneficial in terms of tumour control.

Radiotherapy has become an essential part of the multidisciplinary management of head and neck cancer.

Irrespective of further developments in the management of head and neck tumours, radiation oncologists need to be actively involved, with their surgical colleagues, who specialise in these cancers.

RATIONALE FOR THE TREATMENT OF PERITONEAL SURFACE MALIGNANCY

Prof Kurt Van der Speeten, MD, PhD
[1] Department of Surgical Oncology, Ziekenhuis Oost-Limburg, Genk, Belgium
[2] Washington Cancer Institute, Washington Hospital Center, Washington, DC, USA

INTRODUCTION

The peritoneal surface remains an important failure site for patients with gastrointestinal and gynecologic malignancies. Tumor cells may exfoliate from the primary tumor into the peritoneal cavity preoperatively due to transserosal growth. Transserosal growth of a colon tumor is a consistent predictor of subsequent intraperitoneal recurrence (1, 2), and is an important independent pathological prognostic parameter (4-6). Alternatively, intraperitoneal spread may be the result of surgical trauma that causes release of tumor cells from transected lymph and blood vessels or by manipulation of the primary tumor (7-8). Once released into the peritoneal cavity, loose cancer cells become subject to physiological peritoneal fluid flow. In contrast to circulating tumor cells in blood, bone marrow, or liver, the metastatic efficiency of loose intraperitoneal cells is remarkable and is suspected to play a major impact in development of PC (9-12). The acute inflammatory response and healing processes observed at the site of surgical injury are important for both the formation of postoperative adhesions and the enhancement of tumor growth (13-14). The molecular mechanisms underlying this pathological sequence of peritoneal transport of free tumor cells, mesothelial adhesion, mesothelial invasion, stromal invasion, and eventually proliferation, will eventually result in the development of clinical PC (15-16).

In the past, oncologists and surgeons assumed PC was identical to distant metastases, and as such regarded it as an incurable component of intra-abdominal malignancy. Since the 1980s, different treatment hypotheses for patients with isolated peritoneal metastases of gastrointestinal cancer, ovarian cancer and primary peritoneal malignancies have emerged based on the revised hypothesis that PC is a local-regional disease, and therefore, warrants a local-regional therapeutic approach. These new treatment protocols are based on a combination of cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy. The aim of CRS is to eliminate all macroscopic disease: this implies a series of visceral resections and standardized peritonectomy procedures (17-19). A second essential part of the current management of PC is perioperative intraperitoneal chemotherapy. The underlying rationale of the combined approach is that the aggressive surgical approach combining visceral resections and peritonectomy procedures addresses the macroscopic disease and the perioperative intraperitoneal chemotherapy targets the residual microscopic disease (17). In 1980, Spratt et al. (20) reported the use of heated triethylenethiophophoramide (thiotepa) in a patient with pseudomyxoma peritonei and Speyer & Myers (20) used normothermic intraperitoneal 5-FU and methotrexate in 16 patients with PC. In 1983, Koga et al. (21) reported the use of intraperitoneal chemotherapy in 23 gastric cancer patients with PC. Perioperative intraperitoneal chemotherapy includes Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) and/or Early Postoperative Intraperitoneal Chemotherapy (EPIC). More recently Bidirectional Intraoperative Chemotherapy (BIC), combining simultaneous intraoperative intraperitoneal and intravenous chemotherapy, was introduced.

With the shift in treatment paradigm of PC patients, one randomized control trial (23-24) and several phase II studies have explored the peroperative intraperitoneal route of drug delivery (25-38). In an update on a Phase III trial, Verwaal et al. (24) report a 45% 5-year survival in colorectal PC patients receiving optimal cytoreduction and HIPEC with mitomycin C followed by systemic chemotherapy. Elias et al. (36) analyzed the results of combined CRS and perioperative chemotherapy in 1290 patients with PC from a variety of primary malignancies: at 5 years, 37% of the patients were still alive. These encouraging clinical results are in strong contrast to historical control groups and patients treated with systemic chemotherapy.

Although further clinical data from phase II and III trials supporting this combined treatment protocol are necessary, the wide variation in PC chemotherapy protocols used in these treatment regimens requires optimizing. The pharmacology of perioperative chemotherapy is still not clearly understood, but it is possible increased safety and improvements in treatment may originate from analyzing pharmacological data.

PHARMACOLOGY OF PERIOPERATIVE CHEMOTHERAPY

Pharmacokinetics explores what the body does to the cancer chemotherapy drug and pharmacodynamics explores what the drug does to the body.

Pharmacokinetic Principles of Perioperative Chemotherapy

The intraperitoneal route of delivering chemotherapy is logistically less convenient and technologically more challenging than conventional intravenous chemotherapy. This means the pharmacokinetic rationale of intraperitoneal chemotherapy needs to be explored.

The Peritoneal Plasma Barrier

The rationale of administering chemotherapeutic drugs into the peritoneal cavity is based on the relative transport barrier formed by the tissue surrounding the peritoneal space. The peritoneum is a complex three-dimensional organ covering the abdomino-pelvic organs and the abdominal wall and contains a potentially large space. The most elaborate description of the ultra structure of the peritoneum in man was presented in 1941 by Baron et al. (39). The peritoneum consists of a monolayer of mesothelial cells supported by a basement membrane and five layers of connective tissue, which account for a total thickness of 90 µm. The connective tissue layers include interstitial cells and a matrix of collagen, hyaluron and, proteoglycans. The cellular component consists of pericytes, parenchymal cells and, blood capillaries. This complex is often referred to as the peritoneal membrane and the description is a working model derived from research on the peritoneum as a dialysis membrane.

The accepted function of the peritoneum is twofold. First, it reduces friction between intra-abdominal organs and the abdominal wall by producing a lubricant solution made of glycosaminoglycans and phospholipids (40-41). Secondly, together with lymphoid aggregates dispersed on the visceral and parietal peritoneum, it is of major importance in the host defense against intra-abdominal infection. A third suggested function of the peritoneum in malignancy (42) might be its role as a first line of defense against peritoneal carcinomatosis. Any disruption in the peritoneal lining facilitates the adhesion-invasion cascade of tumor cells, resulting in the development of peritoneal tumor nodules on the abdominal or pelvic surface (15, 42).

Contrary to intuitive thinking, the elimination of the mesothelial lining during peritonectomy procedures does not alter the pharmacokinetic properties of the peritoneum in the transport of chemotherapeutic agents from the peritoneal cavity to the plasma compartment. In a rodent model, Flessner et al. (43) demonstrated that neither removal of the stagnant fluid layer on the mesothelium nor removal of the mesothelial lining influences the mass transfer coefficient (MTC) over the barrier. There is indirect evidence (44-45) supporting this hypothesis in humans in that the extent of the peritonectomy in PC patients does little to alter the intraperitoneal chemotherapy pharmacokinetics of Mitomycin C or 5-fluorouracil. Basic research indicates (46) it is the blood capillary wall and the surrounding interstitial matrix that are the principal barriers for clearance of molecules from the abdomino-pelvic space, not the mesothelial lining. Fluid enters the vascular compartment by diffusion from the peritoneal compartment or by absorption through the peritoneal lymphatic stomata, which are concentrated to the diaphragmatic surface (47-48). Diffusion of fluid through the parietal peritoneum generally

results in flow to the plasma compartment and drainage through the visceral peritoneum covering the surfaces of liver, spleen, stomach, small and large bowel and, mesentery is into the portal venous blood (49).

Dedrick Diffusion Model

The pharmacokinetic rationale of perioperative intraperitoneal cancer chemotherapy is based on the dose-intensification provided by the peritoneal plasma barrier. From peritoneal dialysis research, Dedrick et al (50) conclude the peritoneal permeability of a number of hydrophilic anticancer drugs may be considerably less than the plasma clearance of the same drug. The peritoneal clearance is inversely proportional to the square root of its molecular weight and results in a higher concentration in the peritoneal cavity than in the plasma after intraperitoneal administration (51-52). A simplified mathematical diffusion model considers the plasma to be a single compartment separated from another single compartment, the peritoneal cavity, by an effective membrane **(Figure 1)**.
This results in Equation 1:

$$\text{Rate of mass transfer} = PA\,(C_P - C_B)$$

where: PA = permeability area (PA = effective contact area A x permeability P), C_P = concentration in peritoneal cavity and, C_B = concentration in the blood (53). This simple conceptual model indicates the importance of the effective contact area. Although the equation permits calculation of the pharmacokinetic advantage, the model does not reveal anything about the specific penetration of the cancer chemotherapy drug into the tissue or tumor nodule (54), nor does it predict the value of the effective contact area. The model simply describes the transfer between two compartments.

After Intraperitoneal administration, dose-intensification results in a higher concentration of cancer chemotherapy in the peritoneal cavity than in the plasma. After cytoreduction, this concentration difference increases the possibility of exposing residual tumor cells to high doses of chemotherapeutic agents with reduced systemic concentrations and lower systemic toxicity. This advantage is expressed by the Area Under the Curve (AUC) ratios of intraperitoneal (IP) versus plasma (IV) exposure. The molecular weights and AUC IP/IV for drugs in clinical or experimental use in PC patientsarepresented in **Table 1**.
One important consideration is that high intraperitoneal concentration or AUC IP/IV does not automatically confer a greater efficacy. Even with greatly elevated intraperitoneal cancer chemotherapy concentrations, there may be limited penetration of the chemotherapeutic agent into the peritoneal tumor target. The ideal drug for intraperitoneal chemotherapy has a high peritoneal tissue concentration, because of direct intraperitoneal administration, and a high penetration into the cancer nodule. This should occur in conjunction with slow diffusion of the cancer chemotherapy solution through the capillary endothelium and deep in the subperitoneal space. Low systemic concentrations and reduced systemic toxicity are maintained by rapid metabolism and excretion of the drug within the body compartment.

Pharmacokinetic Variables

Dose

Different chemotherapy agents, drug concentrations, drug doses and, drugs schedules have been developed at many institutions for perioperative cancer chemotherapy. Although most researchers use a drug dose based on calculated body surface area (mg/m^2), Rubin et al. (55) demonstrate there is an imperfect correlation between actual peritoneal surface area and calculated body surface area and there may be sex differences in peritoneal surface areas, which i

n turn affects absorption characteristics. The female has a 10% larger peritoneal surface in proportion to body size than the male. There have been attempts to estimate the functional

peritoneal surface area through applying stereologic methods to CT scans a by extrapolating data from cadaver measurements (56-57).

Body surface area is an accurate predictor of drug metabolism and is useful for estimating systemic drug toxicity. The accuracy of this prediction increases if the volume of chemotherapy solution is also determined by the body surface area (58). With a constant total dose of chemotherapy and chemotherapy solution, bone marrow exposure to cytotoxic drugs can be accurately predicted. If these predictions are unavailable, there is a possibility of overdosing some patients and underdosing others. Many institutions that use a closed method for intraoperative hyperthermic chemotherapy calculate the dose of cancer chemotherapy per liter by body surface area. The total amount of cancer chemotherapy is mixed in a large volume of carrier solution (usually six liters) that is placed in a reservoir. For example, Deraco (59) and Barrati (60) at the Milan Cancer Institute use doxorubicin 15.25 mg/m^2/l and cisplatin 43 mg/m^2/l with a total volume of 6 liters. Glehen (61) and Gilly (62) from Lyon have used mitomycin C 0.5 mg/kg and cisplatin 0.7 mg/kg in a total volume of 4 to 6 liters. In this closed method, the amount of chemotherapy solution in contact with the peritoneal surface is determined by multiple variables: the amount of distention (between 2 and 6 liters) of the abdominal cavity, which is induced by the chemotherapy solution, the patient's sex, the amount of ascites present preoperatively and, the extent of the visceral resection.

A system that allows a variable amount of chemotherapy solution may result in a less accurate prediction of plasma AUC. The total volume of intraperitoneal chemotherapy can vary widely between individuals. An increase in the volume of intraperitoneal chemotherapy solution causes an increase in both diffusion surface and the amount of drug transferred from peritoneal space to plasma. Other factors contribute to the controversy over the proper dosage of chemotherapy solution. Some institutions use a single dose of the intraperitoneal drug; others use a double, or even triple, dose of the same drug over a 90-minute period (63-65).

Volume

As peritoneal metastases and free-floating tumor cells can be present anywhere on the peritoneal surface, the entire surface of the abdominal and pelvic cavity should be targeted. Substantial differences in the body composition of patients and differences in the HIPEC technique (open versus closed abdomen) will result in a wide variety of perfusate volumes. In current practice, the volume of the perfusate is chosen arbitrarily. In the equation for mass transfer over the peritoneal-plasma membrane (Equation 1), an increase in the solution contact area (A) will improve the mass transfer. For example in 10 patients dialyzed with different volumes ranging from 0.5 up to 3 liters, there is a linear rise in mass transfer (66). The importance of the volume of chemotherapy in determining systemic exposure to the drug has been discussed by Elias et al (67). In a clinical investigation (58) where 2-, 4- , and 6-liters of chemotherapy solution was administered with a constant dose of chemotherapy solution, a more dilute intraperitoneal chemotherapy concentration retarded the clearance of chemotherapy and resulted in less systemic toxicity. Therefore, it can be assumed that by the diffusion model, less concentrated chemotherapy would penetrate less into the cancer nodules and into normal tissues. These authors (58,66-67)consider both regulation of the chemotherapy dose and the volume of chemotherapy solution, by patient's body surface area, are necessary. A consistent drug dose and chemotherapy solution volume may be the optimal method for predicting maximal treatment in the abdomen with predictable bone marrow toxicity. However, Sugarbaker et al. (58) suggest variable volume is a dangerous practice with unpredictable systemic toxicities. If the chemotherapy solution is administered until the abdomen is full, the contact area will increase. If the contact area is variable, then the total absorption of drug cannot be predicted.

Timing of Cancer Chemotherapy in Relation to Timing of Surgical Intervention

In the clinical application of chemotherapy in PC patients, intervention can occur at four points in the timeline. First, **Induction Intraperitoneal and/or Intravenous Chemotherapy** is suggested as an option for reducing dissemination to the extra-abdominal space, testing the tumor biology and, for reducing the extent of small PC nodules and, theoretically this approach, called Neoadjuvant Intraperitoneal and Systemic chemotherapy (NIPS) (68), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy. Radiological and clinical responses with NIPS have been reported by several groups (68-70). However, although NIPS may reduce the tumor load to be addressed by CRS, it has several disadvantages. Adhesions from prior surgical interventions may interfere with adequate intraperitoneal drug distribution and, as complete responses are unusual, further cytoreduction-chemotherapy is necessary if the approach is to be curative. NIPS is reported to add to morbidity and mortality of further surgical treatment (71) and, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible to assess.

Intraoperative Intraperitoneal Chemotherapy is the most widely explored modality that has consistent clinically improved outcomes in many phase II trials and several phase III trials (23-38).

Early Postoperative Intraperitoneal Chemotherapy has some conceptual advantages. It is administered after cytoreductive surgery at the time of minimal residual tumor burden and, intraperitoneal treatments initiated before wound healing occurs can minimize non-uniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits. The proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell-cycle specific drugs such as 5-fluorouracil and the taxanes. Most EPIC regimens are administered postoperatively (day 1 to day 4/5) through both an inflow catheter and outflow drains inserted at the time of CRS and, can be applied with or without HIPEC (72).

Long-term Combined Intraperitoneal and Systemic Chemotherapy.

In phase III trials, Armstrong et al. (73), Markman et al. (74), and Alberts et al. (75) demonstrate that intravenous plus intraperitoneal chemotherapy improves survival in patients with optimally debulked stage III ovarian cancer, compared to intravenous chemotherapy alone. This approach may be used as 'chemotherapeutic bridging' between incomplete initial surgery and definitive cytoreduction or second look surgery. This type of chemotherapy is an adjuvant and not a perioperative use of chemotherapy. However, failure analysis for cytoreductive surgery plus perioperative chemotherapy indicates recurrent cancer occurs most frequently within the abdominal and pelvic cavity (76). Although systemic metastases occur, treatment failures rarely occur in liver, lungs or, other systemic sites. In order to optimize the treatment of patients with PC, the greatest benefit will probably result from a combination of the four treatment strategies.

Duration

A wide variation in the duration (ranging from 30-120 minutes) of intraperitoneal chemotherapy protocols are reported. The dose-response curves and their dependency on exposure time have been mathematically modeled by Gardner (77), and according to this model, a plateau in tumor cell kill will be reached, after which prolonged exposure time offers no further cytotoxic advantage. Theoretically, the most advantageous exposure time for cytotoxic effects in PC patients should be carefully weighed against systemic exposure and bone marrow toxicity and, the duration of perioperative chemotherapy regimens should be pharmacology-driven and not arbitrary.

Carrier Solution

The choice of carrier solution for delivering the cancer chemotherapy drug is not pharmacokinetically neutral. Hypotonic, isotonic and, hypertonic solutions have been tested (78-83) with both low and high molecular weight chemotherapy molecules. The ideal carrier solution should provide enhanced exposure of the peritoneal surface, prolonged high intraperitoneal volume, slow clearance from the peritoneal cavity, and, absence of adverse effects to peritoneal membranes (78). This is especially important for EPIC where maintenance of a high dwell volume of chemotherapy solution over a prolonged period improves both the distribution of the drug and effectiveness of the treatment (79). An isotonic high molecular weight dextrose solution prolongs the intraperitoneal retention of artificial ascites (80) and, *in vitro* and animal studies (81-82) suggest a pharmacokinetic advantage of hypotonic carrier solutions in an HIPEC setting. The pharmacokinetics of heated oxaliplatin with increasingly hypotonic carrier solutions in colorectal PC patients (83) indicates no differences in absorption and intratumoral oxaplatin, but there is a high incidence of unexplained postoperative bleeding (50%) and unusually severe thrombocytopenia in patients treated with hypotonic carrier solutions. The safety and efficacy of hypotonic carrier solutions need to be clarified before further clinical use can be recommended.

Pressure

Dedrick and Flessner (84) postulate the penetration distance of the chemotherapy solution is equal to the square root of the ratio of tissue diffusivity and the rate constant for drug removal from the tissue $(D/k)^{1/2}$. Unpublished observations by Flessner in a rat model (43) indicate a doubling of the extracellular space in the anterior abdominal wall of rats when the pressure of intra-abdominal peritoneal dialysis solution is raised from 0 to 4 cm H_2O, thus; an increased effective tissue diffusivity is proposed.
Reports from animal models confirm increased accumulation and anti-tumor effect of intraperitoneal cisplatin, oxaliplatin and, doxorubicin when abdominal pressure is increased (85-88). The useful application of increased intra-abdominal pressure is limited by respiratory and hemodynamic tolerance. Currently, the most useful clinical application is in palliating refractory malignant ascites in PC patients through laparoscopic HIPEC at 12-15 mm Hg (89-92). Esquivel et al. recently reported the feasibility of curative intent laparoscopic CRS and HIPEC in very selected cases (93).

Vasoactive agents

The effects of vasoactive substances in regulating peritoneal blood flow and tumor blood flow has been studied extensively (84,94-98). These agents may contribute to delayed clearance from the peritoneal cavity because the blood flow in the peritoneal and subperitoneal vascular network mainly controls the movement of molecules across the peritoneal and subperitoneal tissues. General statements regarding the effects of vasoactive agents are confusing and sometimes contradictory due to the variety of experimental systems, complex interactions of local-regional and systemic effects of vasopressive agents and, large differences between the neovasculature of tumor nodules and normal capillaries. Both the intravenous and the intraperitoneal administration of vasoactive molecules in combination with chemotherapeutic drugs have been explored (84,94-95). A preclinical study of the use of an intraperitoneal epinephrine plus intraperitoneal cisplatin in a rat model with PC (96) indicates a direct correlation between the intraperitoneal epinephrine concentration and cisplatin accumulation in rat peritoneal tumor nodules. In addition, the safe use of intraperitoneal epinephrine with intraperitoneal cisplatin in 18 patients with advanced PC has been demonstrated by Molucon-Chabrot et al (97), and tumor responses have been obtained in some patients resistant to intravenous platinum compounds. Concurrent intravenous administration of vasopressin can increase the pharmacokinetic advantage of intraperitoneal administered carboplatin and

etoposide but not 5-FU (98). Therefore, further studies on the use of vasoactive agents for improving cancer chemotherapy responses in PC are needed.

Macromolecular Vehicles

The increased interest in macromolecular vehicles and other modulations of chemotherapeutic agents as a means of exploiting the regional dose intensity has emerged has produced conflicting results. Despite their lower diffusivities, macromolecules may penetrate more deeply into the subperitoneal space than previously considered (99) and, the nature of capillary permeability is probably the major factor responsible for increased concentration in the subperitoneal space together with an increased role of convection . However, caution should be exercised when concluding this increased penetration into the subperitoneal space results in increased drug absorption into tumor nodules. The neovascularity of tumor nodules should not be assumed to have the same selectivity for macromolecules as normal capillaries have (100). A second obstacle to cancer chemotherapy penetration into tumor nodules is interstitial pressure in tumor nodules, as it is higher than in the surrounding tissue space (101). Thus, convection may reduce tumor penetration by macromolecules.

Pharmacodynamic Principles of Perioperative Chemotherapy

The efficacy of intraperitoneal cancer chemotherapy protocols is governed by both non-pharmacokinetic variables (tumor nodule size, density, vascularity, interstitial fluid pressure, binding, temperature) and pharmacokinetic variables.

Temperature

Adding hyperthermia to intraperitoneal chemotherapy may increase tumor response to cancer chemotherapy through several mechanisms. First, heat alone has a direct anti-tumor effect. Mild hyperthermia above 41°C induces selective cytotoxicity of malignant cells by several mechanisms: impaired DNA repair, protein denaturation and, inhibition of oxidative metabolism in the microenvironment of malignant cells. This leads to increased acidity, lysosomal activation and, increased apoptotic cell death (102-104). In this setting, thermal tolerance can be induced by up regulation of heat shock proteins (105), which may limit the importance of a direct anti-tumor effect of heat.

Second, applying mild hyperthermia augments the cytotoxic effects of some chemotherapeutic agents. Synergy between heat and cancer chemotherapy drugs may arise from multiple events such as heat damage to ABC transporters (drug accumulation), intra-cellular drug detoxification pathways and, to repair mechanisms of drug-induced DNA adducts (106). Such augmented effects are postulated for doxorubicin (107), platinum complexes (108,110), mitomycin C (109), melphalan (110) and, docetaxel, irinotecan and, gemcitabine (112).

Third, hyperthermia may increase the penetration depth of the cancer chemotherapy solution into tissues and tumor nodules. Jacquet et al. (112) report tissue penetration of doxorubicin is enhanced when the cancer chemotherapy solution is administered intraperitoneally at 43°C. In addition, hyperthermia does not affect the pharmacokinetic advantages of intraperitoneal doxorubicin with low plasma and distant tissue levels.

The elevated interstitial fluid pressure in tumor nodules, compared to normal tissue, is an acknowledged phenomenon (113). Furthermore, in experimental tumors with a single nodule, interstitial fluid pressure is relatively uniform in the nodule and drops precipitously in the periphery at the tumor-normal tissue interface (114). Furthermore, Leunig et al. (115) report a thermal dose-dependent decrease in interstitial fluid pressure in experimental solid tumors in an animal model after hyperthermia.

Tissue Distribution and Penetration Depth

A simplified two-compartment model describes transport over the peritoneal-plasma barrier; however, this does not provide an adequate theoretical model for penetration of chemotherapy administered intraoperatively (either intravenous or intraperitoneal) into the peritoneal wall and

into the tumor nodules. Dedrick and Flessner propose a mathematical model (**Figure 2**) addressing the tissue penetration of low-molecular weight molecules (84, 116).

The drug diffuses from its peritoneal concentration, C_p, to its blood concentration, C_B, along an exponential concentration gradient over the peritoneum and preperitoneal tissues. The extracellular 'deep' concentration, C_e, can then calculated according to Equation 2:

$$C_e = C_B + (C_p - C_B) \exp[- (k/D)^{1/2} x]$$

In Equation 2, k (min^{-1}) is the rate constant for the removal of the active drug from the tissue. Movement through the tissue is characterized by the diffusivity, D (cm^2/min), and the distance (x) from the serosal surface (cm). This model implies an exponential concentration decrease of the drug from the abdomino-pelvic cavity across the membrane to the plasma compartment. Consequently, the depth of penetration of an effective chemotherapy concentration is limited and in the order of 1 to 2 mm (117-118). In a rodent model, Ozols et al. (119) confirmed doxorubicin only penetrates 4-6 cell layers of a tumor on the diaphragm. Therefore, variable penetration for each drug and type of tumor is probable. This has important consequences for implementing perioperative chemotherapy in PC patients. Cytoreduction needs to eliminate all tumor deposits greater than 1-2 mm for subsequent intraperitoneal chemotherapy to be effective. Clinical data strongly supports this pharmacologic prediction: in univariate and multivariate analysis, complete cytoreduction (cancer nodules ≤ 2.5 mm) is the single most important prognostic factor.

PHARMACOLOGIC RATIONALE IN SUPPORT OF PERIOPERATIVE CHEMOTHERAPY IN PC PATIENTS

The last two decades reports with pharmacologic data supporting the use of perioperative cancer chemotherapy in PC from selected origin have been numerous.

Colorectal and appendiceal cancer

HIPEC

Most centers have been using Mitomycin C as their drug of choice when performing HIPEC in PC patients of colorectal and appendiceal origin. Mitomycin C is an anti-tumor antibiotic that is inactivated by microsomal enzymes in the liver and is metabolized in the spleen and kidneys. Mitomycin Cin doses ranging from 12.5 mg/m² to 35 mg/m² has been extensively studied in preclinical and clinical work and is widely used for peritoneal carcinomatosis (109,120-122). It is mostly widely applied as 90-minutes HIPEC at mild hyperthermia (41.5° C). In this setting the area under the curve ratio of peritoneal fluid concentration times time to the plasma concentration times time estimates the added chemotherapy exposure a small peritoneal cancer nodule receives as a result of an intraperitoneal route of administration. Our group and others found this ratio to be between 20 and 35 (63,65,123-125). **Figure 3** demonstrates that this pharmacokinetic advantage persists over the 90 minutes of intraperitoneal chemotherapy lavage. It continues because the tissue uptake, liver metabolism, and urine excretion of mitomycin C is always greater than drug clearance from the peritoneal space into the plasma. Our data (125) show that at the cessation of the 90 minutes of hyperthermic intraperitoneal mitomycin C treatment, 71% of the drug had left the peritoneal space. This means that 29% of the drug was discarded with the removal of the lavage fluid. This fluid represents a considerable environmental safety hazard and must be disposed of properly. Nine percent of the total drug

administered had been excreted in the urine and the urine of these patients should also be considered an environmental safety hazard. We calculated the plasma area under the curve for patients with a low, moderate or high urine output during the 90 minutes of heated intraperitoneal chemotherapy. The plasma area under the curve of mitomycin C was not

elevated with reduced urine output neither were they reduced by a very high urine output. These data suggest that volume of urine excreted has no impact on the amount of mitomycin C eliminated by the kidney. The largest proportion (62%) of the total drug administered remained in the body at 90 minutes. Jacquet et al. and Van Ruth et al. presented similar data (45,65). The location and chemical state of this large amount of retained mitomycin C remains to be

determined. It is possible that active drug remains in visceral surfaces, parietal peritoneum and preperitoneal tissues. Unfortunately, a reliable assay of tissue mitomycin C concentrations does not exist; determination of the anatomic site and anticancer activity of this large proportion of the total mitomycin C administered has not been determined.

We found 10 of our 145 patients to have an unusually small peritoneal space. By the hypothesis offered by Dedrick to predict intraperitoneal pharmacokinetics, the patients with a reduced total diffusion surface would show a reduced mitomycin C clearance from the peritoneal space. Also, a reduced plasma area under the curve was predicted. **Figure 4** presents data to show a reduced plasma area under the curve. These patients are at risk of under treatment and deserve careful follow-up to detect an early recurrence. In contrast patients who present with pseudomyxoma peritonei and a large volume of mucinous ascites will have an expanded peritoneal diffusion surface. As a result of the expanded diffusion surface a more rapid clearance of mitomycin C from the peritoneal space and a higher plasma area under the curve for mitomycin C is expected. Consequently a greater than usual likelihood of bone marrow toxicity occurs. The large variation in total diffusion area in peritoneal carcinomatosis patients poses a challenging problem toward a standardized dosimetry.

More recently oxaliplatin and irinotecan have been explored during HIPEC procedures in PC from colorectal and appendiceal origin (25,27,67,83,87). Oxaliplatin is a third generation platinum complex with AUC IP/IV ratios between 16 and 25. Since oxaliplatin can only be administered in dextrose 5% solution, severe hyperglycaemia and hyponatremia should be expected during the chemoperfusion (126). Irinotecan is a camptothecin analogue interacting with topoisomerase I-DNA complex and prevents resealing of single strand DNA breaks. The pharmacokinetic advantage of IP irinotecan was reported by Guichard et al. in a mouse colon carcinoma model (127). Thermal enhancement of irinotecan in murine fibrosarcoma model was demonstrated by Mohamed et al (111). Pharmacokinetic studies by Elias et al. suggest a beneficial pharmacologic profile at 42.5-43 °C during a 30 minutes HIPEC. The doses used vary between 360-460 mg/m² for oxaliplatin and 360-400 mg/m² for irinotecan.

BIC

The Dedrick-model for peritoneal transport predicts transport by diffusion from the peritoneal compartment through a peritoneal and preperitoneal tissue layer to the plasma and, *vice versa*. Through combining intraoperative intravenous and intraoperative intraperitoneal cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer containing the cancer nodules (**Figure 5**).

In 2002, Elias et al. (27) first reported the clinical use of intraoperative intravenous 5-fluorouracil and leucovorin in conjunction with oxaliplatin-based hyperthermic intraperitoneal perioperative chemotherapy. Most current protocols advocate Bidirectional (simultaneous intraperitoneal and intravenous chemotherapy) Intraoperative Chemohyperthermia (BIC). This two-component approach to PC treatment requires chemotherapy be used as a planned part of the surgical procedure and, proper timing is critical to the success of the chemotherapy in relation to the surgery. The innovation of a combined treatment of CRS plus perioperative intraperitoneal chemotherapy may be the paradigm shift responsible for the current successes in treating PC

patients, compared with previous failure. The bidirectional approach offers the possibility of optimizing cancer chemotherapy delivery to the target peritoneal tumor nodules.
Since their introduction in 1957 by Heidelberger et al. (128), the fluorinated pyrimidines have been successfully used for a wide variety of tumors and, are still an essential component of all successful gastrointestinal cancer chemotherapy regimens (129). This thymidylate synthase

inhibitor binds covalently with the enzyme and prevents the formation of thymidine monophosphate, the DNA nucleoside precursor. The 5-fluoro-uridine diphosphate and 5-fluoro-uridine triphosphate produced have a cytotoxic effect due to their incorporation into RNA. Intravenous 5-fluorouracil, alone or in combination with other cancer chemotherapy agents, has been the mainstay of adjuvant or palliative medical treatment for patients with gastrointestinal malignancies since the 1960s (130-135). We recently reported the pharmacology of 5-

fluorouracil during a BIC-protocol (136). 5-fluorouracil at 400 mg/m^2 was administered by drip infusion intravenously in 250 ml of 5% dextrose and water. The infusion was as rapid as possible through a peripheral vein with infusion time averaging 7.5 minutes. Simultaneously an intravenous administration of leucovorin at 20 mg/m^2 was administered through a separate intravenous line. Also, simultaneous with these intravenous infusions was an instillation of hyperthermic intraperitoneal chemotherapy solution with doxorubicin at 15 mg/m² combined with mitomycin C at 15 mg/m². The carrier solution for the intraperitoneal chemotherapy was 1.5% dextrose peritoneal dialysis solution and the temperature maintained within the abdomen was approximately 41.5ºC. The volume of chemotherapy solution was 1.5 L/m^2. 5-fluorouracil levels were obtained from blood and peritoneal fluid at 15-minute intervals for ninety minutes. **Figure 6** summarizes the pharmacology of 5-fluororuacil in this setting. 5-fluorouracil given intravenously had a definite pharmacologic advantage for local-regional application as it was rapidly circulated within the plasma through both the arterial and venous systems to equilibrate within the body tissues, including the large peritoneal and subperitoneal surfaces of both the abdomen and pelvis. The findings of this study indicate the large volume of peritoneal fluid became saturated by the 5-fluorouracil within approximately 20 minutes. Whereas this rapid distribution of the 5-fluorouracil affects all compartments similarly, metabolism is mainly restricted to the plasma compartment by the liver. The high levels of 5-fluorouracil persist within the peritoneal fluid because the drug can only leave the peritoneal space by back diffusion through the peritoneal and subperitoneal tissues: the enzyme dihydropyrimidine dehydrogenase is not present in the artificial ascites fluid. The marked difference in the rate of metabolism within the peritoneal fluid, rather than in the plasma compartment, in the absence of additional systemic 5-fluorouracil administration, caused the different peritoneal fluid and blood concentrations. Although 5-fluorouracil was administered as a normothermic intravenous solution, it penetrated into the heated tumor nodules. Normothermic administered 5-fluorouracil becomes subject to augmentation of mild hyperthermia of the subperitoneal compartment. Therefore, heat targeting was achieved by modulating the timing of intravenous chemotherapy. Before this study, the actual penetration of 5-fluorouracil into the subperitoneal space surrounding the abdomen and pelvis was unknown. The assumption was higher concentrations of 5-fluorouracil in the peritoneal fluid would result in greater local-regional effects, as suggested by previous experimental work by Mahteme et al. (137). However, the amount of 5-fluorouracil present in the tumor nodule is governed by both non-pharmacokinetic variables (tumor nodule size, nodule density, vascularity, interstitial fluid pressure, and, binding) and pharmacokinetic variables (dose, duration, route of administration, volume, carrier solution and, pressure). The data for the concentrations of 5-fluorouracil in tumor nodules support prior hypotheses and validate the tumor nodule as a new and improved pharmacologic endpoint for evaluating the effect of these treatment protocols for PC patients.

EPIC

EPIC has some conceptual advantages. It is administered after cytoreductive surgery at the time of minimal residual tumor burden and, intraperitoneal treatments initiated before wound healing occurs can minimize non-uniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits. Most EPIC regimens are administered postoperatively (day 1 to day 4/5) through both an inflow catheter and outflow drains inserted at the time of CRS. 5-fluorouracil has been extensively studied in colorectal pc patients as part of an EPIC-protocol. Although a small molecular weight molecule (130.08 Dalton), 5-fluorouracil is

characterized by a pronounced pharmacokinetic advantage when administered intraperitoneally as first reported by Speyer et al (138). Jacquet et al reported an AUC ratio >400 when studying pharmacokinetics of intraperitoneal 5-fluorouracil (139). **Figure 7** demonstrates the dose intensification associated with intraperitoneal 5-fluorouracil administration. These data confirme the exposure the peritoneal surface received from the intraperitoneal administration of 5-fluorouracil. Even though this small molecule moves rapidly out of the peritoneal fluid into the plasma, the rapid metabolism of the drug in the liver and at other sites in the body compartment

maintained a large AUC ratio of peritoneal fluid to plasma. In addition, the early postoperative period allowed the peritoneal surface tissuesto be repeatedly exposed to the drug, which increased the benefit of its cell-cycle specific activity. The peritoneal space remains free of an adhesive process for at least five days postoperatively, which results in excellent drug distribution over this prolonged period. Early perioperative intraperitoneal 5-fluorouracil remains a treatment option for carcinomatosis of colorectal and appendiceal origin.

GASTRIC CANCER

Perioperative cancer chemotherapy in patients with PC from gastric origin has been explored in several settings.

NIPS

First, Induction Intraperitoneal and/or Intravenous Chemotherapy is suggested as an option for reducing dissemination to the extra-abdominal space, testing the tumor biology and, for reducing the extent of small PC nodules and, theoretically this approach, called Neoadjuvant Intraperitoneal and Systemic chemotherapy (NIPS) (140), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy. This approach was explored by several Japanese groups. In the most cited chemotherapy regimen patients typically were treated with 60 mg/m^2 of oral S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) for 21 d, followed by a one week rest. On days 1, 8, and 15 after the start of oral S-1 administration, 30 mg/m^2 of Taxotere and 30 mg/m^2 of cisplatinum with 500 mL of saline were introduced through an intraperitoneal port. This regimen was repeated after a one week rest (141). Radiological and clinical responses with NIPS have been reported by several groups. However, although NIPS may reduce the tumor load to be addressed by CRS, it has several disadvantages. Adhesions from prior surgical interventions may interfere with adequate intraperitoneal drug distribution and, as complete responses are unusual, further cytoreduction-chemotherapy is necessary if the approach is to be curative. NIPS is reported to add to morbidity and mortality of further surgical treatment (142) and, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible to assess.

HIPEC

HIPEC in gastric cancer patients has been explored both in patients with biopsy proven PC and in patients with no visible PC but at increased risk of developing peritoneal surface malignancy due to positive cytology, tumor perforation, T4 status (143-150). The results have been mixed due to wide variety of inclusion criteria, extent of CRS, chemotherapy protocols. Adding to this mixed

results is the widely acknowledged fact that gastric cancer spreads not only by the transcoelomic route, but also via lymphatic and hematogenous dissemination.
PARAGRAAF YONEMURA

BIC

In an attempt to improve results; the concept of BIC was applied to PC from gastric cancer. Our group explored ifosfamide as the IV drug of choice for intraoperative use. Ifosfamide is a difficult

drug to study pharmacologically. Its anticancer effects only occur after the prodrug, ifosfamide, is metabolized in the liver and red blood cells by the cytochrome system to 4-hydroxyifosfamide. The active metabolite is unstable and only exists for a few minutes within the plasma or within the red blood cell. Its unique activity for use along with heated chemotherapy solutions comes from a remarkable augmentation of cytotoxicity by moderate heat. Urano et al. in a mouse foot-pad model demonstrate a tumor growth rate to decrease by one-third when ifosfamide was used at 41.5°C as opposed to room temperature (151). In our patients the initiation of the intraperitoneal chemotherapy treatments, the ifosfamide (1,300 mg/m^2) in one liter of normal saline was started as a continuous infusion at a constant rate over 90 minutes. Fifteen minutes prior to ifosfamide continuous infusion sodium-2-mercaptoethane sulfonate (Mesna) at 260 mg/m^2 was administered intravenously as a bolus in 100 ml of 0.9% sodium chloride. This was repeated at 4 and 8 hours.
Figure 8. demonstrates plasma, peritoneal fluid, and urine concentrations of ifosfamide and 4-hydroxyifosfamide over a 90-minute infusion and 60-minute period of observation.

OVARIAN CANCER

Epithelial ovarian cancer is a major cause of cancer death in postmenopausal women (152). Despite all efforts at early diagnosis of this malignancy, 70% of patients will present at an advanced stage with peritoneal dissemination of their disease. Although major advances have been made in recent years, a 5-year survival of 50% leaves plenty of room for improvement. The fact that epithelial ovarian cancer is relatively sensitive to anticancer drugs and that the disease remains confined to the abdominal compartment for most of its natural history, makes it a good candidate for intraperitoneal treatment (50). Intraperitoneal chemotherapy has been attempted at several points in the timeline of this disease.

Non heated intraperitoneal chemotherapy

Three randomized trials have shown a clear clinical benefit of adding intraperitoneal therapy to optimally debulked advanced ovarian cancer (73-75). All of them use cisplatin as the intraperitoneal component of the treatment regimen. Cisplatin (cis-diamminedichloroplatinum II) is a platinum salt with a MW of 300 Dalton. Most pharmacokinetic studies concern the use of IP cisplatin in a HIPEC setting. The influence of adding hyperthermia to IP cisplatin is still a matter of debate. Los et al. reported a increased intracellular platinum uptake in vitro and in vivo when adding hyperthermia to the intraperitoneal instillation of cisplatin (153). In contrast with these findings, Zeamari et al. did not observe a difference in tumor drug uptake when comparing normothermic administered IP cisplatin to IP cisplatin at mildly hyperthermic (40° C) temperatures (154). A high incidence of catheter-related complications, toxicity and the fact that a substantial part of the patients was not able to complete the IP regimen (58 % in GOG172) has resulted in a slow acceptance of this treatment modality in the scientific community.
The use of carboplatin as a less toxic and potentially more effective alternative is currently being explored (155,156). Carboplatin (1,1-cyclobutanedicarboxylate-platinum II) clears more slowly from the peritoneal cavity due to both its higher molecular weight and its higher hydrophilicity. This pharmacokinetic advantage, expressed as an AUC ratio of 8-16, is counterbalanced by the slower tissue and tumor penetration of carboplatin as demonstrated by Los et al (118).

HIPEC

Based on the above mentioned limitations of intraperitoneal chemotherapy outside of the operating room; new treatment approaches where explored.
Administering intraperitoneal chemotherapy in the operating room at the end of the cytoreductive surgery adds the benefit of hyperthermia to the chemotherapy toxicity. The hyperthermic augmentation of platinum analogues and doxorubicin has been repeatedly

confirmed in vitro and in vivo (107-109, 111-112). Additionally there are no postoperative fibrin deposits hindering the penetration of the chemotherapy in the tumor nodules.
More than 500 cases have been reported in literature (34-35). A single randomized control trial of cisplatin-based HIPEC after interval debulking in ovarian PC is currently going on at the Netherlands Cancer Institute.
The scientific community is divided on the appropriate timing of cytoreductive surgery and HIPEC in the treatment of patients with ovarian PC; upfront, interval debulking of consolidation surgery. Helm et al. in an analysis of their registry confirmed sensitivity to platinum response as an independent prognostic factor for patient survival (35). These findings suggest interval CRS and HIPEC or consolidation surgery to be more pharmacologically sound. In case of documented platinum resistance the intraperitoneal chemotherapy regimen used, can be adapted to include other drugs such doxorubicin, melphalan.

BIC

Our group recently explored the use of peroperative intravenous ifosfamide in addition to CRS and HIPEC. Ifosfamide may be an important drug for clinical trials that evaluate the possible benefits of heat-targeting of chemotherapy. It is one of four drugs that show true heat synergy, with 5 to 10 times the duration of tumor control with 41.5°C heat as compared to normal temperatures (151). The treatment strategy that has been employed in our studies is very similar to that published by Zylberberg and colleagues for ovarian cancer (70). His study showed excellent clinical results when systemic ifosfamide infusion was combined with intraperitoneal cisplatin. We modified his ifosfamide regimen using an infusion over 90 minutes in the operating room. Using this technology one must conclude that the cytotoxic effects of normothermic ifosfamide are maximized on heated peritoneal surfaces but the adverse effects of this heated chemotherapy agent at other sites within the body would not occur.

PERITONEAL MESOTHELIOMA

HIPEC

Malignant peritoneal mesothelioma is a rare progressive disease originating directly at the level of the peritoneal mesothelial lining. Asbestos exposure is considered to be the most prominent risk factor for the development of peritoneal mesothelioma (157). Systemic chemotherapy with cisplatin and pemetrexed results in a median survival of 13.1 months (158). Alternatively a recent phase II trial with systemic gemcitabine and pemetrexed in 20 patients demonstrated a median survival of 26.8 months (159). Both studies reported a significant toxicity. In the latter study 60 % of patients experienced grade III and grade IV neutropenia.
High toxicity of systemic chemotherapy and the fact that this disease is almost always confined to the peritoneal cavity provide a strong rationale for investigating intraperitoneal chemotherapy protocols. Combining CRS with HIPEC has resulted in improved survival in several treatment centers (31,33,160). Cisplatin, Mitomycin C and doxorubicin; alone or in combination have been widely used in this setting.

EPIC-BIC

Some centers add EPIC with paclitaxel to CRS and HIPEC resulting in a median survival of 79 months in 65 patients receiving all three treatments (161). We previously reported the advantageous pharmacokinetics of multi-targeted antifolate (MTA) in rat model (162). Subsequently IP Pemetrexed was explored in an EPIC-BIC protocol. Pemetrexed is a cell cycle specific antifolate active in the S phase of thee cell cycle. For cell cycle specific drugs a repetitive exposure is conceptually more advantageous. After optimal CRS and HIPEC eligible patients received IP Pemetrexed (500 mg/m²) in 1000 ml dextrose 1.5 % as a 60-minute rapid infusion combined with IV cisplatin (75 mg/m²). Figure 9 demonstrates the Pemetrexed pharmacokinetics

in this setting. Keeping in mind the substantial toxicity of combined intravenous cisplatin-pemetrexed; this bidirectional protocol using the same drugs resulted in a favorable tolerance.

RECURRENT PERITONEAL CARCINOMATOSIS

Despite major progress in improving survival in PC patients with these new locoregional treatment approaches; a substantial part of the patients will fail in the peritoneal cavity. In selected patients a new operative effort with CRS and HIPEC is an option. When tumor resistance to the primary HIPEC cancer chemotherapy drug is suspected; melphalan is our salvage drug of choice in most cases. Melphalan or phenylalanine mustard acts directly as an alkalans and has demonstrated a cytotoxicity against a wide range of malignancies. Additionally it shows a favorable heat augmentation. Figure 10 reports the melphalan pharmacokinetics in this setting (163). Melphalan was administered at 70 mg/m² over 90 minutes at 41-42° C.

CONCLUSIONS

Locoregional treatment approaches in patients with peritoneal surface malignancy have resulted in markedly improved clinical results in contrast with previous uniform failure. Now that the proof of concept has been delivered; further improvements should be pursued in additonal phase II-III trials and pharmacological guided changes in the treatment protocols.
Our pharmacokinetic and pharmacodynamic data provide a pharmacologic rationale for perioperative chemotherapy in peritoneal surface malignancy patients. Additionally they provide pharmacologic clues for improving these treatment protocols.

List of Reference available from the Author

TECHNIQUE FOR CYTO-REDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRAPERITONEALCHEMOTHERAPY (HIPEC)

Prof Marcello Deraco-Elena Gil Gomez, Dario Baratti and Shigeki Kusamura
[1] Department of Surgical Oncology, Ziekenhuis Oost-Limburg, Genk, Belgium
[2] Washington Cancer Institute, Washington Hospital Center, Washington, DC, USA

PERITONEAL MESOTHELIOMA

CRS originally described by Sugarbaker (*Sugarbaker PH. Ann Surg 1995;221:29*), with some minor technical variants emerged during a 15-year experience at our center. (*Deraco et al. J Surg Oncol. 2009;100:321*) Patients are put in a modified lithotomy position with gluteal folds advanced to the break in the operatory table to allow full access to the peritoneum. A three-way bladder catheter is inserted to for cold lavage during the hyperthermic phase, in order to avoid heat damage to the bladder wall. A large-bore naso-gastric tube is inserted. The abdomen is opened on the midline from xyphoid process to the pubis. A self retaining Thompson divaricator is used. Briefly, the goal of the surgical cytoreduction is to remove all the visible tumor by the following peritonectomy procedures and multivisceral resections:
1) right sub-diaphragmatic and parietal peritonectomy, with Glisson's capsule dissection;
2) left sub-diaphragmatic and parietal peritonectomy with splenectomy and greater omentectomy;
3) lesser omentectomy, stripping of the omental bursa and cholecystectomy;
4) pelvic peritonectomy, sigmoidectomy with hysterectomy and salpingo-oophorectomy;
5) right/total colectomy;
6) gastric antrectomy or total gastrectomy.
Depending on disease extent, implants on visceral surfaces could be alternatively removed by electrosurgical local dissection. A ball-tip electrosurgical hand piece will be used to dissect the tumor on peritoneal surfaces from normal tissue. The 2-mm ball-tip electrode will be used for dissecting on visceral surfaces, including stomach, small bowel, and colon. When more rapid tumor destruction is required, the 5-mm ball-tip is used.

HIPEC.After the surgical cytoreduction, two inflow catheters are inserted (one in the right subphrenic space and one deep in the pelvic cavity), as are two outflow catheters (one in the left subphrenic space and the second more superficially in the pelvic cavity). Six thermocouples are used to continuously monitor the inflow, outflow, and intraperitoneal cavity temperatures. Temporary abdominal skin closure follows with a tight continuous nylon stitch in the closed abdomen technique while open and semiclosed techniques are available. HIPEC will be performed with a drug association selected according to the primary tumour. Cisplatin, Mitomycin-C, Doxorubicin and Oxaliplatin are the most frequently used drugs. Drugs are administered once the hyperthermic phase has been reached with a mean temperature of 42.5°C. Duration depend of the drug association used and range between 30 to 90 minutes. Patients over 70 years of age or with relevant co-morbidities and those who had undergone previous systemic chemotherapy or extensive cytoreductive surgery received a 30% dose reduction of both drugs. Perfusate volume will be 4-6 L and mean flow 700 mL7min. At the Milan NCI, a extracorporeal circulation device Performer LRT® [RAND, Medolla (MO), I

taly] is used. Following the HIPEC, the perfusate is quickly drained and the abdomen closed after a careful intra-abdominal inspection.

RESULTS OF CRS AND HIPEC IN COLORECTAL PSM AND PSEUDOMYXOMA PERITONEI

Prof Kurt Van der Speeten, MD, PhD

[1] Department of Surgical Oncology, Ziekenhuis Oost-Limburg, Genk, Belgium

[2] Washington Cancer Institute, Washington Hospital Center, Washington, DC, USA

SURGICAL MANAGEMENT OF COLORECTAL HEPATIC METASTASES

About 50% of patients with colorectal cancer develop liver metastasis. 25% present with synchronous liver metastasis[1-3].

Two year survival is unusual in patients with untreated liver metastasis. Five year survival after resection of liver metastasis is 30% with some recent series reporting five year survival rates as high as 58[1,4]%.

Resectability rates have improved from about 10% to 20% [3]. This is attributed to multimodality treatment involving neoadjuvant chemotherapy, portal vein embolisation, two stage resections and local ablative therapies (mainly radiofrequency ablation and microwave ablation). There has also been a shift in the criteria of resectable disease.

Liver secondaries are considered resectable if it is possible to obtain a complete resection (R0) with a liver remnant consisting of at least two segments with preserved inflow, outflow and biliary drainage. The volume of the liver remnant should not be less than 20-30% of the total liver volume in a patient with a healthy liver. The presence of extrahepatic disease is not a contraindication to resection provided the extrahepatic disease is also resectable.

PREOPERATIVE EVALUATION

Meticulous staging to identify extrahepatic disease and anatomically define the lesion(s) in the liver parenchyma is essential. Biopsy is not necessary and is associated with worse outcomes because of the risk of tumour seeding.

CT is the most commonly used modality in these patients. New multi-detector CT scans have a per patient sensitivity of 74.8% and per lesion sensitivity 82.6%. CT does not identify sub-centimeter lesions[5].

Although not routinely used for initial staging of malignancy, MRI is the best modality for detection and characterisation of liver lesions. Overall sensitivity and specificity of contrast enhanced MRI for detection of liver lesions is 81.1% and 97.2% respectively[5].

FDG-PET is the most sensitive means of demonstrating extrahepatic disease. Limitations include sub centimeter disease, mucinous tumours and use after chemotherapy. It has been shown to identify extrahepatic disease in 17% of patients with apparently resectable disease. It may restage up to 28% of patients.

The chance of FDG-PET changing management increases with disease severity (stage of primary, number and size of liver lesions, synchronous disease and CEA level)[5-8].

CHEMOTHERAPY

70% of patients who undergo a hepatic resection for colorectal metastasis develop recurrent disease. The role of chemotherapy in patients with resectable metastasis is to decrease recurrence rates and improve survival. Perioperative chemotherapy has been shown to be effective. The timing of chemotherapy (pre or post liver resection) in patients with resectable disease remains controversial[9].

Chemotherapy can be used in patients with irresectable hepatic metastasis to convert the initially irresectable metastasis into resectable disease. This is termed conversion chemotherapy. Conversion rates of 30-40% are reported when biological agents (e.g. cetuximab, bevacizumab) are added to conventional chemotherapy[2].

PORTAL VEIN EMBOLISATION AND TWO-STAGE OPERATION

The main concern when performing extended resections is that the liver remnant is insufficient to prevent postoperative liver failure. This is a particular concern when the functional residual volume is expected to be less than 30%.

Portal vein embolisation is used before extensive resections to induce ipsilateral atrophy and contralateral hypertrophy to expand the number of patients who are able to undergo a curative resection. Agents commonly used for embolisation include Gelfoam (gelatin sponge particles), Lipiodol, cyanoacrylate and fibrin glue. The increase in volume is about 15% of the total liver volume and maximum regeneration occurs between three to nine weeks. There is some concern that tumours in the contralateral lobe may grow more rapidly after embolisation.

A two-stage hepatectomy strategy can be used in selective patients with multiple bilobar disease when a single stage hepatectomy is not possible. Tumour clearance of one hemiliver is achieved followed by embolisation of the contralateral side. 5-year survival rates of 42% have been reported after staged resection. The second resection can only be completed in 70% of patients and carries a significantly higher mortality (7%) and morbidity (59%) than a first hepatectomy[3,10-12].

TIMING OF LIVER RESECTION

Traditionally patients with synchronous hepatic metastasis have had the liver resection 12-16weeks after the resection of the primary. It has now been shown that synchronous resections can be safely performed.

When deciding on a synchronous resection the site and extent of the primary and hepatic disease as well as the patients overall condition need to be considered. A simultaneous resection is preferred when the resection of the primary and hepatic metastasis are simple procedures (e.g. a right hemicolectomy and a segment 2/3 resection). Synchronous resection would not normally be undertaken for a patient with a rectal cancer or in a patient who requires an extended hepatic resection.

ABLATIVE THERAPIES

Locally ablative therapies include cryotherapy, radiofrequency ablation (RFA) and microwave ablation. Ablative therapies offer significantly improved survival compared

with palliative chemotherapy alone with 5-year survival rates of 17-24%. Success rates are best with lesions smaller than 3cm.

Microwave offers several advantages over RFA including larger and more predictable ablation volumes, shorter ablation duration and the ability to perform multiple simultaneous ablations to increase ablation volume[13].

TECHNIQUE OF RESECTION

A bilateral subcostal incision provides good exposure. An upward extension towards the sternum (Mercedes-Benz incision) is sometimes necessary. A self-retaining retractor such as a Thomson's retractor or Omni-tract improves exposure.

The peritoneal cavity is inspected for evidence of extra-hepatic disease that would be a contraindication to resection. After full mobilization of the liver an intra-operative ultrasound is performed to detect additional lesions and confirm the hepatic vascular anatomy in relation to the metastatic disease. Intra-operative ultrasound modifies the planned approach in up to 50% of cases.

The Brisbane 2000 system of nomenclature of hepatic anatomy and resections is used to provide universal terminology for liver resections[14].

It is necessary for the central venous pressure to be maintained below 5mmHg. All major hepatic resections require control of the inflow vasculature and hepatic venous outflow from the part of the liver to be resected. This may be done extra-hepaticaly with dissection of the relevant portal pedicle and hepatic veins outside the liver alternatively intra-hepatic control can be achieved with major branches being secured within the liver after parenchymal transection.

Various methods can be used to transect the hepatic parenchyma. These range from basic finger or clamp-fracturing to more complex technology such as ultrasonic or radiofrequency energy, water-jet and tissue sealing devices, and surgical staplers. Small vessels (<2mm) can be divided with diathermy. Hepatic veins and larger branches of the hepatic sheaths are clipped or formally ligated and divided[15-18].

COMPLICATIONS

Despite improvements in surgical techniques and perioperative care major complications and death occur after hepatic resection. In a series of 173 liver resections of colorectal liver metastasis at Groote Schuur Hospital the perioperative mortality was 2.9%. The morbidity rate was 19%. Postoperative liver failure developed in 2.8% of patients. All of the patients who developed liver failure had extended resections. 5.8% of patients developed a bile leak, subphrenic or a perihepatic collection. 1 patient had to be returned to theater due to bleeding.

REFERENCES

1. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*. 2002;235(6):759-766.

2. Cai GX, Cai SJ. Multi-modality treatment of colorectal liver metastases. *World J Gastroenterol*. 2012;18(1):16-24.
3. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. *World J Gastroenterol*. 2011;17(36):4067-4075.
4. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol*. 2009;27(22):3677-3683.
5. Grand DJ, Beland M, Noto RB, Mayo-Smith W. Optimum imaging of colorectal metastases. *J Surg Oncol*. 2010;102(8):909-913.
6. Yang YY, Fleshman JW, Strasberg SM. Detection and management of extrahepatic colorectal cancer in patients with resectable liver metastases. *J Gastrointest Surg*. 2007;11(7):929-944.
7. Sacks A, Peller PJ, Surasi DS, Chatburn L, Mercier G, Subramaniam RM. Value of PET/CT in the management of liver metastases, part 1. *AJR Am J Roentgenol*. 2011;197(2):W256-9.
8. Bipat S, Niekel MC, Comans EF, et al. Imaging modalities for the staging of patients with colorectal cancer. *Neth J Med*. 2012;70(1):26-34.
9. Pawlik TM, Cosgrove D. The role of peri-operative chemotherapy for resectable colorectal liver metastasis: What does the evidence support? *J Gastrointest Surg*. 2011;15(3):410-415.
10. Abdalla EK. Portal vein embolization (prior to major hepatectomy) effects on regeneration, resectability, and outcome. *J Surg Oncol*. 2010;102(8):960-967.
11. Narita M, Oussoultzoglou E, Jaeck D, et al. Two-stage hepatectomy for multiple bilobar colorectal liver metastases. *Br J Surg*. 2011;98(10):1463-1475.
12. Narita M, Oussoultzoglou E, Ikai I, Bachellier P, Jaeck D. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg*. 2012;256(3):e7-e8.
13. Pathak S, Jones R, Tang JM, et al. Ablative therapies for colorectal liver metastases: A systematic review. *Colorectal Dis*. 2011;13(9):e252-65.
14. Strasberg SM. Nomenclature of hepatic anatomy and resections: A review of the brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12(5):351-355.
15. Parks RW, Garden OJ. Liver resection for cancer. *World J Gastroenterol*. 2001;7(6):766-771.
16. Heriot AG, Karanjia ND. A review of techniques for liver resection. *Ann R Coll Surg Engl*. 2002;84(6):371-380.
17. Aragon RJ, Solomon NL. Techniques of hepatic resection. *J Gastrointest Oncol*. 2012;3(1):28-40.
18. Lesurtel M, Selzner M, Petrowsky H, McCormack L, Clavien PA. How should transection of the liver be performed?: A prospective randomized study in 100 consecutive patients: Comparing four different transection strategies. *Ann Surg*. 2005;242(6):814-22, discussion 822-3.

Dr Lizette Schoeman-Internal Medicine, University of Pretoria

Quality of life measurement is important mainly because the patient has to be respected, recognized as an individual, and treated holistically. The concept is important in all forms of illness, as it is in health.[1]

In health care services, "quality of life" is the term used to describe a person's overall well-being, including their mental and physical health, ability to perform daily roles and sexual function, as well as an absence of symptoms such as pain and fatigue. Quality of life must thus take into account many aspects of life and importantly, can only be defined by the individual.[2] Quality of life is thus based on personal perception – simply put, quality of life measures the difference, or the gap, at a particular period of time between the hopes and expectations of the individual and that individual's present experiences. [1]

Because of the cultural and psychological overtones associated with cancer, and particularly advanced breast cancer, quality of life it is a useful model to use in the study of this topic. It is not only the toxicity and tolerability of the chosen treatment that may be of concern in patients with breast cancer; body image changes and sexual/psychosexual functioning are important concerns for many women, as well as concerns about their ability to carry out everyday tasks, the psychosocial impact of the treatment, cognitive problems (especially with chemotherapy), and the impact on social and role function.[3] While many women may choose treatments that maximize their survival, quality of life information can be an important determining factor in the decision-making process in others. For instance, if a woman is considering two treatments with equivalent survival for her stage cancer, such as mastectomy and breast conservation, then quality of life outcomes may be important considerations in her treatment decision-making.[4] Mastectomy patients compared to conserving surgery patients usually report a worse quality of life due to lower body image and sexual functioning. Likewise, in clinical trials of equivalent approaches, quality of life may be the identifying factor in determining the most "effective" treatment.[4] This might also be especially true in metastatic breast cancer, where the aim of treatment is not curative but rather supportive and palliative[4]

Almost all studies indicate that breast cancer patients receiving chemotherapy might experience several side-effects and symptoms that negatively affect their quality of life. Fatigue from treatment, especially in association with pain or other symptoms, can increase anxiety and depression, and as a result lower the quality of life.[5] Hormonal therapies were found to have similar negative impact on quality of life, although in general they were associated with improved survival. Poor sexual functioning may also have a negative effect on quality of life. [5]
Satisfaction with breast cancer treatment is however also a function of the process of care, and not just the actual treatment received.[5] The health care services thus has the potential to improve the quality of life of patients. Recognition and management of pain, emesis, fatigue, arm morbidity and postmenopausal symptoms are important issues in improving health-related quality of life. Interventions such as counselling, providing

social support and exercise could also improve quality of life.[7] Higher levels of communication, both physician and patient-initiated, affect women's perceptions of having a choice of treatment, while discussion with patients about the overall impact of treatment on their lives may facilitate a more informed decision-making process, and thus also enhance the quality of life.

Caring for the patients well-being and respecting them as autonomous beings by providing information and assisting them with realistic expectations regarding the outcome of treatments, and helping them to assume more responsibility for their own existence, seem to be contributing factors in the choice of treatment as well as the improvement of quality of life in patients with advanced breast cancer.

PROPHYLACTIC MASTECTOMY:
WHO, WHEN, HOW MUCH AND WHAT IS THE LONG-TERM OUTCOME
Dr Carol Benn-Department of Surgery, University of Witwatersrand (Wits)

Introduction

The decision to undergo a prophylactic (better called risk reduction) mastectomy is not based on any one decision. This procedure is usually accomplished today with an associated immediate reconstruction. Removal of so-called healthy breast tissue creates an intensive debate, amongst both clinicians and women themselves.
With the current recommendations that breast conservation and radiation be the gold standard for stage 1 and 2 breast carcinomas, and the understanding that most women will be alive and well at 5 and 10 years post breast cancer treatment, the concept of removing non cancerous breast tissue must be studied in detail, with a clear understanding as to the risks and benefits of the procedures offered

Definitions

The term prophylactic mastectomy is not accurate. Prophylaxis means to prevent, and although with the techniques used for mastectomies today, over 98% of breast tissue can be removed, this is still never 100%.
Therefore the correct terminology would be a risk-reducing mastectomy.
A clear understanding of the different types of risk reducing mastectomy procedures that can be offered, the amount of residual breast tissue left with each type of procedure and the resultant different rate of risk reduction.

Who

There are 2 types of risk reducing surgery

1. Women who wish to undergo bilateral skin sparing mastectomy, with usually immediate reconstruction
2. Women diagnosed with breast carcinoma who wish to undergo an opposite side mastectomy

Who is at high risk?
Risk models for predicting high-risk patients are many. Variable predictions and success result in confusion and clinical inability to decide what model to use and when.
Models are divided into empiric models or genetic risk models and are beyond the scope of this chapter (JNCI : Comparing Breast Cancer Risk Assessment Models; VOl012, issue 10

Familial "who's"
About 5 to 10% of breast carcinomas are thought to be hereditary, and can be inherited from either the mothers or fathers side of the family
About 20-30% of women with breast cancer have a family member with the disease.
Conversely 70-805 of women who get breast cancer do not have a family member with the disease
Family history of breast carcinoma in the following circumstances

1. Breast carcinoma in a first degree relative (doubles risk)
2. Especially mother or sister who is premenopausal
3. Having 2 first degree relatives increases the risk 5 fold
4. Family history of bilateral breast carcinomas
5. Father or brother with breast cancer
6. Known BRCA 1 and 2 mutation*

a. These are the most common inherited mutations.

b. BRCA mutations are more commonly found in Jewish women of Ashkenazi (Eastern Europe) descent, they are also found African American women, Afrikaner (Dutch descent), Scottish, Hispanic and can probably occur in any racial or ethnic group
c. BRCA 1 carries up to an 80% chance of developing breast cancer in the patients lifetime, with an increase risk in ovarian cancer as well
d. BRCA 2 has a similar breast cancer risk, as well as a higher risk of developing GIT, malignancies, melanoma and gynaecological malignancies

- The ability to test BRCA 1 and 2 mutations in certain population groups is difficult both from a genetic and financial implication in this country
- Ideally the index case should be tested
- A negative BRCA test in an index case does not exclude a genetic (inherited) breast carcinoma, but merely our inability to detect the causative gene or gene combination

e. ATM gene: this usually promotes damaged DNA repair, and the gene has been documented in certain families with breast cancer
f. CHEK2: This gene is seen in some women with a strong family history, and greatly increases risk when present as it has a twofold risk when mutated
g. Li-Fraumeni syndrome (P53): The p53 suppressor gene is associated with multiple types of cancers such as leukemia, sarcomas, brain tumours and breast carcinomas
h. Cowden's Syndrome (PTEN): This gene that regulates cell growth, causes increased risk for both benign and malignant breast tumours, as well as tumours of the digestive tract, uterus and ovaries
i.

Genetic testing can be done to look for certain mutations, testing may however not result in positive results even in women with significant family histories and the pros and con's should be discussed in details with patients

Pathological "who's"

The following pathological abnormalities predisposing to the development of breast cancer

1. Atypical ductal hyperplasia confers a risk of development of breast cancer that is 3.5. to 5 times that of the reference population. This category includes both atypical ductal hyperplasia and atypical lobular hyperplasia.
2. Lobular carcinoma in situ results in a relative risk for the subsequent development of invasive carcinoma among patient with lobular carcinoma in situ (LCIS) ranges from 6.9 – 12 times that expected in women without LCIS.
3. Sclerosing adenosis (5x)
4. Papillomatosis with and without atypia

Currently a new classification for risk lesions exists

Traditional terminology	Ductal Intraepithelial Neoplasia (DIN) Terminology
Usual Ductal Hyperplasia (UDH)	Usual Ductal Hyperplasia (**UDH**)
Flat epithelial atypia	Ductal Intraepithelial Neoplasia Grade 1a (**DIN 1a**)
Atypical Ductal Hyperplasia (ADH)	Ductal Intraepithelial Neoplasia Grade 1b (**DIN 1b**)
DCIS Low Grade (Grade 1)	Ductal Intraepithelial Neoplasia Grade 1c (**DIN 1c**)
DCIS Intermediate Grade (Grade 2)	Ductal Intraepithelial Neoplasia Grade 2 (**DIN 2**)
DCIS High Grade (Grade 3)	Ductal Intraepithelial Neoplasia Grade 3 (**DIN 3**)

(From FA Tavassoli & P Devilee, editors, Pathology & Genetics of Tumours of the Breast & Female Genital Organs, 2003, IARC Press, p. 64, Table 1.11.)

Family history and pathological risk factors increase the risk a further 10 fold

Radiological "who's"

Radiological density has been touted as an independent risk factor for the development of breast carcinoma. The extent of radio-graphically opaque areas on the mammogram are an important measure of the risk of developing breast cancer, with more than 50% of the breast considered dense, this constitutes one of the largest independent single risk factor in a population group attributing to breast cancer development. Although density decreases after menopause, risk is apparent for both premenopausal and postmenopausal women. Factors such as parity, weight and use of Hormone Replacement Therapy influence breast density, but the available evidence suggest that the impact of breast density is independent of other risk factors. Inability of radiologists to discern changes in breast tissue, may result in repeated core biopsies, and can contribute to a woman's decision to undergo risk-reducing surgery

Psychological "who's"
Significant psychological dynamics occur in women who elect to undergo risk-reducing surgery
All patients considering any risk reduction surgery should be seen by the unit psycho-oncologist
Factors that require assessment and may play a role in decision-making are as follows:

1. Women who have repeated core needle biopsies, and "difficult " to assess breast tissue may experience psychological stress when being called in for repeated biopsies or reassessments
2. Death of a family member or close friend from breast cancer
3. Patient anxiety and cancer fear
4. Special emphasis needs to be made about counseling regards decreased nipple areola sensation should nipple sparing mastectomies be performed
5. Assessing the patient's body image and personality typing prior to the procedure also ensures better patient satisfaction
6. Patients with Narcissistic type personalities are not good candidates for risk reducing surgery
7. The women should have a combined appointment with her partner to determine whether the decision is correct for this patient
8. The psychologist must recap the principles of this surgery, its impact on quality of life, its psychological, aesthetic, sexual, functional and pain repercussions should be addressed
9. It should not and must never be offered in an emergency situation.
10. Multi-disciplinary unit patient counseling involving discussions with other patients and discussions around the reconstruction should occur prior to patients undergoing the procedure.

Aesthetic "who's"
A small percentage of women, who still elect to go for a mastectomy and no reconstruction, may elect to undergo a bilateral mastectomy for symmetry, particularly if large breasted
Women undergoing opposite side risk reduction may make the decision based on wanting similar looking breasts (Barbie Doll breasts)

Patient contra-indications for immediate prosthetic reconstruction include women who are smokers; relative contra-indications are patients with conditions resulting in poor blood supply or tissue healing (diabetics, systemic lupus and other connective tissue diseases).
Women who are at higher risk for complications are advised to undergo expander reconstruction

Options for reconstruction also include autologous tissue reconstruction. The most described technique being the use of the DIEP flap, for bilateral risk reducing surgery
Other options include TRAM flap reconstruction for unilateral mastectomies,
Latissimus flap reconstruction can be used for bilateral reconstructions and the procedure is often done as an immediate delayed. Bilateral mastectomies on one day, and Lat flap reconstructions 48hours late

The appointment with the reconstructive surgeon is made looking at issues around long-term prostheses complications, prosthetic failure and whether the patient would make the same decision should no reconstruction be offered.

General "Who" principles

Prior to a patient consenting to a risk-reducing mastectomy, all other options should be discussed in detail with the patient stressing the following:

1. There is no such thing as an emergency mastectomy, in particular when faced with a decision around risk reduction (once the breast is in the bucket you cant return to sender)
2. Most breast carcinomas once spread to axillary lymph nodes are more likely to reoccur elsewhere in the body, than for a second primary to develop
3. The safety belt of good radiology, mammography, ultrasound, MRI and breast tomosynthesis, will detect 95% of all suspicious lesions
4. Certain medications are available for risk reduction (Chemoprophylaxis)

a. Patients on endocrine therapy for their breast carcinoma have a 50% risk reduction to the opposite breast with regards to developing second primaries
b. Tamoxifen has been well shown in the risk reducing setting to decrease breast carcinoma presentation by 50%
c. Aromatase inhibitors can also be used as risk reducing agents
d. Evista (Raloxifene) class SERM has also been used as an agent to decrease the onset of breast carcinomas in high risk individuals

5. Surgical prophylaxis (bilateral oophorectomy) has been shown to decrease the development of breast carcinoma. The long-term side effects of early menopause with regards to bone and cardiac health must be discussed in detail with patient

What the literature says

1. The Prose Study Group, Rebbeck et al measured the incidence of breast cancer in 483 BRCA1/2 mutation carriers. The data indicated that bilateral prophylactic mastectomy reduces the risk of breast cancer by approximately 90 %.
2. Hartman et al evaluated the efficacy of bilateral prophylactic mastectomy in a retrospective cohort analysis of 639 moderate- to high-risk women who had bilateral prophylactic mastectomy at the Mayo Clinic between 1960-1993. The median length of follow up was 14 years. Initially the BRCA status was not taken into account and later 18 women were found to be mutation carriers. A control study of the sisters of the high risk patients identified and the Gail model were used to predict the number of breast cancers expected in these two groups in the absence of prophylactic surgery. The study found that women at a high risk of breast cancer on the basis of a family history of breast cancer prophylactic mastectomy reduces the incidence of mortality from breast cancer by 90% (reduction in risk, 89.5% ; $P < 0.001$). Thus there is a statistically significant reduction in the incidence of breast cancer and of death from breast cancer after prophylactic mastectomy, as compared with the expected incidence in women with a family history who did not undergo the procedure.
3. Another study of BRCA1/2 mutation carriers by Meijers-Heijboer et al compared breast cancers post bilateral prophylactic mastectomy in 76 BRCA1/2 mutation carriers after 2.9 years of follow up, to 63 mutation carriers who did not undergo bilateral prophylactic mastectomy ($P = 0.003$). No cases of breast cancer were diagnosed after bilateral prophylactic mastectomy compared with eight diagnosed breast cancers after 3 years of follow-up in women who did not have the surgery. The study suggested a significant risk reduction in mutation carriers but an accurate estimate of the magnitude of the risk reduction could not be determined.

4. CG41NICE Guidelines are a useful reading tool
5. NCCN guidelines state:

   "In the updated NCCN Guidelines, it states that prophylactic mastectomy (the removal of a noncancerous breast) contralateral to a known unilateral breast cancer is not recommended except as outlined in the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian and the NCCN Guidelines for Breast Cancer Risk Reduction. When prophylactic mastectomy is being considered, the NCCN Guidelines note that the small benefits must be balanced with the risk of recurrent disease from the known breast cancer, the psychological and social issues associated with bilateral mastectomy, and the overall risks of contralateral mastectomy.

   The practice of removing noncancerous breasts to reduce the risk or prevent cancer has become increasingly common among women. A study recently published in the journal Cancer found that among women who had cancer in one breast, the number who opted to have the other breast removed, more than doubled from 1995 through 2005 in New York state. However, there is no data to demonstrate that having prophylactic mastectomy actually improves survival."

When

The decision to undergo a risk reducing mastectomy at the time of opposite side breast cancer management is difficult particularly when a women is at her most vulnerable (post diagnosis)
Careful consideration to this decision should be made by the patient and her family and not by the treating physician
Multi-disciplinary unit guidance, however is advisable, as well as repeated appointments with the onco-psychologist in the unit
Should the women not be sure of this decision, it is always advisable to delay the decision and surgery on the other breast

A study from our unit looking at risk of disease in the opposite breast in women with a unilateral breast carcinoma who elected to undergo an opposite side risk reduction showed the following results.

Over the 10-year study period 412 patients underwent bilateral mastectomy following an initial diagnosis of unilateral breast cancer. Records were identified relating to 382 patients (30 excluded due to lack of data). A further 24 had a contralateral cancer (n=10), high-risk lesion (n=6) or recurrent cancer (n=8) diagnosed prior to definitive surgery, and were also excluded. The remaining 358 patients had a unilateral invasive breast cancer or DCIS excised through mastectomy with a contralateral prophylactic mastectomy.

It may be feasible to assume that a percentage of these patients would develop breast cancer should they had not chosen to undergo risk reducing surgery

In terms of decisions around bilateral risk reduction, there are no rules
Guidelines are as follows:

1. Age of earliest diagnosed familial breast cancer may play a role in decision making
2. Post completion of family
3. Sudden life changing events, death of a family member and or close friend from breast cancer
4. Advice from radiologist
5. Repeated core biopsies
6. Diagnosis of a high risk lesion

How Much

The premises when it comes to risk reduction is clearly more is better than less,
Original studies on risk reduction surgery were based on subcutaneous mastectomies and this resulted in a substantial proportion of breast tissue being left including the nipple areolar complex
Over time with the development of skin sparing mastectomy techniques, less and less breast tissue is left

The current item up for debate is the concept of nipple sparing mastectomies.

The nipple areolar complex is regarded as the signature of the breast or likened to the tip of a nose and has significant aesthetic impact and has both sexual and psychological importance due mainly to its nerve sensation (erectile ability, erogenous sensation).
Emotive reasons for nipple sparing mastectomies may negatively influence the ability to accurately assess the procedure.
The current gold standard when required to do a mastectomy and reconstruction, is a skin sparing mastectomy and immediate prosthesis or expander prosthesis reconstruction. This traditionally includes removal of the nipple areolar complex and to ensure clear surgical margins.

Looking at retrospective studies on patients undergoing SSM for invasive cancer or DCIS, the nipple is affected by tumour cells in 5%-10% of cases.
It is for this reason that the concept of nipple sparing mastectomies has been proposed.

There has been much controversy regarding the oncologic safety of NSM as well as the introduction of a set of complications, such as nipple and areolar necrosis, that were not a concern previously with total mastectomy.

Complicating these issues is the data analysis; the lack of randomized control trials, no long term follow-up, and small isolated centre based retrospective audits.

Looking at nipple sparing mastectomies in the risk reduction setting is critical as prophylactic mastectomy has been the subject of major publications by many international groups. Its oncology benefit is undisputed in patients with a genetic mutation, and often questioned in other patients undergoing the procedure

Immediate bilateral breast reconstruction by expander or definitive implant with skin flap preservation and retention of the nipple-areolar complex may constitute a positive radical issue for requesting and motivating patients at high genetic risk, managed by a multidisciplinary team to undergo this procedure.
The incidence of cancer in the retained nipple after risk-reducing mastectomy is documented at less than 1 per cent.

Technical problems with the procedure may be avoided by careful patient selection.
Reconstructive difficulties occur more frequently in patients who have large breasts or very ptotic breasts, and may require the use of mastopexy type skin sparing mastectomies. The nipple blood supply in these settings is often further compromised. Clearly the most significant concern is nipple viability followed by flap necrosis.
As with any procedure attention to careful patient selection and technical capability of the surgeon plays a role as well as understanding the learning curve associated with the procedure.
The lowest recurrence rates are seen in multi-disciplinary units that use intra-operative pathology after coring out the nipple to assess that the tissue is free of malignant or atypical cells

Complications occurring are:

1. Partial necrosis of the nipple with residual depigmentation.
2. Sloughing of the nipple areola complex
3. Infection

After dissection of all the breast tissue, the skin envelope with the areola is turned inside out and all milk ducts and any tissue beneath the areola are precisely dissected under the surgeon's visual control. Intra-operative pathological assessment of this retroareolar tissue next to the skin is performed using both imprint cytology and histology to decide whether the NA-skin can be preserved or not

Incisions vary from centre to centre with areola crossing, and radial incisions being the most commonly used. Circumareolar/nipple-areola free graft, inframammary and crescentic mastopexy may also be used.

Immediate reconstruction can be performed with tissue expander placement or one stage implant latissimus dorsi muscle, transverse rectus abdominis muscle, or deep inferior epigastric perforator muscle flaps

Long term outcome

Recurrence risk

Clearly in patients undergoing risk reducing surgery with diverse indications such as confirmed BRCA 1 and 2, strong family history of breast cancer, atypical ductal hyperplasia , lobular carcinoma in situ and other risk lesions have extremely low recurrence rates irrespective of whichever technique is used. The reason for this is that the actual incidence of these patients developing breast cancer post mastectomy cannot be accurately quantified

Aesthetic Outcome

Studies looking at patient satisfaction with objective observer assessments are few. Important aspects to assess are appearance, symmetry, colour, position, and breast texture as well as nipple sensation and arousal. Most studies are small, and most patients are satisfied with the appearance, symmetry, colour, position of the nipple and the breast texture. However there is lower satisfaction amongst all patients with nipple sensation, most patients rating this as poor. Long term aesthetic outcome varies from study to study and is based on a multitude of factors, from patient related (e.g. weight gain and habits)

Psychological Outcome

Most patients, who have undergone the procedure, if they have been properly counselled, do not regret the decision at all

Studies are few

Conclusion

Risk reducing mastectomy is an important procedure that can and should be discussed with women who consider themselves to be of high risk.

It should only be offered in multi-disciplinary units, after careful consideration is given to all the cons of the procedure and should never be offered as an emergency.

Opposite side risk reduction mastectomy, although on the increase should be entirely a patient based decision, after extensive counselling, as the risk of contralateral disease is low

PROPHYLACTIC OESOPHAGECTOMY: WHO, WHEN HOW MUCH AND WHAT IS THE LONG-TERM OUTCOME

Prof Taole Mokoena-Department of Surgery, University of Pretoria

Cancer of the oesophagus is a deadly disease. By the time patients are symptomatic the disease is already advanced and curative management becomes but an illusion. Median survival of patients with symptomatic carcinoma oesophagus (CO) who have been treated with curative intent has been estimated around 18 months. Therefore if such dismal results are to be improved upon, C.O. should be diagnosed early. Early diagnosis demands screening of populations at risk of developing CO.

There are two distinct types of C.O., squamous cell carcinoma and adenocarcinoma, each with a distinct risk profile. Squamous cell carcinoma oesophagus (SCCO) is endemic in certain regions of the world which includes the eastern seaboard of Africa with its epicentre the Eastern Cape. It is also prevalent in countries around the Caspian Sea whose epicentre is Iran. South West China and Japan are also high prevalence regions. SCCO is also a significant cause of cancer death in Western countries but its incidence is stable. Adenocarcinoma of the oesophagus (ADCO) on the other hand is more prevalent in the West and its incidence is rising to epidemic proportions.[1]

The risk factors for SCCO are primarily smoking, alcohol, micronutrient deficiencies, nitrosamines, mycotoxins and possibly *Human Papilloma Virus*. New evidence suggests that atrophic gastritis especially associated with *Helicobacter pylori* infection of the gastric fundus is associated with high incidence of SCCO.[22]

The risk factors are very common in all vulnerable populations which would require screening of all adult populations, a feat not feasible in all target countries who are poor and developing except Japan. Targeted screening could be directed to patients with previous caustic oesophageal burns or achalasia but the yield would be very low. Since there are no prodromal signs or precancerous lesions for SCCO, such screening can only hope to detect early but cancerous lesions whose treatment would be therapeutic and not just prophylaxis. The only truly prophylactic treatment for SCCO could be oesophagectomy in patients with palmar-plantar hyperkeratosis (tylosis)which carries a life time risk of more than 95%. [2]

In contrast,the "new" ADCO epidemic is associated with Barrett's oesophagus which in turn results from gastro-oesophageal reflux disease (GORD) with a life time risk upto than 25%.The target population is relatively affluent males. Screening could be targeted at affluent males (especially white) with GORD and those with Barrett's disease should be offered more intense investigation to further detect those with Barrett's dysplasia which is precancerous.[1,3,4.5] However there should be a caveat, that many patients with Barrett's oesophagus are symptom-free and thus would not present *ab initio*.

There are a number of strategies to address Barrett's columnar metaplastic oesophagus with the aim of arresting or preventing progression to dysplasia and ADCO. Although intestinal type metaplasia is thought to present the highest risk for dysplasic change , some studies have shown all columnar metaplasia to be of equal risk. [6,7]

(I) Medical Prophylaxis

a. Life-long use of acid secretion suppression with proton pump inhibitors (PPIs) or histamine receptor type 2 antagonists(H_2 RA). There are no

randomised controlled trials (RCT) which showed reduced incidence of ADCO in the target group. [4]

b. Selective COX-2 inhibitor did not perform better than placebo. [4]
c. Other pharmacologic treatments e.g. statins show less Barrett's ADCO in chronic users.[8]

(II) Nonsurgical Endoscopic Prophylaxis[3]

a. Nd-YAG laser photocoagulation
b. Argon plasma coagulation
c. Multipolar electrocautery
d. Photodynamic therapy
e. Radiofrequency ablation
f. Cryotherapeautic ablation

None showed prevention of ADCO whileradiofrequency ablation was promising but not statistically better than sham treatment control.[20]

(III) Surgical Prophylaxis

Antireflux surgical procedures, principally Nissen fundoplication reduced progression of Barrett's intestinal metaplasia to dysplasia but not development of ADCO.[9]

The Economics of Surveillance for Barrett's Oesophagus

The risk of ADCO from Barrett's oesophagus is variously put between 68% and 86%. Furthermore the risk of developing ADCO from Barrett's high grade dysplasia is 50-66%. this implies that Barrett's oesophagus patients warrant surveillance in order detect high grade dysplasia and treat it. The economics of such screening programme although substantial for the health system, compares favourably with screening for breast cancer.[10,11,12] Patients who underwent surveillance had an 80% 5-year survival compared to less than 20% for non-surveillance group.[10]

Treatment of Barretts's Dysplasia[1,3,5,13]

Barrett's dysplasia is precancerous. The aim of its treatment is to extirpate it in order to prevent progression to ADCO.The problem is that it is difficult in a given patient to determine or exclude a focus that is already invasive or cancerous.For this reason total extirpation of high grade dysplastic mucosa is advocated. Since some areas might be invasive already, histologic examination of the removed mucosa is mandatory because even early invasive carcinoma may be accompanied by lymph node metastasis which require management on their own merits.

Controversy remains on the management of low grade dysplasia but most would merely submit such patients to surveillance although one study recommends resection.[21]

Classification of Early Oesophageal Cancer[14]

Early invasive cancer of the oesophagus is classified in relation of its invasion of the oesophageal wall. Tis is high grade dysplasia or carcinoma–in–situ, T1 is carcinoma limited to the sub-mucosa while T2 is onto the muscularis propria, T3 is through the adventitia and T4 into adjacent organs.
Tis and T1 can further be stratified into m1 = epithelial cancer, m2 = mucosal cancer invading into lamina propria, m3 = mucosal cancer invading muscularis mucosa and sm =submucosal cancer. Once the lesion is beyond the basement membrane, submucosa

lymphatic invasion and lymph node metastasis may found. Lymph node metastases may be found away from the local site of the primary lesion. [15,16]
This biologic behaviour of oesophageal cancer makes mucosal extirpation by any means that destroys the mucosal lesion undesirable for one cannot determine the depth of cancer invasion and therefore plan for appropriate further treatment such as formal oesophagectomy and lymph node dissection as necessary.

Options for Surgical Extirpation of Barrett's Dysplasia
Non-surgical modalities of extirpation of Barrett's dysplasia do not avail tissue for histological examination and thus should be used with great circumspection.

Endoscopic Mucosal Resection (EMR)[17,18]
EMR is a less invasive mode of extirpating Barrett's dysplasia and avails specimen for histological examination. There are number of techniques and strategies to achieve EMR including stepwise suction-ligation or injection-resection. EMR is associated with low mortality and few complications e.g. perforation or post-op strictures

Formal Oesophagectomy[19]
There are many options to achieve oesophagectomy. The standard would be through two stage Ivor-Lewis thoracotomy and laparotomy resection . Transhiatal oesophagectomy and segmental oesophagectomy with jejunal interpositions are other options. Minimally invasive oesophagectomy through thoracoscopic and/ or laparoscopic approaches are feasible. The key determinant is dissection of lymph nodes one region proximal and one level distal to the primary lesion.
Operative mortality in expert hands in dysplasia patient should be below 1%.
A proportion of patients deemed pre-op to have Tis are found to have T1 lesions and lymph node metastasis. Presence of lymphatic spread adversely affects longterm prognosis.

Conclusion
Prophylaxis for prevention of invasive adenocarcinoma of the oesophagus from Barrett's oesophagus requires extirpation of high grade dysplastic oesophageal mucosa. While many techniques have been applied for this purpose many destroy the mucosa which is thus not available for further histological examination. The latter is important for determining whether the mucosal dysplasia has areas of invasive carcinoma and whether the basement membrane has been breached. When the basement membrane has been breached, oesophagectomy is mandatory. The least invasive method of achieving dysplastic mucosa extirpation while availing specimen for further histological examination is endoscopic mucosectomy when expertise is available, otherwise patients should be submitted for oesophagectomy *ab initio*.

Recommended Reading

1. Enzinger PC, Mayer RJ. Esophageal Cancer. N Engl J Med 2003; 349: 2241-52
2. Marger RS, Marger D. Carcinoma of the Esophagus and Tylosis: Lethal Genetic Combination. Cancer 1993; 72:17-1
3. Green S, Tawil A, Barr H *et al*. Surgery versus radical endotherapies for early cancer and high grade dysplasia in Barrett's oesophagus (Review). Cochrane Review. The Cochrane Library 2009; Issue 2: 1-22

4. Rees JRE, Lao-Sirieix P, Wong A, Fitzgerald RC. Treatment for Barrett's Oesophagus (Review) Cochrane Review. The Cochrane Library 2011, Issue 7:1-31
5. Buttar NS, Wang KK, Sebo TJ *et al.* Extent of High-Grade Dyplasia in Barrett's Esophagus Correlates with Risk of Adenocarcinoma. Gastroenterology 2001; 120:1630-1639
6. Kelty CJ, Gough MD, Van Wyk G *et al*. Barrett's oesophagus: Intesinal metaplasia is not essential for cancer risk. Scand J Gastroeterol 2007;42:1271-1274
7. Liu W, Hahn H, Odze RD, Goyal RK. Metaplastic Esophageal Columanr Epithelium Without Goblet Cells Show DNA Content Abnormalities Similar to Goblet Cell-Containing Epithelium. Am J Gastroenterol 2009;104:816-824
8. Nguyen DM, Richardson P, El-Serag HB. Medication (NSAIDs, Statins, Proton Pump Inhibitors) and Risk of Esophageal Adenocarcinoma in Patients with Barrett's Esophagus. Gastroenterology 2010;138:2260-2266
9. Kanttu TME, Rantanen TK, Schvoei et al. Esophageal Adenocarcinoma Arising after Antireflux Surgery: a population-based analysis. Eur J Cardio-thorac Surg 2011; 40:1450-1454
10. Van Sandick JW, van Lanschot JJB, Kuiken BW *et al*. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. GUT 1998; 43:216-222
11. Wright TA, Gray MR, Morris AI et al. Cost effectivenessof detecting Barrett's Cancer. Gut 1996; 39: 574-579
12. Yousef F, Cardwell C, Cantwell MM et at. The Incidence of Esophageal Cancer and High-Grade Dysplasia in Barrett's Esophagus: A Systematic Review and Meta-Analysis. Am J Epidemiol 2008; 168: 237-249
13. Chennat J, Waxman I . Endoscopic treatment of Barrett's esophagus from metaplasia to intramucosal carcinoma. World J Gastroenterol 2010; 16:3780-3785
14. Kuwano H, Masuda N, Kato H, Sugimachi K. The subepithelial extension of esophageal carcinoma for determining the resection margin during esophagectomy: A serial histopathologic investigation. Surgery 2002; 131: 514-21
15. Natsugoe S, Aikou T, Yoshinaka H et al. Lymph Node Metastasis of Ealry Stage Carcinoma of the Esophagus and of the Stomach J Clin Gastroenterol 1995; 20:325-328
16. Rice TW. Superficail oesophageal carcinoma: Is there a need for three-field lymphadenectomy. Lancet 1999; 354: 792-794
17. Pech O, May A, Rabenstein T, Ell C. Endoscopic resection of early oesophageal cancer. Gut 2007; 56:1625-1634
18. Peters FP, Kara MA, Rosmolen WD *et al*. Stepwise Radical Endoscopic Resection Is Effective for Complete Removal of Barrett's Esophagus with Early Neoplasia: A prospective study. Am J Gastroenterol 2006; 101: 1449-1457
19. Headrick JR, Nichols FC III, Miller DL et al. High-Grade Esophageal Dysplasia: Long-Tem Survival and Quality of Life After Esophagectomy. Ann Thorac Surg 2002; 73: 1697-1703
20. Falk GW. Radiofrequency Ablation of Barrett's Esophagus: Let's Not Get Ahead of Ourselves. Dig Dis Sci. 2010; 55: 1811-1814
21. Romagnoli R, Collard J-M, Gutschow C et al. Outcomes of Dysplasia Arising in Barrett's Esophagus: A Dynamic View. J Am Coll Surg 2003; 197: 365-371

22. Cook MB. Non—Acid Reflux: The missing Link Between Gastric Atrophy and Esophageal Squamous Cell Carcinoma? Am J Gastroenterol 2011; 106:1930-1932

PROPHYLACTIC OESOPHAGECTOMY: WHO, WHEN HOW MUCH AND WHAT IS THE LONG-TERM OUTCOME
Prof Heine van der Walt

ROLE OF SURGERY IN MANAGEMENT OF HEPATIC METASTASIS FROM NEUROENDOCRINE TUMOURS (NET'S)

Prof Martin Smith,-Department of Surgery, University of Witwatersrand (Wits)

Neuroendocrine tumours are a heterogeneous group of tumours with common distinct morphological and biological characteristics. They are defined as either functional or non-functional tumours depending on the production of amines with a clinical expression. They are a rare group of tumours making individual experience difficult. In addition they are generally well differentiated tumours with an indolent biological behaviour and relatively long term survival making investigation into their behaviour and the consequences of interventions aimed at tumour regression very difficult to interpret. It is now understood that NETs arising in different areas of the body have different behaviour. Epidemiological data suggests a raising prevalence of Nets world-wide. This, together with an increased awareness and improved diagnostic modalities make this a more common tumour in our practice in South Africa.

Markers of prognosis such as the mitotic index, Ki67 and tumour differentiation have allowed better staging of the tumour allowing for a grading system that is well accepted. This grading system facilitates treatment choices.

In general about 12% of patients present with metastatic disease. The liver is the most common site of metastatic disease (besides regional lymph nodes). About 75% of patients with small bowel Nets and between 30 -85% of pancreas Nets present with or develop liver metastasis (LM's). A small group of patients (5-10%)present with LM of unknown primary.

LM's are the most powerful predictor of survival regardless of the primary site. This is clearly reflected in the survival data and also applies to the functional and non-functional tumours. The 5 year survival in patients with untreated LM is 13 -54% compared to 75 -99% in those free of LM's.

The diagnosis of Net's and LM relies on morphological and biochemical parameters. While the role of chromogranin A (CgA) has improved follow up of these patients , its role in diagnosis is less clear. It does however appear to be higher in patients with LM. In functional Net's the urinary 5-HIAA is of value. There are a number of non-specific peptides that may play a role in the diagnosis but will not be discussed further.

Somatostatin receptor scintingraphy (SRS) is the gold-standard imaging procedure for Net's and has evolved over the years due to the identification of more somatostatin receptors and today the development of both DOTATOC and DOTANOC have allowed for PET scanning in the diagnosis and evaluation of these patients. Both CT and MRI are the standard cross sectional imaging modalities with sensitivities of 94-100% reported when combined with PET scanning.

The optimal treatment of LM is still poorly defined. There have been numerous reviews of this aspect of the treatment of Net's but in the absence of adequate trials comparing treatment modalities in homogenous groups of patients, no optimal therapeutic strategies exist. A number of guidelines have addressed this topic but even a Cochrane review has failed to reach firm conclusions. There is however a significant body of evidence addressing the management of LM using a range of modalities.

The crucial issue is to identify patients for surgery with a curative intent. In this regard the following prerequisites have been suggested for consideration

1. Well differentiated Net
2. Reasonable performance status
3. Exclusion of non-resectable extra hepatic disease

4. Possibility of R0 resection with >30% functional liver reserve
5. Absence of advanced carcinoid heart disease with high CVP pressures and the resultant increase bleeding during liver surgery
6. Acceptable morbidity and mortality of the planned procedure. (<15% and 1-1.5% respectively)

Ideally the primary should have been resected before liver surgery but this can be performed synchronously. This does not exclude surgery in patients with unknown primaries from liver surgery but a close follow-up is then required. The final outcome of the patient will be determined by the primary and therefore even if there are unresectable LM's resection of the primary if feasible is recommended. There is evidence to suggest that this approach slows down the rate of progression of the disease in these patients.

The usual expertise in liver surgery and the adequate radiological support is required before embarking on this type of surgery. This implies that a range of techniques and combination of techniques should be available including portal vein embolization to increase the size of the future liver remnant and ablation techniques or the expertise to perform sequential resections to achieve tumour clearance.

Some of the difficulty in evaluating the outcome after liver surgery is due to the poor definition of the completeness of resection. However there is common consent that radical surgery that clears the primary tumour and the LM's may prolong survival and offer symptom control in patients with resectable Net's. In addition, unless in specific situations liver resection should not be attempted unless complete tumour removal is possible. In symptomatic functional tumours, when all other modalities have failed to relieve the symptoms resection of >90% of the tumour bulk from the liver is acceptable treatment.

The overall survival rates have been reported as 46-86% at 5years and 35-79% at 10 years. Again the range is explained by the heterogeneity in reporting and the underlying primary site. Unfortunately a local recurrence rate of 97%in the liver is reported even when complete resection is reported. Usually this recurrence rate will mitigate against major liver surgery but in the context of the biology of this tumour with slow progression and prolonged survival, if adequate morbidity and mortality is expected, radical surgery is still recommended.

In a large series reported from the Mayo clinic of 170 patients the overall 5 year survival was 61% with a medium survival of 81 months. The morbidity was 14% and 2 patients died post operatively. 84% developed local recurrence at 5 years with the medium time to recurrence of 21 months. In 44% of patients who had a complete resection the 5 year recurrence was 76% with a medium time to recurrence of 30months. Again they conclude that liver surgery is unlikely to be curative but that overall with low morbidity and mortality and improved symptoms patients did benefit.

There is little data comparing the effectiveness to other non-surgical modalities. It would appear that surgery still has better survival advantage.

Liver transplant has been performed with good results in limited patients. There is no clear guidelines as to which patients will benefit but it would appear that patients with slow growing tumours or patients with stable disease following other modalities can be considered for transplant.

This presentation will not deal with other modalities but local ablative techniques have been shown to have better results following laparoscopic and open surgery than via percutaneous route. As such they are considered here. These studies are not comparative and report case series making comparison to radical liver surgery difficult. However they have been shown to have good results with low morbidity and almost no mortality. The benefit of this procedure includes the ability to repeat treatment and it can be combined with other modalities. Radio frequency ablation seems to be the modality of choice and while small series using cryotherapy and ethanol injection have been reported, RFA is currently recommended. The use of microwave technology has recently been introduced and early data suggests it may have an advantage over RFA in larger lesions or those closer to major blood vessels.
Other available techniques against which surgery will have to be compared includes hepatic trans-catheter arterial embolization with the audition of catheter directed chemotherapy and radio-embolization with radioactive beads . These techniques are widely described in other liver metastasis but only small series are reported in Net's but with fair results. Again they may have a role to play in combination with liver surgery.

Systemic treatment options include the Peptide Receptor Radionuclide therapy using somatostatin receptor targeted therapy. This emerging therapy has it main role in palliative treatment. However considering the high recurrence rate after radical surgery, comparison with this modality is required to evaluate the role of surgery.
The role of post-operative adjuvant systemic therapy is not well defined and because the role of systemic therapy in general is not well defined it is not possible to make any recommendations currently. However the role of somatostatin analogues is currently been evaluated and many centres would add long acting somastostatin analogues to the therapy especially when incomplete resections is performed. In non-function Net's octreotide has been shown to have an anti-proliferative affect and therefore may have value in these patients.
The role of radical surgery in NET's remains unclear. However the survival data clearly supports radical liver resections in centres where the morbidity and mortality results are low and the multidisciplinary approach to the management of neuroendocrine tumours is undertaken.

Recommended reading

1. Multimodal management of Neuroendocrine liver metastases. Frilling A, Sotiropoulos GC, Li J, et.al. HPB 2010; 12: 361-379
2. Hepatic resection for metastatic neuroendocrine carcinomas. Que FG, Nargorney DM, Batts KP, Linz LJ, Kvols. Am J Surg. 1995; 169:36-42

ROLE OF SURGERY IN MANAGEMENT OF HEPATIC METASTASIS FROM NEURO-ENDOCRINE NEOPLASIA (NEN)

Dr Johan van Beljon-Montana private Hospital

The role of surgery in the treatment of above mentioned disease is well defined.

Surgical resection of Hepatic metastasis from Neuro-Endocrine tumours represents a paradigm shift. The main Aim of Liver resection for Neuro-endocrine liver metastasis is Palliation and to prolong survival whereas Liver resection for metastasis from other solid cancers are usually done with curative intent.

The unique slow growing nature of these tumours renders them less responsive to the usual Palliation treatment options. Symptoms are directly related to overall mass of tumour. CytoneDuonive Surgery is the most direct and immediate method to provide symptomatic relief.

It has been shown that Hepatic Cytoreduction whether Hepatic resection or Liver Transplantation can address endocrinopathies and improve survival.

Hepatic resection for metastatic neuroendocrine cancer is recommended id:

1. Primary tumour and regional disease are resect able or resected
2. Greater than 90% of Hepatic metastasis are resect able.

Local recurrence is common after cytoreductive surgery. Liver transplant offers the possibility of cure instead of Palliation alone.

Prof Modise Koto,-Department of Surgery, University of Limpopo (Medusa)

The mainstay of jaundice palliation for malignant obstruction is currently endoscopic with self-expanding metallic stents.

The role of surgical palliation has traditionally been left for patients who are for resection and are found at surgery to be unresectable.

With more quality imaging most patients with head of pancreas tumours can be accurately assessed for resectability and the decision to palliate can be made with improved accuracy pre-operatively.

With the advent of minimally invasive techniques, surgical bypass is still an option with less morbidity associated with the procedure.

Surgical palliation

Historical perspective
External drainage of bile by T-tube is associated with major morbidity
- Loss of appetite
- Electrolyte and fluid imbalances.

It is certainly not a viable treatment strategy today.

Internal biliary drainage
These are preferred.
The commonly performed procedures are:
1. Cholecystojejunostomy
2. Choledocho- or hepatico- jejunostomy
3. Choledochoduodenostomy

Cholecystojejunostomy
It was preferred in the past because of its simple technical demand, it is easy to perform.
In an extensive review, there is fairly robust data showing that:
- Success rate to lower jaundice was lower compared with choledochojejunostomy.

Choledochojejunostomy
This is more technically demanding operation. In a randomized controlled trial by Sarfeh et al 1988 showed:
1. Lower recurrence rate of jaundice
2. Lower recurrence rate of cholangitis
3. Better patency of the bypass

Mortality rates
In the early 90's, the reported mortality rate of this procedure was as high as 24% - (15-24%).
More recent studies show mortality rates of 1% to 8%, morbidity rates of 21% to 29%.
Shorter hospital stays (10-17 days)
Mean survival rates between 7-9 months.

Choledochoduodenostomy
There is relative widespread concern about the usage of this procedure in malignant obstruction of the biliary tree. The concern revolves around the possible occlusion of the anastomosis by growing tumour.
However, there is fairly good evidence from published data looking at the effectiveness of this procedure in these cohort of patients with no major problems of secondary obstruction.
This remains unpopular nonetheless.

Stenting v/s gastrojejunostomy
A recent systemic review showed no difference.
1. Technical success (96% vs 100%)
2. Early and late major complications
3. Persisting symptoms

Hospital stay was longer for gastrojejunostomy (13 vs 7 days)
The authors concluded that gastrojejunostomy should be used for patients with longer expected survival and stent for patients who are likely to leave shorter

Surgical drainage v/s endoscopic drainage

What is the status of data?

Five prospective randomized trials are available to date looking at the status of surgical drainage.
Four of these trials directly compare surgical drainage with endoscopic drainage.
The trial by Bornman et al, no difference was noticed between percutaneous and surgical palliation (1986).

Other studies performed between 1988 and 1994.

From the available published data, a few conclusions can be made:

1. Surgical palliation in unresectable pancreatic cancer is associated with higher
   - overall morbidity
   - longer hospital stay
   - higher initial mortality rate

But long term results are better

Endoscopic drainage

Associated with lower initial morbidity and mortality
It more frequently leads to late biliary complications, more re-intervention rates related to stent obstruction, sepsis, and gastric outlet obstruction.

Gastric outlet obstruction (GOO)

Symptoms of nausea and vomiting are quite frequent in patients with cancer of the head of pancreas (11-50%). Not all of these patients have duodenal obstruction.

It is estimated that mechanical duodenal obstruction occurs in 15 – 20% of patient with HOP tumours.
The other reason for the nausea and vomiting is mostly disorders of the small bowel function caused by infiltration of the coeliac plexus by tumour and mesentery.
It is important to differentiate the two.

Surgical palliation is offered only if the obstruction is caused by mechanical means. It is important to confirm mechanical obstruction by radiologic means or endoscopy.

For patients who are found at surgery to be unresectable an additional gastrojejunostomy is offered to these patients and no additional morbidity is found.

Endoscopic stenting of the duodenum is also acceptable.

Prophylactic gastrojejunostomy

Between 40% to 80% of patients who are offered laparotomy for Whipple resection are found to be resectable.
There is thus a significant number of patients who will end up with palliative procedure.
Should they get a prophylactic gastrojejunostomy?
Two randomised controlled trials evaluated these cohort of patients who were earmarked for Whipple resection and found to be unresectable – (Lillemoe et al; 1999, Van Heek of 2003)

Lillemoe and colleagues 87 patients randomized to biliary bypass alone and biliary pass with a retrocolic gastrojejunostomy and chemical splanchnicectomy.
Results no difference in procedure related morbidity or mortality
19% in the group of biliary bypass only developed obstruction - which was statistically significant.

Van Heek et al (2003) in a multi-centre trial to double bypass and single bypass. The outcome of the interim analysis of 50 patients showed similar results to Lillemoe – the trial was discontinued.
During follow up GOO was diagnosed in 5,5% of patients with single bypass and 41,4% of patients with double bypass which was significant.

Pain management

A significant number of patients with HOP tumours already complain of pain at the time of presentation – the number rises significantly with time. These patients often complains of epigastric pain and backache due to tumour infiltration into the mesentery and coeliac plexus

The other mechanism of pain may be neurogenic inflammation.

Initial pain management should be pharmacologically - NSAID and narcotic analgesia. The next step is coeliac plexus block which can be done percutaneous.

For those that undergo surgery, they should be offered coeliac block routinely if found to be unresectable.

Summary

Surgical palliation for advanced malignant obstruction of the biliary tree is still a viable option with declining utility. Its role is still eminently in patients who are defined to be unresectable at laparotomy for Whipple resection.

With the advent of minimal invasive surgery there is resurgence albeit small because of less morbidity.

The mainstay of palliation for those patients that are clearly unresectable is still endoscopic stent placement.

ETHICAL PROBLEMS AND ISSUES IN SURGICAL MANAGEMENT OF CANCER IN HIV/AIDS PATIENTS IN THE HAART ERA: AIDS DEFINING NEOPLASIA

Prof Leon Snyman-Gynaecological Oncology Unit, Department Obstetrics & Gynaecology, University of Pretoria and Kalafong Hospital

---

Abstract

AIDS defining neoplasia include cervical cancer, Karposi Sarcoma, Non-Hodgkins Lymphoma and. Cervical cancer is a preventable disease, yet it is estimated that up to 10 women die every day of this disease in South Africa.

Human papilloma virus (HPV) infection is a necessary agent in the development of cervical cancer. HPV infection with high risk strains is common in HIV infected patients.

HIV has a negative impact on cervical cancer. Ethical problems that will be discussed include issues with regards to screening HIV infected women for cervical cancer, primary prevention of the disease and treatment related issues.

ROLE OF THE GENERAL SURGEON IN ADJUNCTIVE SURGERY FOR GYNAECOLOGICAL CANCER: ROLE OF GENERAL SERGEON

Prof Thandinkosi Madiba-Department of Surgery, University of KwaZulu-Natal, Durban

Introduction

The most commonly seen gynaecological tumours include tumours of the vulva, cervix, uterus, and ovary. These tumours spread by (i) direct spread, (ii) lymphatics, (iii) bloodstream and trans-coelomic routes. The propensity for one method of spread over another varies from tumour to tumour depending on tumour biology.

Disease profile

Gynaecological cancer requiring adjunctive surgery by the general surgeon includes (i) advanced disease, (ii) recurrent disease, (iii) complications of malignant disease and (iv) complications of treatment.

Ovarian cancer remains the leading cause of death from gynaecological malignancy in the world. It is diagnosed at an advanced stage in about 75% of patients. It commonly spreads along the peritoneal surfaces in the abdomen without respecting organ boundaries and often involves the serosa of the bowel by direct extension or serosal implantation

Metastases to peritoneum, omentum and mesentery lead to “caking” of the bowel. Metastases to bowel lead to bowel invasion which may in turn lead top gastrointestinal haemorrhage, intestinal intestinal obstruction and fistula formation. Common distant organ involvement include the liver and lungs

Gastrointestinal fistula is divided into internal and external fistulae. Internal fistulae include recto-vaginal, colo-vaginal, entero-vaginal fistulae. External fistulae indicate an abnormal communication between a hollow viscus and the skin.

It is uncommon for uterine cancer to necessitate the involvement of a general surgeon. Advanced vulval and cervical cancer may lead to invasion of the surrounding structures as well as malignant fistula. The participation of a general surgeon is limited to diversion of the faecal stream.

Radiation treatment for gynaecological cancer, especially ca cervix is mainly to the pelvis. Organs at risk for radiation injury in this situation include rectum and sigmoid colon, and small bowel in the Pouch of Douglas. Consequences include internal fistulae such as recto-vaginal fistula, colo-vesical fistula, entero-vesical fistula and entero-vaginal fistula.

Complications of gynaecological surgery include (i) bowel injury which can be due to direct damage or post-coagulation syndrome and (ii) intestinal obstruction.

Surgery

The objectives of surgery in advanced gynaecological cancer comes in many forms including (i) making a diagnosis, (ii) Staging laparotomy to determine the aim of

treatment (cure vs palliation) and the distribution of disease, (iii) salvage surgery back to cure , (iv) palliative surgery and (v) defunctioning stoma.

Cyto-reductive surgery
The current standard treatment for ovarian cancer consists of maximum cyto-reductive surgery to reduce residual tumour to a minimum, followed by platinum-based chemotherapy. The size of residual disease after surgery is one of the most important prognostic factors for survival and the only prognostic factor that the physician can influence. Survival of patients with optimal tumour cyto-reduction (residual lesion smaller than 1 cm) is significantly higher than that of patients with larger residual lesions. The role of general surgeon in this contact will be bowel resection, pelvic exenteration.

Haemorrhage
Investigations of gastrointestinal bleeding includes colonoscopy, enteroscopy, capsule endoscopy, angiography and red cell scan

Gastrointestinal fistula
The malignant fistula can be managed by palliative resection as part of cyto-reductive surgery, defunctioning stoma, or surgical bypass. Iatrogenic recto-vaginal fistula can be managed by primary repair. The management of radiotherapy-induced recto-vaginal fistula is difficult owing to severe inflation and fibrosis. In the presence of minimal fibrosis a fistula repair can be undertaken either by abdominal or perineal approach.

In the presence of severe fibrosis repair is not possible and the only options available are (i) resection and primary anastomosis, (ii) sleeve recto-anal anastomosis, (iii) Parks colo-anal sleeve anastomosis (iv) anterior resection and (v) abdomino-perineal resection. In extreme cases, diversion is the only option.

Intestinal obstruction
Patients with malignant obstruction have a number of options available, namely bowel resection as part of cyto-reductive surgery and temporary or permanent diversion of the faecal stream. The optimal management of bowel injury depends on early detection of injury and prompt intervention in the form of an exploratory laparotomy with injuries managed on their merit.

Patients with postoperative adhesive obstruction can be managed like all patients with intestinal obstruction which may be conservative or by laparotomy depending on the compelling nature of the presenting clinical scenario.

Metastatic disease
The mainstay of treatment with a promise of survival is the resection of metastases. Liver and lung metastases are amenable to resection with good results. However, there are specific criteria which make such resection eligible under these circumstances. The outcome may be improved if the surgery is preceded by neo-adjuvant therapy

Metastases cane be categorised into resectable, potentially resectable and irresectable. Those considered resectable are referred for resection. Those considered potentially resectable are referred for neo-adjuvant therapy prior to consideration for resection.

Bibliography

1. Cai H-B, Zhou Y-F, Chen H-Z, Hou H-Y. The Role of Bowel Surgery with Cytoreduction for Epithelial Ovarian Cancer.Clinical Oncology (2007) 19: 757e762
2. Pothuri P, Guirguis A, Gerdes H, et al. The use of colorectal stents for palliation of large-bowel obstruction due to recurrent gynecologic cancer. Gynecologic Oncology 95 (2004) 513–517
3. Martínez A, Filleron T, Vitse L, et al. Laparoscopic pelvic exenteration for gynaecological malignancy: Is there any advantage? . Gynecologic Oncology 120 (2011) 374–379
4. Andreyev HJN. Gastrointestinal Problems after Pelvic Radiotherapy: the Past, the Present and the Future . Clinical Oncology (2007) 19: 790e799

SURGICAL OPTIONS IN MANAGEMENT OF CHOLANGIO-CARCINOMA: RADICAL SURGERY

Prof Martin Smith-Department of Surgery, University of Witwatersrand (Wits)

CCA remains a very challenging cancer to manage surgically despite significant advances in surgical outcomes. The majority of these tumors are not amenable to surgical resection and require a palliative approach. However most surgeons agree that surgery remains the only therapy with curative intent. Recent technical advances include the need for additional liver resection, especially segment 1, as a routine approach. The value of vascular resections have been described, including portal vein and hepatic artery resections and reconstruction. The rates of resection with curative intent vary widely from 28 -95% and the rate of complete resection (R0) resections remain low. The 5 year survival rates are 25 – 40% and also remain low. There is a reduction in morbidity and mortality following these procedures based on the many advances made in resectional liver surgery in the recent past.

The initial challenge in managing these patients is to adequately image these tumors and determine resectability. Issues related to a pre operative tissue diagnosis and being able to exclude benign causes of the strictures present the surgeon with a significant challenge .Fifteen percent of resections for malignant disease are eventually shown to be benign, this includes autoimmune cholangitis or even TB and Primary Sclerosing Cholangits. Furthermore the role of preoperative biliary drainage has not been conclusively determined.

Advances in imaging have made determination of vascular invasion easier but are still not complete. The extent of the proximal biliary invasion also remains difficult to determine. It spreads superficially along the bile ducts resulting in positive margins in some patients.

Table 1:

Meta-analysis of imaging studies on staging HCCA (AMC Amsterdam)
26 studies (448 patients)
Ruys AT et al reported at the E-AHPBA 2011

	Accuracy	Sensitivity	Specificity
Ductal Extent	86%		
Portal Vein Invasion		89%	92%
Hepatic Artery Invasion		83%	93%
Lymph Node Status		61%	88%

The most commonly used staging classification system for CCA is the Bismuth – Corlette system which described the extent and position of the biliary stricture but it does not reflect the vascular and lymph node stage of the disease. Modern imaging better defines these lesions and therefore a better classification is offered by the MSKCC and the AMC in Amsterdam.

Amsterdam Staging System

Stage	Present	Absent
Stage I		Bilateral INVOLVEMENT OF BILIARY RADICLES Vascular INVASION Suspicious LYMPH NODES
Stage II	Involvement OF PORTAL VEIN OR HEPATIC ARTERY	Bilateral INVOLVEMENT OF BILIARY RADICLES Suspicious LYMPH NODES
Stage III	Bilateral INVOLVEMENT OF BILIARY RADICLES Suspicious LYMPH NODES	
Stage IV	Unresectable DISEASE ACCORDING TO UPDATED RESECTION CRITERA	

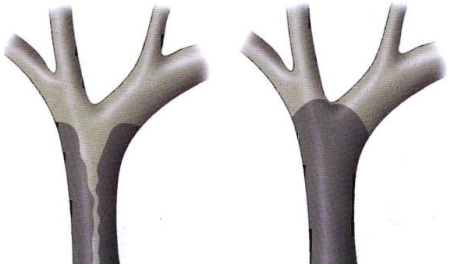
The role of Laparoscopy has been investigated as a preoperative tool. The accuracy and impact on treatment has varied between different studies. There are reports that the yield from preoperative laparoscopy may be as high as 25% supporting a benefit to routine laparoscopy. A recent study however from the AMC in Amsterdam showed only a 14% yield and they conclude that there is no value to routine laparoscopy.
The value of preoperative biliary drainage remains uncertain as does the best method of drainage. Nimura from Japan believes the value of drainage includes the treatment of segmental cholangitis, improved regeneration of the remnant liver and definition of the proximal biliary infiltration of the tumor. Cherqui from Paris does not support this view believing that it is associated with an increased risk of thrombosis or haemobilia, cholangitis and infectious complications and also an increased risk of tumor cell seeding. When drainage is undertaken there is good evidence to support the percutaneous transhepatic route when compared to the endoscopic placement of stents. This evidence includes a lower rate of sepsis number of procedures required and success rates for percutaneous approaches.
Having determined resectability and having confirmed no metastatic disease, addressed co-morbities and decided on treatment the following table highlights the results over a 20 year period
Table 2: **F. Ito, Ann Surg 2009**

Authors	Published Year	Resections (n)	Resectability (%)	Negative Margin (%)	Liver Resection (%)	Morbidity (%)	Mortality (%)	5-yr Survival Rate (%)
Hadjis NS et al	1990	27	NA	56	60	NA	7	22
Nimura et al	1990	55	83	84	98	41	6	41*
Nakeeb et al	1996	109	56	26	14	47	4	11
Su et al	1996	49	28	49	57	47	10	15
Klempnauer et al	1997	151	45	77	77	NA	10	28
Miyazaki et al	1998	76	NA	71	86	33	13	26
Burke et al	1998	30	43	83	73	NA	6	45
Neuhaus et al	1999	80	NA	61	85	55	8	22
Kosuge et al	1999	65	73	52	80	37	9	33
Launois et al	2000	131	35	NA	37	NA	19	NA
Gerhards et al	2000	112	NA	14	29	65	18	NA
Nimura et al	2000	142	80	61	90	49	9	26†
Todoroki et al	2000	101	89	14	58	14	4	28
Jarnagin et al	2001	80	50	78	78	64	10	26
Kawarada et al	2002	65	89	64	75	28	2.3	26
Capussotti et at	2002	36	NA	89	83	47	3	27
Kawasaki et al	2003	79	75	68	87	14	1.3	22
Seyama et at	2003	87	94	64	67	43	0	40
Rea et al	2004	46	NA	80	100	52	9	26
Kondo et al	2004	40	95	95	65	48	0	NA
IJitsma et al	2004	42	NA	65	100	76	12	19
Hemming et al	2005	53	50	80	98	40	9	35
Jarnagin et al	2005	106	70	77	82	62	8	NA
Dinant et al	2006	99	NA	31	38	66	15	27
Ito et al	2008	38	55	63	53	32	0	33

It is clear from this table which includes data from the major centers around the world that in all reported domains including, resection rates, R0 resections, morbidity and mortality and 5 year survival rates, the range is so large making conclusions very difficult to determine.

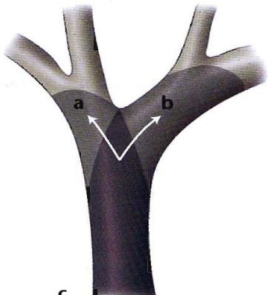
The next question is what type of resection to perform and this should be discussed with reference to the Bismuth- Colette classification.

Type 1 and 11: The options include a local excision versus a bile duct excision or a liver resection. There is a advantage to including a liver resection and this would be the current recommendation in 2012



Bismuth – Colette Type 1 and 11

In Type 111a and 111b there is little role for any other resection besides a major liver resection. In this study reported from the MSKCC in 2005 the following predictors of outcome were identified. The value of an R0 vs an R1 resection was confirmed. The value of a liver resection was confirmed, and that fact that portal vein involvement



when resected does not predict outcome on univariate analysis.

Variable	Median Survival (mo)	*P* (Univariate)	*P* (Multivariate)	Hazard Ratio (95% CI)
Resection margin				
R0 (82)	42.9 (36.9, 55.0)	0.0003	0.006	0.44
R1 (24)	24.0 (12.6, 35.1)			(0.25–0.8)
Liver resection				
Yes (87)	42.9 (33.0, 53.7)	0.021	0.003	2.69
No (19)	28.8 (19.0, 39.0)			(1.41–5.14)
Well differentiated†				
Yes (35)	55.7 (39.0, 99.0)	0.0001	0.0001	3.62
No (68)	28.8 (23.4, 37.1)			(1.91–6.87)
Papillary tumor				
Yes (25)	55.7 (41.6, NR)	0.013	0.015	2.49
No (81)	33.5 (24.4, 39.0)			(1.19–5.18)
Regional nodes (+)				
Yes (22)	27.3 (19.5, 36.9)	0.0007	0.64	0.87
No (84)	40.5 (35.1, 53.7)			(0.48–1.56)
Lobar atrophy				
Yes (33)	47.1 (30.0, 99.0)	0.08	—	—
No (73)	37.6 (27.4, 42.3)			
Portal vein involved				
Yes (31)	47.1 (30.0, 99.0)	0.07	—	—
No (75)	37.6 (26.9, 41.6)			

Therefore major liver resection is recommended in type 111a and b to ensure a R0 resection.

Remaining issues that need to be discussed include contraindications to resectional surgery. These include peritoneal disease, liver metastasis and involvement of para-aortic lymph nodes.

These is a clear benefit to a lymph node resection in the porta-hepatis and the exact extent of the clearance is not clear

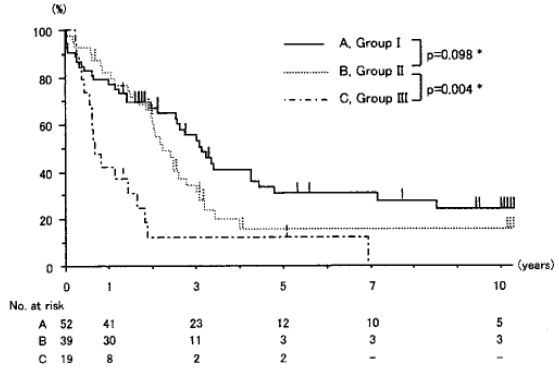


Figure 1

Y. Kitagawa, Ann Surg 2011.

Survival according to nodal status in 110 patients with hilar cholangiocarcinoma who underwent resection with regional and paraaortic lymphadenectomy (all deaths included). Group 1, patients without lymph node metastasis; group 2, patients with regional lymph node metastasis; group 3, patients with paraaortic node metastasis. *, by log-rank test 01

mass and do routine arterial and venous bypass and they resect the tumor without determining vascular invasion. These are significant procedures with low mortality in their hands but with high morbidity and this should not be considered standard of care today.

Therefore in conclusion, surgery remains the only potential treatment for cure. However most patients are not resectable and require a palliative approach. In the group that may be resectable, determination of resectability must include vascular involvement and lymph node involvement and the proximal extent of the biliary invasion. A combination of cross sectional imaging will assist in this regard. Pre operative tissue diagnosis is not required but a 15% resection of benign disease must be acceptable. Preoperative biliary drainage is my own approach largely to assist in post operative live remnant regeneration. Local resection is no longer acceptable and even for Type 1 and 11 tumor's a limited liver resection is required. The type of surgery for type 111a and b lesions remains uncertain but should include a major liver resection with or without vascular resections. These patients should be referred to major HPB centers where the decision regarding resectability and the management of this surgery is performed by multidisciplinary teams with a range of expertise and experience.

Recommended reading

1. Surgical Outcomes and Predicting Factors of Curative Resection in Patients with Hilar Cholangiocarcinoma: 10-Year Single-Institution Experience. Min Soo Cho & Sung Hoon Kim & Seung Woo Park & Jin Hong Lim & Gi Hong Choi & Joon Seong Park & Jae Bock Chung & Kyung Sik Kim. J Gastrointest Surg. 2012; 16:1672–1679
2. Lymph Node Metastasis from Hilar Cholangiocarcinoma: Audit of 110 Patients Who Underwent Regional and Paraaortic Node Dissection. Yuichi Kitagawa, MD, Masato Nagino, MD, Junichi Kamiya, MD, Katsuhiko Uesaka, MD, Tsuyoshi Sano, MD, Hideo Yamamoto, MD, Naokazu Hayakawa, MD, and Yuji Nimura, MD. ANNALS OF SURGERY. 2011; 233, No. 3: 385–392
3. Hilar Cholangiocarcinoma: A Review and Commentary. Ronald S. Chamberlain, Leslie H. Blumgart. Annals of Surgical Oncology. 2000; 7(1):55–66
4. Papillary Phenotype Confers Improved Survival After Resection of Hilar Cholangiocarcinoma. William R. Jarnagin,Wilbur Bowne, David S. Klimstra, Leah Ben-Porat,† Kevin Roggin, Karina Cymes, Yuman Fong, Ronald P. DeMatteo, Michael D'Angelica, Jonathan Koea, Leslie H. Blumgart. Ann Surg 2005;241: 703–714

CCA is a cancer of the Biliary Pithelium and can develop anywhere along the Biliary tree.
Anatomically CCA can be classified as:

1. Intrahepatic when it develop in the liver
2. Extra hepatic when it develops outside the liver –

Extrahepatic CCA can be subdivided into:

1. Hilar CCA when it arise at the confines of the left and right Hepatic Ducts (Klatskin)
2. Distal CCA when it arises in the intra-pancreatic portion of the biliary system.

The traditional poor prognoses of CCA have led to a Nelticistic approach. Multimodisty treatment options, including radical surgery options to obtain RRRRO Resections, has led to a more optimistically approach to patients with CCA.
Key factors to take into account when surgery is planned include:

1. Tumour location
2. Extent of disease

EXTRAHEPATIC CCA
Two Surgical objectives should be met:

1. Complete Ro Resection of Liver
2. Restoration of Biliary-Enteric Continuity

Because of the anatomic location (The Hepatic Hilum's an anatomically complex area) and the invasive nature of these tumours, Ro Resections are difficult to perform. Ro Resections can only be obtained in 10-50% of resected specimens. Most patients that die after resection for CCA die of local recurrence.

a- HILZAR CCA

Surgical treatment of Hilar CCA still remain a challenge for the Surgeon, because it usually requires several modesties to obtain detailed information about cancer location, spread as well as complicated operative procedures.

2

Selection of Surgical procedure should be based on both tumour extent and Hepatic Reserve (Long term Jaundice with subsequent liver damage should be kept in mind).
Tumour staging and planning of surgical procedure should keep the Bismuth-Corlette staging system in mind.
Recent better survival rates for Hilar CCA is the result of more aggressive surgery that often includes major Hepatectomy with nodal dissection.

The most common reason for the inability to perform R0 Resections is the involvement of the Portal vein. The role of portal vein resection remains in evolution.
The various surgical options will be discussed.

b- MIDDLE AND DISTAL CCA

Distal CCA should be treated like the other forms of periampuliary carcinomas.

Pancreatico-Deodenectomy is the treatment of choice.
The role of major vascular resections, including portal vein resection, is under investigation.

Segmental bile duct resection is an option in selected early cases of mid bile duct tumours.

Major Hepatectomy with PPD remains Controversial.
Total Pancreatectomy should not be done to CCA.

B. INTRAHEPATIC CCA

Intrahepatic CCA are classified as hepatomas and thus staged as such.
Segmentectomy or lobectomy are the preferred procedures for solitary intrahepatic CCA segment I of the liver is the most frequent sit of local recurrence after surgery. Resection of segment I may become standard practise since it offers improved cell-free margins.

3

The role of LTX is controversial and may be offered to a select few patients with early stage CCA in a research protocol.

PALLIATIVE SURGERY

Palliative surgery in the setting of extra hepatic CCA should be reserved for patients that are explored for possible curative resection and found to be non-resectable during exploration.

For patients with Hilar CCA various forms of segmental bypass procedures are available most notesably is the segment III bypass. These procedures have good long term palliation of Jaundice.

For patients with distal CCA Biliary as well as intestinal bypass should be considered.
Patients deemed non-resectable with pre-operative investigation should be palliated by non-surgical means.

THE SURGICAL MANAGEMENT OF PULMONARY METASTASES FROM THE BREAST, COLORESTAL CARCINOMA, MELANOMA AND SARCOMA

Dr Aldrich Jacobs, Department of Cardiothoracic, University of Pretoria

Background

The lung is a common site of metastatic disease in many cancers. After the resection of isolated pulmonary mets, about 25% of patients will survive 10 years, most of them disease free. Although there have been no randomized trials, retrospective analyzes have shown that metastasectomy can be considered an effective treatment in selected patients with metastatic cancer.

Objective

The purpose of this talk is to discuss pulmonary metastatic disease with reference to its history, to patient selection, prognostic factors, and operative approach.
Further discussion will focus on the value of pulmonary metastasectomy in pulmonary metastasis in breast carcinoma, colorectal carcinoma sarcoma, and melanoma.

Metastatic melanoma

- Usual sites: distant skin, subcutaneous nodules, L/nodes Lung/liver/other visceral organs/brain

Prognosis

- Very poor
- Median survival 6 – 9 mnths with lung/ L/node/ skin only may be up to 15 mnths
- Surgical treatment should always be considered

Chemotherapy

- Melanoma is generally resistant to chemotherapy
- Dacarbazine - is FDA approved
  - Response rate of 7% but other clinical trial have reported higher RR of up to 15%
  - OS - 8 mnths

Immunotherapy

- Interleukin-2: - FDA approved
  - RR of 6 – 9%
  - Atkins et al, in 199 published in JCO – HD IL-2 data
    - 720 000iu/kg iv bolus
    - OOR - 15,5%
    - Brain mets were excluded
- Durability of CR is the hallmark of IL-2 therapy
- 80% of complete responders are likely cured
- Toxicity: very toxic –e.g capillary leak syndrome
- Need ICU

- Ipilumamab: FDA approved
  Anti-CTLA-4 Monoclonal antibody
  ORR 10 – 15%
  Disease control rate of 30%
  Toxicity is manageable
  Induce long-term responses in minority of pts

- Vemurafenib: TKI, BRAF inhibitor
  BRAF activating mutation is

found in approx 40-60% of melanoma pts
Response is seen within 2 wks

but PD of disease is notice at 6 months

- Vemurafenib: Important mutation is V600E

Combination Chemotherapy

- Only in Clinical trials
- None has shown better results

- Immunotherapy plus targeted therapies?

References

- To be added later

TACE: Trance Arterial Chemo Embolization for

Primary Hepatic Tumors like Hepato Celllular Carcinoma with or /without

Radiofrequency Ablation.

Newer advances like Radioembolization using RadioIsotope Y90

Microspheres,injection in the Hepatic artery as a once off treatment

for primary or metastatic carcinoma of the liver

Slides of cases done at Steve Biko Academic Hospital

Prof Mike Sathekge-Department of Nuclear Medicine, University of Pretoria

Selective internal radiation therapy (SIRT) with yttrium-90 (Y) microspheres[90Y-SIR-spheres and 90Y-TheraSpheres] is an effective liver-directed therapy which serves as an outstanding example for multidisciplinary management. SIRT is tumoricidal to the tumor without damaging adjacent normal liver tissue. Because SIRT is delivering implantable microspheres labeled with (90)Y into the arteries that feed liver tumors in order to provide a high dose of radiation to tumor nodules, while preserving the non-tumoral liver tissue from receiving a harmful level of radiation. Metastatic tumours of the liver are responsible for significant morbidity and mortality, and only a small percentage is resectable with curative intent. In the remaining patients chemotherapy andexternal beam radiotherapy will only provide palliation. In spite of the availability of various treatment options,due to their late discovery, liver metastases prove difficult toeradicate. SIRT is emerging as a powerful tool to achieve regional tumor response and disease control in hepatic malignancy of various origins. It has been demonstrated to be potent against hepatocellular carcinoma/hepatoma, colorectal cancer, and neuroendocrinetumors. Whiles hepatic metastases of numerous other tumor entities including breast cancer,cholangiocarcinoma, and pancreatic cancer are also proving to be treatment-sensitive.

Current data show that SIRT with (90)Y combined with radiosensitizing chemotherapy is a safe and efficient modality that extends the time to progression in liver metastatic colorectal cancer and unresectable hepatocellular carcinoma , however the survival benefits still remains controversial. Thus a larger study needs to be done in the South African setting to verify whether; the chemo-SIRT combination will produce superior objective responses compared with chemo-only treatment in a front-line treatment setting in patients with metastatic tumours of the liver.

Although SIRT is by and large well tolerated, it may produce relevant toxic effects as a result of radiation of non-target organs including cholecystitis, gastrointestinal ulceration, pneumonitis, and most importantly, liver toxicity. A significant effect on tumor growth in the treated lesions is consistently observed with disease control rates in excess of 80%. Also, SIRT may allow downstaging large or multiple lesions to radical treatments with curative intent.

This treatment response after SIRT seems to be better assessed using metabolic response assessments with serial fluorodeoxyglucose positron emission tomography (FDG-PET) in cases of FDG-avid tumours than with morphological criteria measured on computed tomography or magnetic resonance imaging. The fact that FDG PET imaging is more sensitive in the assessment of early response allows clinicians to proceed with further therapeutic options. Furthermore FDG PET also helps with the radiobiologic approach, based on patient-specific dosimetry, and could improve the (90)Y-microsphere therapeutic approach, maintaining an acceptable liver toxicity.

SIRT is a safe and efficient treatment modality in salvage therapy of metastatic tumours of the liver and in unresectable hepatoma. Emphasizing SIRT as an outstanding example for multidisciplinary management will help optimize treatment and patient selection.

TECHNIQUE FOR CYTO-REDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRA-PERITONEAL CHEMOTHERAY (HIPEC)

Prof Marcello Deraco-Elena Gil Gomez, Dario Baratti and Shigeki Kusamura Peritoneal Surface Malignancies Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan-Italy

CRS originally described by Sugarbaker (*Sugarbaker PH. Ann Surg 1995;221:29*), with some minor technical variants emerged during a 15-year experience at our center. (*Deraco et al. J Surg Oncol. 2009;100:321*) Patients are put in a modified lithotomy position with gluteal folds advanced to the break in the operatory table to allow full access to the peritoneum. A three-way bladder catheter is inserted to for cold lavage during the hyperthermic phase, in order to avoid heat damage to the bladder wall. A large-bore naso-gastric tube is inserted. The abdomen is opened on the midline from xyphoid process to the pubis. A self retaining Thompson divaricator is used. Briefly, the goal of the surgical cytoreduction is to remove all the visible tumor by the following peritonectomy procedures and multivisceral resections:

1) right sub-diaphragmatic and parietal peritonectomy, with Glisson's capsule dissection;
2) left sub-diaphragmatic and parietal peritonectomy with splenectomy and greater omentectomy;
3) lesser omentectomy, stripping of the omental bursa and cholecystectomy;
4) pelvic peritonectomy, sigmoidectomy with hysterectomy and salpingo-oophorectomy;
5) right/total colectomy;
6) gastric antrectomy or total gastrectomy.

Depending on disease extent, implants on visceral surfaces could be alternatively removed by electrosurgical local dissection. A ball-tip electrosurgical hand piece will be used to dissect the tumor on peritoneal surfaces from normal tissue. The 2-mm ball-tip electrode will be used for dissecting on visceral surfaces, including stomach, small bowel, and colon. When more rapid tumor destruction is required, the 5-mm ball-tip is used.

HIPEC.After the surgical cytoreduction, two inflow catheters are inserted (one in the right subphrenic space and one deep in the pelvic cavity), as are two outflow catheters (one in the left subphrenic space and the second more superficially in the pelvic cavity). Six thermocouples are used to continuously monitor the inflow, outflow, and intraperitoneal cavity temperatures. Temporary abdominal skin closure follows with a tight continuous nylon stitch in the closed abdomen technique while open and semiclosed techniques are available. HIPEC will be performed with a drug association selected according to the primary tumour. Cisplatin, Mitomycin-C, Doxorubicin and Oxaliplatin are the most frequently used drugs. Drugs are administered once the hyperthermic phase has been reached with a mean temperature of 42.5°C. Duration depend of the drug association used and range between 30 to 90 minutes. Patients over 70 years of age or with relevant co-morbidities and those who had undergone previous systemic chemotherapy or extensive cytoreductive surgery received a 30% dose reduction of both drugs. Perfusate volume will be 4-6 L and mean flow 700 mL7min. At the Milan NCI, a extracorporeal circulation device Performer LRT® [RAND, Medolla (MO), Italy] is used. Following the HIPEC, the perfusate is quickly drained and the abdomen closed after a careful intra-abdominal inspection.

ETHICAL PROBLEMS AND ISSUES IN SURGICAL MANAGEMENT OF CANCER IN HIV/AIDS PATIENTS IN THE HAART ERA: GENERAL CONSIDERATIONS AND MEDICOLEGAL:

Dr Theresa Rossouw-School of Medicine, University of Pretoria

ETHICS OF TREATMENT OF ADVANCED CANCER IN HIV/AIDS PATIENTS

In medicine, whenever we are face with an ethical dilemma, we usually default to the four principles approach developed by Beauchamp and Childress.[i] Even though this ethical approach has become very popular, mostly due to its appeal to common morality and lack of philosophical complexity, it does not allow for the resolution of all ethical questions. Let's see how this approach fares when applied to a complex problem, such as the ethics of treatment of advanced cancer in HIV/AIDS patients.

Autonomy - the idea that every competent person has the right to have a say in his/her treatment - is of course integral to any discussion about patient treatment and certainly relevant to the problem at hand. I do however think that it is usually only tacitly acknowledged when a patient consents to the proposed treatment advice. I argue that issues of autonomy only really emerge when the doctor and patient disagree about the treatment plan.

What happens when a doctor recommends treatment but the patient refuses? In such cases, appeals to beneficence - the ethical imperative of doing good or helping - might be used to counter the principle of autonomy. A third principle, non-maleficence - the first principle in biomedical ethics: "First, do no harm" - might also be brought to bear on the problem. If, for instance, there are clear risks of harm that might outweigh the anticipated benefits, the argument might turn in favour of respecting the refusal of treatment. Invariably, such cases end in an ethical stalemate, since no ethical principle, not beneficence, non-maleficence or autonomy, has overriding authority. Ethical argument then becomes a complex weighing and balancing of principles without clear guidance on how to do so. Refusal of treatment that flies in the face of a doctor's treatment recommendation often damages the therapeutic relationship, which is hardly a successful outcome for either the doctor or patient.

Conversely, what happens when a patient (or the family) demands treatment but the doctor advises against it? In such cases, the autonomy/beneficence/non-maleficence stalemate necessitates appeals to alternative ethical principles. Distributive justice, as the last principle proposed by Beauchamp and Childress, is often appealed to at this point. Distributive justice is a normative principle designed to guide the allocation of the benefits and burdens of economic activity in society.[ii] It is most often conceptualized and concretized as fairness associated with outcomes decisions and distribution of resources. In my opinion, this is very unsatisfactory since distributive justice invariably implies the weighing of benefits and risks to the individual patient against that of the wider community. In the context of scare resources, the individual cannot reasonably expect to be the victor of this exercise. The more relevant ethical consideration seems to be that of futility.

In contrast to distributive justice, the central question of futility judgments is not, "How much money does this treatment cost?" or "Who else might benefit from it?" Instead, it asks: "Does the intervention have any reasonable prospect of helping this patient?" The ethical authority to judge the futility of treatments resides with the

medical profession as a whole, in accordance with general professional standards of care. It does therefore not reside with the individual doctor or the individual patient.

How are futility judgments balanced with appeals to autonomy? “Although the ethical requirement to respect patient autonomy entitles a patient to choose from among medically acceptable treatment options (or to reject all options), it does not entitle patients to receive whatever treatments they ask for. Instead, the obligations of physicians are limited to offering treatments that are consistent with professional standards of care.” [iii]

How are futility judgments balanced with the principles of beneficence/non-maleficence? “The goal of medicine is to help the sick. Physicians have no obligation to offer treatments that do not benefit their patients. Futile interventions are ill advised because they often increase a patient's pain and discomfort in the final days and weeks of life, and because they can expend finite medical resources.” [iii]

Futility judgments should be mindful of the inherent dignity of persons and should therefore be respectful of the patient. This can be achieved through clear, compassionate and effective communication with the patient and the family. It should specify which interventions will be withheld or withdrawn, as well as the rationale for such decisions. At times, it may however be appropriate to temporarily make a futile intervention available to enable the patient or family to come to terms with the situation and reach a point of personal closure.

Futility judgments cannot operate independently, but need to be firmly grounded in acceptable and accountable concepts of social justice. The principles of a socially just society are equality and solidarity, an understanding and commitment to human rights, and recognition of the dignity of every human being in society. [iv] All persons, irrespective of ethnicity, gender, possessions, race, religion, or in this case, illness, are accordingly afforded fair treatment. “The AIDS epidemic…involves, all at once, the main themes of our existence: sex, death, power, money, love, hate, disease, and panic.” [v]HIV/AIDS is often shrouded by perceptions of infidelity, sin, punishment and blame.

In a socially just society, there is no space for prejudice and unfair discrimination. How can we safeguard against this? There have been many theories of social justice that might apply, but the one I will briefly explore is the Theory of Justice developed by John Rawls. Rawls argued that the only way society could decide on principles of fair treatment of its citizens is through a thought experiment he called the “original position” in which everyone decides principles of justice from behind a veil of ignorance. This "veil" is one that essentially blinds people to all facts about themselves that might cloud what their notion of justice is.The original position therefore lies outside society and precedes participation in society. From this position, nobody in society knows what position they will occupy: they have no idea about their gender, race, sexual orientation, socio-economic situation, intellectual capacity, political affiliation, etc. Rawls argued that ignorance of these details about oneself would lead to principles that are fair to all. If people do not know where they will end up in society, they will not privilege any one class of people, but rather develop a scheme of justice that is fair to all.

I have attempted to show that the essence of the arguments about treatment of terminal HIV/AIDS patients is very poorly captured by the four traditional

principles. I argue that wider considerations, such as futility judgments framed by a well-developed sense of social justice, might be better suited to this task

[1] Beauchamp TL & Childress JF. 1994. Principles of Biomedical Ethics, 4th ed. Oxford: Oxford University Press.
[1]Lamont, Julian and Favor, Christi, "Distributive Justice", The Stanford Encyclopedia of Philosophy (Fall 2008 Edition), Edward N. Zalta (ed.). Available from: http://plato.stanford.edu/archives/fall2008/entries/justice-distributive/. [Accessed 20 August 2012].
[1]The World Federation of Right To Die Societies. Available from: http://www.worldrtd.net/qanda/medical-futility [Accessed 23 August 2012].
[1] Zajda J, Majhanovich S & Rust V (eds.). 2006. Education and Social Justice. The Netherlands: Springer.
[1]White E. 1983. States of Desire: Travels in Gay America. Available from: www.bartleby.com/66/20/63920.html [Accessed Feb 2011].

ETHICAL PROBLEMS AND ISSUES IN SURGICAL MANAGEMENT OF CANCER IN HIV/AIDS PATIENTS IN THE HAART ERA: AIDS DEFINING NEOPLASIA

Dr Richard Khanyile-Department of Oncology, University of Pretoria

Introduction

- Malignancy develops in approx 20% ofpts with HIV
- Often is the first evidence of HIV infection
- Leads to 28% of HIV pts death

	Standard incidence	Ratio
Tumor	**Pre-HAART**	**HAART**
Kaposi's sarcoma	**52900**	**3640**
NHL	**79.8**	**49.5**
Burkitt lymphoma	**57.4**	**49.5**
DLBCL	**98.1**	**29.6**
PCNSL	**5000**	**1020**
Crvix	**7.7**	**5.3**
HL	**7.0**	**13.6**
ANUS	**18.3**	**19.6**

KAPOSI'S SARCOMA

- First described by Moritz Kaposi in 1872 as indolent
- It is now clinically aggressive
- Common in young pts
- Associated with human herpes virus-8

KAPOSI'S SARCOMA

- First described by Moritz Kaposi in 1872 as indolent
- It is now clinically aggressive
- Common in young pts
- Associated with human herpes virus-8

Treatment

- HAART is fundamental
- Local therapies: RT, penretin gel, 3% Na+ tetradodecyl sulphate
- ABV
- Paclitaxel
- Liposomal daunorubicin/peg liposomaldoxorubicin
- RT for limited disease

NHL

- DLBCL: 'B' symptoms are common
  Presents with L/adenopathy with/out splenomegaly
  Can present with CNS involvement
  Staging – like any other NHL

- **Poor prognostic features:**

- stage 4
- PS
- CD4 Count ≤ 100 and high viral load
- Hx of OI

- Treatment: CHOP
  CDE/EPOCH
  Relapse: ICE/ESHAP/PBSCT
- BURKITT LYMPHOMA: in the era of HAART
  treat like in HIV negative.
  Be aware of BL-like NHL
- PCNSL: prognosis is poor
  Treatment: HD MTX, WBRT, Steroids

Anal carcinoma

- No improvement in the risk even in the era of HAART
- Don't require immune suppression
- Not AIDS defining
- Treatment depends on PS, CD 4 count, and stage: - Chemo-RT – may need adjustments
  - Chemotherapy - 5FU/cisplatin – stage 4
  - ? Palliative RT alone?

REFERENCES

1. DeVita, Hellman, and Rosenberg's CANCER: Principles & Practice of Oncology, 8th Edition

ETHICAL PROBLEMS AND ISSUES IN SURGICAL MANAGEMENT OF CANCER IN HIV/AIDS PATIENTS IN THE HAART ERA: AIDS DEFINING NEOPLASIA

Prof Leon Snyman-Gynaecological Oncology Unit, Department Obstetrics & Gynaecology, University of Pretoria

Abstract

AIDS defining neoplasia include cervical cancer, Karposi Sarcoma, Non-Hodgkins Lymphoma and. Cervical cancer is a preventable disease, yet it is estimated that up to 10 women day every day of this disease in South Africa.

Human papilloma virus (HPV) infection is a necessary agent in the development of cervical cancer. HPV infection with high risk strains is common in HIV infected patients.

HIV has a negative impact on cervical cancer. Ethical problems that will be discussed include issues with regards to screening HIV infected women for cervical cancer, primary prevention of the disease and treatment related issues.

CHALLENGES IN SURGICAL MANAGEMENT OF NON-AIDS DEFINING CANCER IN HIV POSITIVE PATIENTS

Prof Taole Mokoena- Department of Surgery, University of Pretoria

SUMMARY

The HIV/AIDS pandemic has changed the epidemiology of malignant diseases.

There are emerging cancers previously seen rarely in the general population which have became very common in HIV infected individuals that they have became the hallmark of AIDS eg. Kaposi, non-Hodgkins lymphoma and uterine cervix carcinoma.

There is another category of cancers whose incidence has increased in the HAART era among HIV/AIDS patients. These include anal, lung, liver and Hodgkins lymphoma.

Many of these malignancies are associated with a proven or putative viral aetiology. In this regard vaccines directed at particular viruses such as hepatitis, human papilloma (HPV), may be important adjuncts in populations at risk to prevent respective cancers. Anal squamous cell carcinoma is especially prevalent in homosexual men and in women who practise anal sex and is associated with sexually transmitted HPV. These patient populations must be recruited for regular screening by both PAP cytology and targeted biopsy so that early chemo-radiotherapy may be given. Surgery is reserved for salvage where such treatment has failed.

When any cancer presents in an HIV infected patient, both the stage of the cancer and progression of the HIV/AIDS must be taken into account. It is prudent to start HAART in most patients with clinical cancer before definitive cancer treatment regardless of CD4 lymphocyte count in collaboration with an immune therapist if the cancer presentation does not warrant emergency cancer treatment.

Emergency surgical cancer treatment in HIV/AIDS patients must be approached on their own merits while **exercising compassion** that it might be prudent to **allow a moribund AIDS patient to die in dignity than be subjected to futile surgery.**

The role of surgery in HIV/AIDS associated cancer is largely limited to diagnostic work up or management of complications most being otherwise amenable to chemo/radiotherapy.

INTRODUCTION

The Human Immunodeficiency Virus (HIV) pandemic infection has altered the pattern and incidence of cancer worldwide. There are classes of cancer that are more common in HIV positive patients and these tend to occur at a younger age and are more aggressive compared to the general population.[1, 2]

An approach to surgery for HIV infected patients should recognise three distinct subsets of cancer patients, viz:

i) Acquired Immune Deficiency Syndrome (AIDS) defining malignancies,
ii) non-AIDS defining malignancies associated with HIV infection, and

iii) malignancies occurring generally in any given population that can also be present in HIV infected individuals at no increased incidence in AIDS or the HIV positive population.

AIDS-defining malignancies (ADM) manifest because of the collapse of immune surveillance and cancer immune response. Non-AIDS-defining malignancies (NADAM) have emerged latterly after introduction of combination Anti-Retroviral Therapy (cART) including Highly Active Anti-Retroviral Therapy (HAART).This is attributed to chronic immune inadequacy reflected in part by low CD4 count and to prolonged living of HIV/AIDS patients (Table I).

Table I: Malignancies associated with HIV/AIDS

AIDS Defining
Kaposi sarcoma
Non-Hodgkins lymphoma
Carcinoma of uterine cervix

Non-AID Defining
Hodgkins lymphoma
Lung cancer
Anal cancer
Liver cancer

Spano et al 2008

AIDS-defining cancers have shown a declining incidence in the cART era while there is emerging trend of increased non-AIDS-defining cancer in the HIV positive population.[3]
The risk of non-AIDS-defining malignancies is higher when cART is interrupted (as per current CD4 count based cART treatment regimens) compared to continuous cART administration (Table II).[3]

TABLE II: Interrupted CD4 level based HAART carries more risk for cancer compared to continuous HI Viral Suppression Therapy

		Rate per 1000 py		
Malignancy	No. Patients	IT	CT	pValue
ADM or NADM+6	70	11.6	7.6	0.08
ADM	13	3	0.5	0.04
NADM	58	8.8	7.1	0.04
AIDS Defing				
Kaposi Sarcoma	8	1.9	0.3	
Lymphoma	5	1.1	0.3	
NI Cervix Ca	1	0	0.3	
Non-Aids Defining				
Skin	116	2.2	2.2	
Lung	8	1.7	0.5	
Anal Squamous	3	0.3	0.5	
Hepatocellular	3	0.6	0.3	

HI=human Immunodefieciency; ADM=AIDS-defining malignancy; NADM=AIDS-defining malignancy IT=interrupted therapy; CT=Continuous therapy; py=patient year

Modified from SMART Trail Results: Silverberg et al 2007

In many respects NADM share a similar pattern to therapeutic chronic immunosuppression seen in organ transplant rejection suppression. The management of the latter should be used as a guide to approach NADM in HIV setting.

MANAGEMENT OF CANCER IN HIV INFECTED PATIENTS

Management of cancer in HIV positive patients depends on both the oncological staging of the cancer and the clinical stage of the HIV/AIDS disease process.

HIV positive patients with common NADM malignancies who do not yet have full blown AIDS present a difficult management challenge. The use of CD4 levels for starting HAART is arbitrary but currently forms the basis to determine which patients must first be put on HAART before definitive therapy for malignancy can commence.

The role of surgeons in management of cancer in HIV positive patients involves two aspects viz diagnostic work up, principally to obtain tissue samples for diagnosis, and surgical resection. It seems prudent to start all HIV patients on HAART before starting definitive elective cancer treatment.

Presentation of Malignancies in HIV/AIDS Setting

Maliganancies in HIV/AIDS patients tend to present at a younger age and tend to be more aggressive and therefore present at an advanced stage and progress faster than in the general population (Table III).[1]

TABLE III: TYPICAL PRESENTATION OF HIV /AIDS RELATED CANCERS

AIDS Defining Cancers

- Kaposi Sarcoma:
  Multiple typical skin nodules which in HIV may be exuberant with typical surrounding skin induration. GIT Kaposi often presents with bleeding
- Non-Hodgkins lymphoma (NHL):
  Mass lesion commonly in the clavipectoral region. These may grow surprisingly rapidly to attain large proportions.Tendency to be multinodal. GIT NHL is not uncommon.
- Uterine cervix carcinoma:
  Presents in younger women and progresses rapidly. Diligent PAP smear screening will detect these early when combined cancer specific and HIV therapy can save lives.

Non-AIDS-Defining Cancers

- Hodgkins lymphoma:
  typically more aggressive grades
- Lung cancer:
  tends to be adenocarcinoma rather than squamous cell
- Anal cancer:
  presents in younger principally homosexual males but also young females with HPV infection. Periodic screening with PAP smear diagnoses early lesions
- Liver cancer:
  is associated with HBV/HCV infections. HIV patients with hepatitis virus infection should be screened with alpha-feto-protein. Otherwise patients present too late for cure

Surgical Treatment of Cancer in HIV Infected Patients

Morden treatment of cancer in general involves a multidisciplinary team approach whose minimum members should consist of the surgeon, radiotherapist and medical oncologist. Other desirable members of the team should be nutritionist, physiotherapist, psychologist, social worker and reconstructive surgeon. For HIV positive patients an HIV /immunetherapist should also be recruited.

Cancers whose primary treatment involves a surgical option

The majority of cancers associated with HIV/AIDS are treated by non-surgical means.[1,5]

Anal Carcinoma

Anal Carcinoma is relatively rare. But its incidence has sharply increased with the advent of the AIDS pandemic particularly among homosexual men practising receptive anal sex. There has also been a significant increase in women who also practise anal sex. This anal cancer epidemic parallels that of uterine cervix cancer and is likewise associated with the sexually transmissible Human Papilloma Virus (HPV).[5, 6, 7]

Management approach to anal cancer follows similar principles as uterine cervix cancer. Therefore the primary aim should be prevention and when that fails, early detection and treatment.

Prevention of Anal Carcinoma

The responsible HPV stains for anal cancer have been identified and these overlap greatly with those for cervix carcinoma. The HPV vaccines that have been developed for cervix carcinoma give hope that both cervical and anal cancer may be prevented. Even though these vaccines are in early mass application, the fact that they cover the most commonly found HPV in ano-genital cancer is encouraging.

Other strategies for prevention such as condom use and refraining from multiple partners or risky sexual behaviour for both homosexual or bisexual males and heterosexual women must be encouraged.

Early Detection of Anal Carcinoma

Like for cervical cancer regular screening of populations at risks by Papanicolaou (PAP) smears from anal mucosa can detect early neoplastic changes in asymptomatic individuals. Suspicious PAP smears should be followed up by biopsy, preferably in a targeted manner.[1, 8] Biopsies will direct clinicians to appropriate treatment depending on the grade and extent of the pathology (Table IV).

Table IV: Pathologic evaluation of intraoperative biopsies at the time of first surgery

Pathologic Diagnosis	Number (%)
Normal or inflamamtory changes	10 (5)
LSIL	26 (14)
HSIL	138 (73)
Superficially invasive SCC*	9 (5)
Invasive SCC	5 (3)
Total	188

Pineda[8] et al 2008

Early lesions are amenable to extirpation by surgical and non-surgical means including laser, electrocautery and cryotherapy. Surgical extirpation has the advantage of an operative specimen to confirm histological completeness. However recurrence rate is high after these limited procedures (Table V).

Table V: Incidence of recurrence according to disease extent

Disease extent	*Incidence of recurrence (percent)*	
Circumferential	64	
Extensive		62
Limited		37
P value	0.012	

Pineda et al 2008

Primary treatment of invasive cancer is by chemoradiation.[9] Such treatment gives good long-term results while preserving anal sphincter function. Surgery in this instance is reserved for salvage therapy and entails abdominoperineal resection when chemoradiation has failed.

Management of Gastric Carcinoma in HIV/AIDS Setting

There has been an increase in mucosa associated lymphoid tumour (MALT) associated with Helicobacter pylori infection. This has been reported more increasingly in HIV infected individuals. Their treatment is primarily non-surgical. Eradication of H.pyloric and chemotherapy gives good results and surgery is hardly needed or justified.

A less common association of gastric neoplasm with HIV infection is adenocarcinoma. Its treatment of choice is surgical resection and reported cases have shown good long term results for stage of the disease. [10]

Management of Colorectal Carcinoma in HIV/AIDS Setting

Colorectal carcinoma is unusually reported in HIV infected patients. However when reported it has been found in younger patients who present at an advanced disease stage with "early" liver metastases. Adenocarcinoma tends to present in the right colon in these patients contrary to the general population. Surgical management in this setting should follow the usual principles but surgeons must be aware of increased postoperative complications mainly infection.[11]

Management of Complications of Cancer in the HIV/AIDS Setting

Many of the ADM and NADM may present for the first time with GIT complications or develop these during their non-surgical cancer treatment.

The more common ADM to afflict the GIT are Kaposi and NHL. These may present with haemorrhage, obstruction or perforation. Such complications should be treated according to their own merits. While surgery should be used to improve patient comfort, however in a moribund patient with full blown AIDS it may be more humane not to subject a dying patient to surgical trauma of doubtful benefit and to allow the patient to die with dignity.

References

1. Spano J-P, Costagliola D, Katlama C et al. AIDS-related malignancies: State of the art and therapeautic challenges. J Clin Oncol 2008;26: 4834-4842
2. Angeletti PC, Zhang L, Wood C. The viral aetiology of AIDS-associated malignancies. Advances in Pharmacol 2008; 56:509-557
3. Silverberg MJ, Neuhaus J, Bower M et al. Risk of cancers during interrupted antirectroviral therapy in the SMART study. AIDS 2007; 21:1957-1963
4. Grulich A, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancer in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta analysis Lancet 2007; 370: 59-67
5. Berretta M, Cinelli R, Martellotta F et al. Therapeautic approaches to AIDS-related malignancies. Oncogene 2003; 22:6646-6659
6. Abbasakoor F, Boulos PB. Anal intra-epithelial neoplasia. Br J Surg 2005; 92:277-290
7. Uronis HE, Bendell JC. Anal cancers: an overview. The Oncologist 2007;12:524-534
8. Pineda CE, Berry JM,Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intra-epithelial lesions: A ten-year experience. Dis Colon Rectum 2008; 51:829-837
9. Cleator S, Fife K, Nelson M et al. Treatment of HIV-associated invasive anal cancer with combined chemoradiation. Eur J Cancer 2000, 36:754-758.
10. Manfredi R, Sabbatani S, Fasulo G. HIV-associated early gastric adenocarcinoma sussessfully cured with surgery, and followed up over eight years. Internat J STD & AIDS, 2007,18:501-504
11. Yequez JF, Martinez SA, Sands DR, Sands LR, Hellinger MD. Colorectal malignancies in HIV-positive patients. Am Surgeon 2003;69: 981-987

ETHICAL PROBLEMS AND ISSUES IN SURGICAL MANAGEMENT OF CANCER IN HIV/AIDS PATIENTS IN THE HAART ERA
HIV/AIDS AND CULTURAL DIVERSITY
Dr Elbashir Osman-Department of SurgeryUniversity of Pretoria

Abstract
The HIV/AIDS pandemic and its rapid spread worldwide have brought to light the role of culture and traditions in the way people and health care providers should deal with it. As no cure has yet been discovered for the disease the focus remains, and will continue to be on prevention through health education. Culturally and linguistically diverse communities (CALD) may need diverse health educational messages that are appropriate to their culture.
This article intends to discuss the meaning of culture, cultural diversity, behaviour, and their effect on the HIV/AIDS pandemic
The issues of denialism, stigma, cultural sensitivity and cultural competency are highlighted.
Key words: HIV/AIDS prevention. Cultural diversity. Cultural sensitivity. Cultural competency

Introduction
The HIV/AIDS pandemic and its rapid spread worldwide have brought to light the role of culture and traditions in the way people and health care providers should deal with it. As no cure has yet been discovered for the disease the focus remains, and will continue to be on prevention through health education. Much is written in the literature about the complex and often politically explosive relationship between race, culture, and HIV risk[3].
The fact that transmission of HIV/AIDS is mainly through sexual contacts has necessitated a deep appreciation of peoples understanding of sexual norms and taboos. Health professionals are even more challenged to provide and guide care of people living with the disease and promote adherence to lifelong anti-retroviral medication with all its complications and cost.
The mortality that accompanies the disease questions our preparedness to deal with issues of end of life and care of the dying
In today's world where multiple cultures live together physically, or are brought closer through massive media coverage, a clear understanding of culture is mandatory. Global population mobility and accelerating international migration to high income countries has transformed the demography of most industrialized countries over the last 50 years [1]creating new culturally and linguistically diverse communities (CALD)[5].

Definition of culture
Some argue that culture is not synonymous with ethnicity or religion and calls for a clear distinction between these entities [14]. Many HIV/AIDS prevention programs are often targeted to racial populations. However, it is important to acknowledge that race is socially constructed and heavily influenced by underlying cultural and socioeconomic conditions, such as poverty, discrimination and unemployment, many of which are associated with high risk behaviour[4].
Culture is broadly understood within UNESCO to include: ways of life, traditions and beliefs, representations of health and disease, perceptions of life and death, sexual norms and practices, power and gender relations, family structures, languages and means of communication; as well as arts and creativity[2].

Hufford in 1995 defines culture as everything that human being inherits from one generation to the next that is not passed on biologically [14]. A critical question remains. Are cultures homogeneous? In the sense that, does every individual within a culture

carry the same identical characteristics? Bonnie calls for the use of term cultural diversely to refer both to the diversity among cultures and diversity within cultures[14].Galanti argues that knowing about a certain culture doesn't predict for any given individual's behaviour therefore it is crucial to individualize approach while keeping the cultural background in mind[14].

Culture is an integral part of the individual's identity and high value and emotions are attached to it. In order to facilitate acceptance, culture must be respected and valued. There is a danger that challenging one's norms may be viewed as attacking one's very existence thereby provoking defensive resistance to change.

Every culture has a world view, an understanding how things are, and every world view carries with it a presumption of its own correctness[14].This is even more relevant when it comes to social and sexual behaviour.

Denialism and Stigma

Denialism has never been as strong as with HIV/AIDS. It has been practiced by every entity ranging from nations to communities and, not surprisingly, individuals. Badri believes that American scientists are desperately trying to prove that AIDS originated outside the United States. He wrote "to believe that the gene mutation of HIV took place from green monkeys to Africans, from Africans to Haitians, and from Haitian to Americans in order to avoid the obvious fact that the mutation might have taken place in the rectums of San Francisco homosexuals, is indeed an extremely far-fetched, racist, and unfair way to ward off stigmatism and ease cognitive dissonance [13].

In his address to the International AIDS Conference in Durban, Mbeki reiterated his view that HIV was not wholly responsible for AIDS[9].He likened the mainstream AIDS research community to supporters of the Apartheid regime[10]. Mbeki attacked Makgoba, ablack South African scientist as a racist defender of "Western science" for opposing HIV/AIDS denialism[11].

As a champion of the African renaissance theory, Thabo Mbeki's strong views about the origins of AIDS and its very existence in my opinion were a form of retaliation against the American theory of the African origins of the disease. As a further evidence of denialism among cultural groups, Lekhy reported that South Asian emigrants in Toronto didn't believe that they were at risk because they were not white or gay and they don't use drugs[7].

AIDS-related stigma is a problem for all. It imposes severe hardships on the people who are its targets, and it ultimately interferes with treating and preventing HIV infection[18].Historical examples abound of stigma interfering with effective collective response to diseases ranging from cholera to syphilis to TB. In all of these cases, the social construction of the illness incorporated moral judgments about the circumstances in which it was contracted as well as pre-existing hostility toward the groups perceived to be most affected by it[18]. By attacking AIDS-related stigma, we create a social climate conducive to a rational, effective, and compassionate response to this epidemic" (Herek&Glunt, 1988, p. 890)[18]

On the other hand some believe that stigma helps people avoiding the risky behaviour that is associated with the disease hence the question are there occasions when the mobilization of stigma effectively reduces the prevalence of behaviours linked to disease and death?

Although it contradicted other aspects of his campaign against venereal disease, Surgeon General Thomas Parran, in the 1930s, "advocated that 'syphilis ignorance' be replaced with 'syphilophobia,'" arguing that the fear of syphilis "never killed anyone…never brought a handicapped child into the world, never infected an innocent person" (as cited in Brandt, 1987, p. 155)[18]Badri calls for the use of Islamic terms like

sodomy for homosexuality, adultery for extramarital sex with their strong stigmatizing connotation to inhibit such deviant behaviour. He called upon his fellow Muslim psychologists to refrain from using the rather secular terms like gay and extramarital affairs which express cheerfulness and joviality [13].

Careful attention to the experience of individuals whom society sought to discredit made it clear that those who were the targets of stigmatization had the capacity to resist such efforts[18]. Inother words the stigmatized people may turn the tide and refuse the notion to accept victimhood and stigma. Like in the case of the Treatment Action Campaign (TAC) and the similar organizations, who manage to use the knowledge and the suffering of its members to mobilize the whole country behind its campaign.The use of famous public figures has been identified by some as an important de-stigmatizing factor [19]. Today, AIDS in South Africa is less of a stigma and more of manageable chronic disease.

Power and gender relations

In communities where heterosexual transmission is prevalent, gender relations plays a significant role in determining the role played by culture in prevention or augmentation of the disease spread. In many African and Muslim cultures polygamy is acceptable. In certain Kenyan tribes a widow of a diseased brother will be inherited by the living one. In Nigeria HIV +v women are denied inheritance rights leaving them more vulnerable to engage in risky behavior[20]. Some Muslim sects allow the practice of 'Nikah mut'ah which allows marriage and sexual intercourse with a temporary spouse[6].

Representations of health and disease

What does disease and health mean is diverse among different cultures. This is indeed determines when and where to seek help and treatment. In Southern African cultures the belief in witchcraft and the role of Sangomas (local traditional healers) is undeniably strong. Chinese traditional medicine TCM provides variable descriptions of the workings of the human body and, further, of the connections of the individual body to social, environmental and even cosmological forces. [15]

Many Latinos cultures conceptualize symptoms, disease and treatments in terms of inherent hot and cold qualities, and that treatment is aimed at restoration of appropriate balance between hot and cold in the body .[16]

Moral and religious beliefs among immigrants from Caribbean countries, dictates that AIDS is like a biblical plague, like a retribution for having done something very bad[7]. The same is echoed by Islamic scholars who have stuck to their teachings that AIDS, as a new disease is a form of punishment from Allah to those who deviated from the norms. Their approach to prevention is based on the hadith by the prophet Mohammad "if fahisha or fornication and all kinds of sinful intercourse become rampant and open without inhibition in any group or nation, Allah will punish them with new epidemics and new diseases that were not known to their forefathers and earlier generations [13].

Cultural Competence

Cultural competence is "a set of academic and interpersonal skills that allow individuals to increase their understanding and appreciation of cultural differences and similarities

within, among, and between groups" OSAP 1992 [14]as such then a conscious attention should be paid to acquiring those set of skills. Bonnie[14]explained that the first step is self-awareness that is discovery of our own assumptions and stereotypes and identification of personal and professional goalsand values. The second is nurturing the attitude of acceptance and flexibility.

At a wider scale cultural competence as " a set of congruent behaviours, attitudes and policies, including a consideration for linguistic, socioeconomic and functional concerns that influence behaviour that come together in a system, agency, or among professionals, thus enabling that system, agency or those professionals to work effectively with the target population resulting in services that are accepted by the target population[4], this has been articulated well by the Australian national health and medical research councilframework for cultural competency that covers four dimensions systemic, organizational, professional and individual. These dimensions interrelate so that cultural competence at individual and professional levels is underpinned by organizational and systemic commitment[5]

Cultural competence is an interactive process that requires "a willingness and ability to draw on community-based values, traditions and customs and to work with knowledgeable persons of and from the community in developing interventions and communications, and other supports´ OSAP[14].

AIDS prevention and cultural sensitivity

Are they compatible?

What is for cultural sensitivity?

It may be more effective to develop and implement health education programs that are adapted to a community's existing practices rather than try to change them to fit the program[17].

1. Pragmatic and instrumental reasons

   The AIDS prevention messages seek to modify concepts and attitudes in a given community and as cultural views are perceived to be correct, sensitivity to the existing norms would facilitate effectiveness and prevent rejection of the messages[12]. Condom use is seen as a sign of embarrassment, immorality and corruption in Middle Eastern culture in addition to the importance of fertility and having male children is deeply ingrained in these cultures. Ehsanzadeh-Cheemeh et al concluded that when educating this population, safe sex with condom use as an HIV prevention message must be done within this cultural context[6].

2. Ethical and political

   The basic principle of ethics that individuals should be treated with respect and their dignity should not be violated is by extension applied to culture[12]. A failure to respect the cultural integrity of others is almost always characterized as an imposition of the values of the dominant and powerful on the subordinate and the marginal.

Ronald Bayer argues that cultural sensitivity in its principled conception may prove counterproductive[12]. He found that a profound clash between the goals of public health and the demand that interventions respect group's cultural integrity becomes clear. He cited the example of resistance to condom distribution among high schools students that had been staged by political conservatives, many working and middle class parents, and churches, who they sought todefend their moral and religious views of appropriate sexual behaviour for their children against the forces of secularism[12]. He maintains that if we torespect those points of views, then we put those children at real risk of acquiring the infection. He concluded by stating that homilies about cultural sensitivity should be replaced by a forthright acknowledgement that we can't seek radical behavioural and

normative change while adhering to a dictum that serves principally to protect the status quo. Robert et al reported that when students and teachers from different cultural backgrounds asked about cultural sensitivity, there was unanimity of opinion that materials should be factual and that the facts were the same for every one[19].
Intercultural sensitivity is not natural. It is not part of our primate past, nor has it characterized most of human history. Cross cultural contact usually has been accompanied by bloodshed, oppression or genocide….in seeking a different way; we inherit no model from history to guide us (Bennett 1993, p 21)[14]. Therefor conscious efforts should be made to acquire cultural competency skill through training and continuous engagement with communities to allow for successful culturally appropriate intervention

Conclusion

As a conclusion to the above discussion, educators, professional and organizations in their quest to achieve successful HIV/AIDS prevention interventions may consider that:
Culture can be both a barrier and medium for bringing behavioural change
Cultural views are perceived to be correct, sensitivity to the existing norms would facilitate effectiveness and prevent rejection of the messages
The starting point should be through self-awareness of one's own culture in order to appreciate other's point of view
Cultural competence entails empowering systems, organizations and professionals with the necessary skills to promote and sustain the HIV prevention message
As Cultural competence is continuous process, flexibility and adaptation to different situation is mandatory
Knowing about a certain culture doesn't predict for any given individual's behavior therefore it is crucial to individualize approach while keeping the cultural background in mind.
By attacking AIDS-related stigma, we create a social climate conducive to a rational, effective, and compassionate response to this epidemic
The best advocates for patients remain patients themselves, the role of civil society has never been as strong and influential as in the case of HIV era. The treatment action campaign is a shining example
The universal provision of antiretroviral medication and the resultant prolonging of life of people living with HIV/AIDS, has brought surgeons who initially thought they were not part of heath care providers to HIV patients, closer to these patients.
Finally, whatever medium we use, and in whatever cultural entity, for a message to be effective, facts remain the most important component in that message and people with different background tend to take note of it.

References

1. The World Bank. Country Groups. Available from: http://web.worldbank.org (Cited 22 December 2009.)
2. UNESCO. AIDS and culture: http://portal.unesco.org accessed 16/07/2012
3. Castles S. Ethnicity and globalisation. London: Sage; 2000.
4. Vinh-Thomas P. Bunch MM. Card JJ. A research-based tool for identifying and strengthening culturally competent and evaluation-ready prevention programs.AIDS Education and prevention. 15(6):481-98, 2003Dec
5.

6. McMahon T. Moreton RJ. Luisi BN. Guarding against emerging epidemics: addressing HIV and AIDS among culturally and linguistically diverse communities in NSW,New South Wales Public Health Bulletin. 21(3-4):83-5, 2010 Mar-Apr.
7. Ehsanzadeh-Cheemeh P. Sadeque A. Grimes RM. Essien EJ. Sociocultural dimensions of HIV/AIDS among Middle Eastern immigrants in the US: bridging culture with HIV/AIDS programmes. Perspectives in Public Health. 129(5):228-33, 2009 Sep.
8. Lechky O. Multiculturalism and AIDS: different communities mean different educational messages required.CMAJ Canadian Medical Association Journal. 156(10):1446-8, 1997 May 15.
9. Jones SG. Silitsky C. Mothers' voices: culturally diverse mothers' experiences talking with their children about HIV/AIDSJournal of Cultural Diversity. 11(2):58-64, 2004
10. "Controversy dogs AIDS forum, from the BBC. Accessed 26 Feb 2007. In AIDS denialism in Wikipedia
11. Biography of John Lauritsen at Virusmyth.com, a dissident website. Retrieved 7 September 2006 in AIDS denialism in wikipedia
12. Dugger, Celia (25 November 2008). "Study Cites Toll of AIDS Policy in South Africa". *New York Times*. http://www.nytimes.com/2008/11/26/world/africa/26aids.html. Retrieved 17 December 2008. AIDS denialism in Wikipedia
13. Bayer R. AIDS prevention and cultural sensitivity: are they compatible. A commentary. American Journal of Public Health.vol 84, no6, Jun1994
14. Malik Badri. The AIDS Crisis: An Islamic sociocultural perspective. Book review in the American Journal of Islamic Social Sciences by Sabeena M. Watanabe
15. Bonnie B. O'Conner. Promoting Cultural Competence in HIV/AIDS Care.JANAC Vol. 7,suppl.1,1996
16. Beinfield, H. Krongold, E. Between heaven and earth; a guide to Chinese medicine 1991 New York
17. Harwood, A Ethnicity and medical care. Cambridge, MA: Harvard University Press
18. Airhihenbuwa, C. DiClemente, R. Wingwood, G. Lowe, A. HIV/AIDS education and prevention among African Americans: A focus on culture. AIDS prevetion and Education, 4,267-276, 1992
19. Bayer R. Stigma, Prejudice, Discrimination and Health: Volume 67, Issue 3, August 2008, Pages 463–472
20. Robert S. Gold and Mim A. Kelly: cultural sensitivity in AIDSeduaction: a misunderstood concept. Evaluation and Program Planning, Vol. 14, pp. 221-231, 1991
21. Enwereji E E. Sexual behaviour and inheritance among HIV-positive women in Abia state Nigeria.Tanzania journal of heath research. 10(2): 73-8, 2008Apr