Faculty of Health Sciences

Department of Surgery

CONTROVERSIES AND PROBLEMS IN SURGERY

27TH SYMPOSIUM

04-05 OCTOBER 2024

THEME: “ENDOCRINE AND METABOLIC SURGERY FOR GENERAL SURGEONS IN 2024”

Endocrine and metabolic surgery for general surgeons in 2024.

It is with great pleasure and anticipation that I welcome you to the 27th Annual Controversies in Surgery symposium. We are delighted to have such a diverse and esteemed group of professionals gathered here at the University of Pretoria to engage in what promises to be a thought-provoking and dynamic discussion.
In the ever-evolving field of surgery, we are constantly faced with challenges that test our knowledge, skills, and decision-making. This symposium is designed to explore and dissect some of the most contentious issues in our field—issues that often spark passionate debates and require us to think critically and collaboratively.
We will delve into a range of topics that push the boundaries of conventional thinking. From emerging technologies and innovative techniques to ethical dilemmas and differing clinical practices, our discussions aim to illuminate various perspectives and foster a deeper understanding of the complexities involved in surgical practice.

I encourage each of you to actively participate, ask questions, and share your own experiences. It is through such interactions that we can truly advance our knowledge and improve our practice. Your contributions are invaluable and will undoubtedly enrich our discussions.
As we embark on this symposium, let us approach each session with an open mind and a spirit of inquiry. It is through robust dialogue and a willingness to engage with differing viewpoints that we can find common ground and drive progress in our field.

Thank you for joining us for this important symposium. I look forward to the stimulating conversations and collaborative learning that lie ahead.
Let’s make the most of our time together and embrace the challenges and opportunities that await us.

Welcome to the "Controversies in Surgery" symposium!

Prof Tiaan de Jager
Dean
Faculty of Health Sciences

WELCOME NOTE BY PROF O.D. MONTWEDI

It gives me great pleasure to welcome you all to this 27th Annual Controversies and Problems in Surgery.
The theme for this year is “Endocrine and Metabolic Surgery for General Surgeon”.
We trust you will enjoy and learn from various speakers. I encourage you to robustly debate this issue but with civility.

I would like to thank the speakers for accepting our invitation and doing all the hard work of preparing to present at this symposium.

I should extend a special word of thanks to our regular attendees present here and hope the new comers will also become regulars in future. I am well aware that there are other competing events and I thank you for choosing us over the others.

The Ethics topic “What constitutes negligence in Surgical Practice” is relevant more so now with such a highly litigation society we are dealing with and I hope this will put into perspective some of the neglected aspects of practice we should be paying attention to.
The Symposium would not be possible without the Trade Support, your support of the academic programme cannot go unnoticed. I hope this will strengthen our relationship going into the future.

I would like to express my gratitude and appreciation for members of our department, both academic and support staff, for the effortless preparation of the conference which makes my job light and most delightful!

Prof OD Montwedi

Thank you to our sponsors and exhibitors

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27th ANNUAL CONTROVERSIES AND PROBLEMS IN SURGERY SYMPOSIUM 2024

DATE: ***04 - 05 October 2024***
VENUE: ***Sanlam Centre***
THEME: ***Endocrine and Metabolic Surgery for General Surgeons in 2024***

DAY 1: 4 OCTOBER 2024

TIME	*TOPIC*	*NAME*
07h00 – 08h00	REGISTRATION AND TEA	
	BREAST CHAIRPERSON	Dr Jackson
08h30 – 08h40	Welcome note	*Dean's office*
08h40 – 09h00	Current primary surgery for early Breast cancer	*Dr F Malherbe*
09h00 – 09h20	Management of the axilla in early Breast cancer	*Dr F Malherbe*
09h20 – 09h40	Current primary surgery for T3 Breast cancer	*Prof J Edge*
09h40 – 10h00	Hormones and receptor status in Breast cancer, current status	*Dr N Murugan*
10h00 – 10h20	Approach to apparently benign breast lump in a young woman	*Dr I Buccimazza*
10h20 - 10h50	TEA TIME AND VISIT TO THE STALLS	
	ENCOCRINE CHAIRPERSON	Dr Makgoka
10h50 – 11h10	Surgery for nodular colloid goitre, when and how much?	*Prof T Luvhengo*
11h10 – 11h30	Management of recurrence hyperparathyroidism	*Prof L Cairncross*
11h30 – 11h50	Is there a role for sentinel node biopsy for thyroid cancer?	*Dr I Conradie*
11h50 – 12h10	Comparison of different risk stratification for well differentiated thyroid cancer, which one should we be using?	*Prof S Kinoo*
12h10 – 12h30	Approach to adrenal incidentalomas	*Dr B Jackson*
12h30 – 12h50	Diagnostic workup of endocrine hypertension	*Prof I Bombil*
12h50 – 14h00	LUNCH	
	HPB CHAIRPERSON	Prof Brand/Dr Maluleke

14h00 – 14h30	Management of hepatic metastasis from carcinoid tumours (Nuclear medicine, Endocrine surgeon)	*Prof M Sathekge* *Dr T Kemp* *Prof J Devar*
14h30 – 14h50	Indications for intervention in acute pancreatitis	*Dr S Sardiwalla*
14h50 – 15h10	Management of insulinoma	*Dr T Rampai*
	VASCULAR: CHAIRPERSON	Dr Sikhosana
15h10 – 15h30	Carotid body tumour	*Dr S Morrison*
15h30 – 15h50	Renovascular hypertension	*Dr B Dube*
15h50 – 16h10	Pathophysiology of reperfusion syndrome and current management approach	*Dr S Tsotetsi*
16h10	END OF DAY 1 DINNER: 18H00 FOR 18H30	

DAY 2: 5 OCTOBER 2024

07h30 – 08h00	REGISTRATION AND TEA	
	UPPER GIT: CHAIRPERSON	Dr Maluleke /Kinoo
08h00 – 08h20	Are there any indications for definitive surgery in peptic ulcer disease	*Dr M Phakula*
08h20 – 08h40	Non-operative management of oesophageal cancer, is it an option?	*Dr S Mbatha (UP)*
08h40 – 09h00	Long term outcome of bariatric surgery, is there a difference in different procedures?	*Dr B Mbatha (WITS)*
	COLORECTAL CHAIRPERSON	Dr Ramabulana
09h20 – 09h40	When and what procedure should be done for haemorrhoids?	*Dr M Oyomno*
09h40 – 10h00	Comparison of conventional and complete mesocolic excision for right colon cancer	*Prof D Montwedi*
10h00 – 10h20	Management of a perforated T4 colon cancer	*Dr T Sumbana*
10h20 – 10h40	Long term management of ulcerative colitis, when is surgery indicated?	*Prof M Kgomo*
10h40 – 11h00	Surgical options for management in the full spectrum ulcerative colitis	*Dr L Fourie*
11h00 – 12h00	BRUNCH AND VISIT TO THE STALLS	
	ETHICS CHAIRPERSON	Dr Osman
12h00 – 13h30	Ethics topic: What constitute negligence in surgical practice?	*Prof N Pearce* *Advocate M Makamu*
13h30	CLOSURE	*Prof Montwedi*

Dr F Malherbe
Surgery for primary breast cancer

Breast surgery has a long history, with the Halstead radical mastectomy once being the standard of care in 19th-century medicine. This approach was revolutionary for its time, based on the belief that cancer cells in the breast always passed through the lymph nodes before spreading to other parts of the body. As a result, the surgery involved removing the skin, muscle, sometimes bone, and all nearby lymph nodes in an attempt to prevent metastasis. However, it's important to remember that at that time, no systemic treatments for breast cancer existed, and surgery was the only hope for a cure. Despite this aggressive procedure, the five-year survival rate was only 40%, partly because tumour cells were often dislodged during the operation. Survivors were left with significant scarring and a poor quality of life.

Fortunately, a pioneering surgeon named Dr. Bernard Fisher introduced new concepts and clinical trials that revolutionised breast cancer treatment. Often referred to as the father of modern breast surgery, Fisher's work changed the landscape of breast cancer care. He famously said, "In God we trust; all others must bring data," reflecting his commitment to evidence-based medicine. His landmark NSABP B-04 trial compared outcomes for patients undergoing mastectomy versus those having a lumpectomy plus radiation. After 20 years, the survival rates for both groups were identical. Despite initial resistance, Fisher's findings gained support, notably from the National Women's Health Network, which highlighted mastectomy as an example of sexism in modern medical care in the United States. Fisher's ideas not only became a medical issue but also a political one.

The field of breast surgery has evolved dramatically, with substantial evidence now guiding modern practices. In many high-income countries, breast surgery has become a standalone sub speciality. I examined the indications for mastectomy from the year 2000 to see how they have changed over the last 24 years.

In 2000, the indications for mastectomy included factors that increased the risk of recurrences, such as extensive malignant calcifications visible on mammograms, multiple tumours (both multicentric and multifocal), failure to obtain tumour-free margins, central tumours, physical disabilities that precluded the use of radiotherapy, absolute contraindications for radiotherapy (like pregnancy or previous radiation), relative contraindications (such as SLE or scleroderma), and large tumour size relative to breast size. Patient preference also played a role.

Today, multiple synchronous tumours can often be safely treated with breast-conserving surgery, provided it is technically feasible and achieves acceptable cosmetic results. High-volume breast surgeons should be capable of performing advanced oncoplastic techniques, which are often required. Literature, including a recent scoping review by Yasin, shows no significant difference in overall or disease-free survival between patients with multifocal/multicentric breast cancer and those with unifocal disease as long as the disease can be entirely removed.

Regarding failure to obtain clear margins, current guidelines recommend re-excision if the tumour is on the margin for invasive cancer or if the margin is less than 2 mm for DCIS. Cavity shaves can be employed during initial surgery to improve margin clearance, as demonstrated in a randomised controlled trial published in the New England Journal of Medicine. This trial showed that intraoperative cavity shaves significantly reduced the rate of positive margins and the need for second surgeries.

Central tumours were once considered a contraindication for breast-conserving surgery, but this is no longer the case. Oncoplastic techniques can be used to recreate the breast mound, and various techniques exist to achieve this, including as simple as vertical excision. Tumours that are large in proportion to breast size can now be reduced with neoadjuvant therapy, particularly in

postmenopausal patients or those with HER2-positive cancers, making breast-conserving surgery a viable option.
Patient preference remains important. It is crucial to provide patients with all relevant information about surgical options so they can make informed decisions. A study on factors influencing patient decision-making found that the main reasons for choosing mastectomy over breast-conserving surgery were fear of cancer recurrence, the belief that health outweighs breast retention, and concerns about needing a second surgery for involved margins. However, many patients who initially chose mastectomy indicated that they would have preferred breast-conserving surgery if given a second chance.

In 2024, the primary indications for mastectomy include widespread disease that cannot be removed, failure to obtain clear margins, physical disabilities that prevent the use of radiotherapy, absolute contraindications to radiotherapy, and relative contraindications like scleroderma.

A study investigating the trend in mastectomy rates in the United States from 2005 to 2017 showed a decrease in mastectomy rates and an increase in contralateral prophylactic mastectomy, even though breast-conserving surgery has been proven safe. A recent meta-analysis of 35 observational studies involving nearly one million patients found that breast-conserving surgery with adjunct radiotherapy was associated with better survival than mastectomy. Breast-conserving surgery should be the first choice for treating breast cancer when possible.

The benefits of breast-conserving surgery extend beyond improved survival. It is associated with a lower complication rate, shorter hospital stays, and a reduced need for medication. Patients often experience faster recovery, return to work and social life sooner, and avoid the need for breast reconstruction, which carries a higher complication rate and often requires multiple surgeries. Furthermore, if radiation therapy is needed for the reconstructed breast, the risk of long-term complications and poor cosmetic outcomes increases.
However, in resource-constrained environments like South Africa, where 85% of the population lacks access to private healthcare, radiotherapy is not always available, and surgery lists are limited. Many patients present with advanced-stage disease, making breast-conserving surgery less feasible. A study conducted by one of my students, Laurie Mulligan, highlighted the challenges in South Africa, where only 80% of hospitals offer breast-conserving surgery and access to specialised techniques like sentinel node biopsy is limited.

Despite these challenges, breast-conserving surgery should be prioritised, and proper training is essential. In South Africa, mastectomy remains the most commonly performed operation, and there is a need to focus on improving surgical skills, especially in performing oncologically sound and aesthetically pleasing mastectomies.
Advanced oncoplastic mastectomy techniques, such as skin-sparing and nipple-sparing procedures, require a significant learning curve. For example, the Goldilocks mastectomy offers a simpler alternative for public sector patients, allowing general surgeons to achieve good results without using prostheses.

In conclusion, breast-conserving surgery is the preferred option for many reasons, including better survival and fewer complications. However, it requires more training and resources, which are limited in many parts of the world. As surgeons, we must strive to provide patients with the best possible care, whether through breast-conserving surgery or mastectomy, adhering to oncological principles and aiming for optimal cosmetic outcomes.

Dr F Malherbe

The Management of the Axilla in Early Breast Cancer

The management of the axilla in early breast cancer has undergone significant changes over time, driven by a deeper understanding of breast cancer metastasis, the various subtypes of the disease, and their different responses to chemotherapy. With improvements in survival rates, many breast cancer patients report that their quality of life is significantly impacted by the long-term side effects of axillary lymph node dissection (ALND). Given these challenges, it is crucial to reconsider why axillary surgery is still performed. Primarily, axillary surgery is diagnostic, aimed at assessing whether metastasis has occurred and determining the extent of nodal involvement. This information is vital for guiding both local and systemic adjuvant treatments and is a strong determinant of prognosis. Additionally, axillary surgery removes disease to aid local control, although this is more of a secondary benefit.

A critical question is whether axillary surgery affects survival outcomes. According to data from the NSABP-04 trial, for node-negative patients, the type of axillary management—be it axillary clearance, axillary radiation, or mere observation—does not impact survival after ten years. This finding is consistent even for node-positive patients, as axillary clearance and axillary radiation do not affect survival. Further supporting this, a meta-analysis titled "An Overview of Axillary Treatment in Early Breast Cancer: Patient-Level Meta-Analysis of Long-Term Outcomes" was conducted in 2024. This comprehensive analysis included data from 20,000 women across 29 randomised controlled trials between 1958 and 2009, with a median follow-up of 10 years. The results showed no significant differences in the risks of distant recurrence, breast cancer mortality, or all-cause mortality based on the extent of axillary treatment when comparing axillary clearance to radiotherapy.

In terms of sentinel lymph node biopsy (SLNB) techniques, it is standard practice for the tracer to be injected the day before surgery. A single tracer is typically sufficient; additional scintigraphy is only necessary if the patient has undergone previous surgery. There is growing support for the idea that routine scintigraphy should be discontinued for most patients, as it does not provide additional benefits beyond increasing costs. It is essential to distinguish between false-negative results in SLNB—when the sentinel node appears clear of metastasis, but other nodes are affected—and true negatives, where no metastasis is present.

The first important step in the management of a newly diagnosed breast cancer is usually the decision of which patient will require new adjuvant chemotherapy. Neoadjuvant chemotherapy is often indicated for specific subtypes of breast cancer, including triple-negative, HER2-positive, or node-positive premenopausal breast cancers. Conversely, postmenopausal luminal breast cancer patients with node-positive disease and a low recurrence risk, as well as those with HER2-negative luminal breast cancer, generally do not require chemotherapy and instead undergo upfront surgery.

For patients who are clinically node-negative and scheduled for upfront surgery, SLNB remains the standard of care. This procedure has proven highly feasible and accurate, with identification rates exceeding 97% and false-negative rates below 10%. SLNB also offers significant advantages over ALND, including reduced arm morbidity, lower rates of lymphedema, fewer sensory deficits, and an overall improvement in quality of life. However, there are instances where patients are clinically node-negative but are later found to be pathologically node-positive on final histology. This scenario occurs in approximately 20-30% of patients. Initially, ALND was recommended for complete staging and regional control in all patients with positive lymph biopsies. However, it has since been recognised that many patients with clinically node-negative disease and positive lymph biopsies have only low-volume nodal disease. Trials such as ACOSOG Z0011, AMAROS, and IBCSG 23-01 have provided evidence that axillary recurrence rates and overall survival are similar whether a completion axillary dissection is performed or axillary radiation is given instead.

In patients with a clinically node-positive axilla undergoing upfront surgery, the ongoing TAXIS trial (Tailored Axillary Surgery) investigates whether limited axillary surgery, combined with planned adjuvant radiotherapy, can safely replace ALND in patients with clinically palpable disease. The results of this trial are anticipated to guide future axillary management strategies. This scenario usually applies to luminal post-menopausal node-positive patients, representing a lower-risk group.

The question of whether SLNB should be performed before the initiation of neoadjuvant chemotherapy is also under review. Performing SLNB before chemotherapy can lead to a significant loss of predictive value regarding the response of the axilla. Additionally, repeat SLNB after chemotherapy has proven unreliable, with identification rates as low as 60% and false-negative rates as high as 51%, as seen in the SENTINA trial. This practice could unnecessarily commit patients with initially positive nodes to completion ALND following neoadjuvant chemotherapy, which might not be needed.

In patients that are node negative before new adjuvant chemotherapy a SLNB can be performed in the standard way after new adjuvant chemotherapy. The main question is whether it is necessary to do a frozen section and proceed to an axillary lymph node dissection if the frozen section is positive. Trials have shown that the SLNB positive rate in these patients is very low in the region of 2 to 3%. Therefore, the axillary node dissection can be performed as a separate surgery once the final histology is known. This means a second surgery where an ALND is performed would be necessary. An alternative would be axillary radiotherapy, which is currently not standard practice because evidence is lacking, but I do believe that future trials will prove that radiotherapy is as effective as axillary lymph node dissection.
The most difficult scenario is patients who are clinically node-positive but convert to clinically node-negative after new adjuvant chemotherapy. Trials have shown that performing a standard SLNB technique leads to very high false negative rates and an adjusted technique is, therefore, necessary. The two options are to either do targeted axillary dissection, where the abnormal node is marked before chemotherapy is started and the marked node is then removed with SLNB nodes. Or the technique that is used in most high-volume breast centres at the moment is to use a dual technique of blue dye and a radiotracer and remove a minimum of three nodes. With this technique, the false negative rate should be around 4%, nearly equivalent to targeted axillary dissection.

Currently, there is very little evidence of what to do in node-positive breast cancers that receive neoadjuvant endocrine treatment because neoadjuvant endocrine treatment is usually used in lower-risk luminal post-menopausal patients. These patients can potentially undergo limited axillary surgery, as is currently investigated in the TAXIS trial, or these patients can receive an axillary lymph node dissection.
Recent findings have further supported the decision to omit axillary surgery in some instances. The ongoing SOUND trial, which enrolled 1,463 women with breast cancer up to 2 cm in size and negative preoperative axillary ultrasound, compared SLNB to no axillary surgery. The results confirmed that axillary surgery could be safely omitted in selected patients without adversely affecting outcomes. Five-year distant disease-free survival rates were comparable, and the cumulative incidence of isolated axillary recurrences was low.

In summary, the management of the axilla in early breast cancer is continuously evolving as new evidence emerges. Frozen sections are now rarely necessary in 2024, and targeted axillary dissection is increasingly considered unnecessary due to its limited benefits. The approach to axillary surgery is increasingly being tailored to the biology of the tumour and patient-specific factors, with a more conservative approach being considered, particularly for elderly patients or those with small tumours. As research progresses, the trend toward less invasive strategies for managing the axilla in breast cancer patients is likely to continue, further improving the balance between treatment efficacy and quality of life.

Current Surgical management for T3 breast cancer
Prof Jenny Edge
Dept surgery
University Witwatersrand

Definition
T3 breast cancer implies the primary lesion is > 5 cm with no skin nodules/ulceration/peaud'orange.
Skin tethering over the lesion is included in the definition of T3

Assessing a T3 lesion
All patients with a T3 lesion should have a staging CT scan regardless of their axillary status as systemic metastases must be excluded (The CT must include chest and abdomen to exclude mets to lung, liver and bone)
The axilla should always be assessed thoroughly as it may rule out surgery.

The remainder of this chapter will concentrate on management of the primary breast lesion as the decision about the management of the axilla is an independent decision.

THE BEST PRIMARY SURGICAL MANAGEMENT FOR T3 CANCERS IS NEOADJUVANT SYSTEMIC THERAPY

Systemic therapy is always recommended for T3 lesions and should be given as neoadjuvant therapy (rather than adjuvant therapy) as:
The response to systemic therapy can be assessed,
Further systemic chemotherapy can be given as adjuvant therapy if indicated
Downsizing the tumour may make surgery technically easier and may allow a patient to have breast conservation (BCS) rather than a mastectomy

Choice of Neoadjuvant therapy

Broadly speaking, systemic therapy falls into the following categories:
Chemotherapy (NAC)
Targeted therapy (including immunotherapy and Trastuzumab)
Endocrine therapy

The choice of which systemic therapy depends on

1. ***Molecular subtype of cancer.*** **Breast cancers are classified (according to ER, PR, HER2 and Ki67%) into 4 broad groups:**

   Luminal A (ER+ PR+ HER2 – Ki67<14%)
   Luminal B (ER+ PR+ HER2 – Ki67 >14%)
   HER2 enriched cancer (ER+/-, PR+/-, HER2+, Any Ki 67)
   Triple negative breast cancer (ER- PR- HER2 – And Ki67)

2. ***Menopausal status of the patient.***
   Most studies evaluating the efficacy of Neoadjuvant Endocrine Therapy (NET) have assessed the response in post-menopausal women who have been given an aromatase inhibitor. (AI)
   There is very little data on giving Tamoxifen as NET.
   If neoadjuvant therapy is the preferred systemic treatment in a premenopausal woman, Goseralin (Zoladex) be given with an aromatase inhibitor

3. ***General medical status of the patient***

   The most commonly used chemotherapy regimens are based on an anthracycline. The major side effect of anthracyclines is cardiac toxicity. This is dose dependent, irreversible and is limiting. Oncology centres vary but many require an ECHO before starting chemotherapy. The alternative would be to use the older CMF regimen.
   Taxanes are generally used as second line drugs and are less cardiotoxic.
   Trastuzumab is tolerated better than chemotherapy as it is a targeted agent but can also cause cardiac toxicity which is generally reversible.

   The major side effect of AIs is loss of bone density. Ideally all patients should have a bone density scan before starting AIs and be given Ca and Vit D supplements. However, the side effect that causes patients to stop their AI is arthralgia

   Tamoxifen can cause thrombogenic effects which limits its use.

4. ***Patient preference***
   Some patients refuse to have chemotherapy. They must be fully informed about the consequences of their decision.

5. **The *age* of the patient should be the last consideration.**

Response to Neoadjuvant treatment.

Ideally all patients should be evaluated radiologically just before the end of their chemo regimen to assess their suitability for surgery.

If endocrine therapy is given, they should be assessed after 4 months (to check there is no progression of disease) and then after 9 months. The ideal time for operating on patients after NET is between 9-18 m as the tumour often starts growing after 18m of endocrine therapy.

The response to neoadjuvant therapy should be quantified using the RECIST criteria:

Response:
Complete, partial, progression and stable
Means of evaluation:
Clinical, Radiological, Pathological

Surgical options (breast)

Surgery should not be considered for any patients who will not be able to get clear margins. This is uncommon unless a patient has T4 disease.

The default operation for all patients with operable breast cancer should be breast conservation surgery (BCS) and mastectomy should be performed if there is a contra indication.
Prior to starting neoadjuvant therapy, all patients should have their tumours marked with a clip as there may be a complete radiological response making BCS impossible if the tumour bed has not been marked.

NB:- Only the residual footprint of the post NAC/NET tumour should be removed
Cavity shaving increases the rate of negative margins

The only absolute contraindication to a mastectomy is patient choice

Relative contraindications to BCS include:

- Multiple synchronous lesions
- Estimated excision > 30%
- BRCA positivity
- Carcinoma that does not show up on mammogram easily and MRI not available
- Contraindication to Radiotherapy

All surgery to the breast should follow oncoplastic surgery principles
Oncoplastic surgical procedures fall into 2 groups:

- Level 1 oncoplastic procedures: 90% of BCS can be done using level 1 procedures

Surgery is done on the side of the cancer alone.
There are 7 steps:

- Planning
- Incision
- Developing parenchymal flaps
- Excision of the tumour
- Clipping of the base
- Approximation of the parenchymal flaps
- Closure of the skin

The incision depends on the size and position of the tumour.

- Level 2 oncoplastic procedures:

The cancer should be removed according to Level 1 principles.
These techniques are reserved for situations where there will be marked asymmetry after surgery. They are often done in conjunction with a plastic surgeon.
There needs to be either:

- volume replacement on the side of the cancer with a local flap/prosthesis
- volume displacement on the contralateral breast. (Usually a cosmetic reduction)

In summary

The best primary management for a patient with a T3 tumour is systemic.
Surgery to the breast should be offered appropriately depending on the response.
Although surgery to the axilla has not been discussed here, thorough evaluation of the axilla must be done before considering what procedure is relevant

Further reading and references:
St Gallen Guidelines 2017
ESMO guidelines
NCCN guidelines

Dr Nivashini Murugan

Hormones and receptor status in Breast cancer

Introduction

Breast cancer is the most commonly diagnosed cancer globally and remains the leading cause of cancer-related deaths among women in both high and low-income countries.[1] A highly heterogenous disease, breast cancer is driven by a combination of genetic, environmental, and lifestyle risk factors that influence its onset and progression. Breast cancer assessment has historically relied on tumour traits such as histopathologic type, grade, size, lymph node status, and the presence of distant metastases. However, with advancements in tumour biology and the discovery of prognostic and predictive biomarkers, there has been a significant improvement in diagnostic precision and the ability to tailor treatments to individual patients. Undoubtably, the understanding of the pivotal role of hormones and tumour receptors has revolutionized modern breast cancer management, offering insights into disease behaviour and responses to therapy.

The endogenous steroid hormones, oestrogen and progesterone, produced by the ovaries, play critical roles in the physiological development and regulation of breast tissue. Oestrogen stimulates the growth and proliferation of breast cells, promoting ductal development and overall tissue growth, especially during puberty and the menstrual cycle. Additionally, oestrogen is responsible for the regulation of gene expression in cell cycle progression and apoptosis in breast tissue.[2]

Progesterone, primarily involved in regulating the menstrual cycle and pregnancy, also complements the effect of oestrogen in breast tissue by promoting the differentiation of breast cells and the development of lobules, which are essential for milk production.[2] However, these hormones have a dual influence on both the normal development of breast tissue and carcinogenesis, by allowing the proliferation of abnormal cells within the breast tissue. Prolonged exposure to high levels of estrogen and progesterone, such as with hormone replacement therapy (HRT) or certain contraceptives, has been linked to an increased risk of developing hormone receptor-positive breast cancers.[3]

The mechanisms by which oestrogen and progesterone potentiate cancer growth include the activation of oestrogen receptors (ERs) and progesterone receptors (PRs) in breast cells. The binding of oestrogen or progesterone to their corresponding receptors triggers a cascade of complex intracellular signalling events that regulate cell proliferation and prevent cell death. If oestrogen levels are too high or progesterone signalling is impaired, these pathways can become disrupted, potentially leading to unchecked cell growth and tumor development.[4]

Furthermore, hormonal imbalances can also affect the microenvironment of breast tissue. For instance, oestrogen encourages the formation of new blood vessels and boosts the production of growth factors, which can support tumour angiogenesis and the spread of cancer cells[5]. Additionally, oestrogen can alter the immune response within breast tissue, possibly affecting the immune system's ability to detect and eliminate tumours, thereby aiding the cancer in evading immune surveillance.[5]

The role of Receptors in Breast Cancer:

These receptors are proteins expressed by mammary cells, utilized as tumour molecular biomarkers, that are activated by circulating hormones. The predominant receptors assessed in breast cancer are the ER, PR and Her2 receptors.
The molecular characterization of breast cancer using ER, PR, HER2 as well as the Ki67 index has led to increased diagnostic accuracy, more personalized treatment as well as the ability to predict future disease behaviour. This has dramatically changed the landscape of how breast cancer is managed.
As such, the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual now recommends combining traditional anatomical staging with biological markers, such as ER, PR, HER2, and multigene assays, to establish a Clinical Prognostic Stage Group.[6]

Oestrogen (ER) and Progesterone (PR) Receptors

The oestrogen receptor (ER) was one of the earliest biomarkers to be studied in breast cancer and is expressed in approximately 70-84% of breast cancer cases.[7]
The oestrogen receptor (ER) has two main forms: ERα and ERβ. Among these, only ERα has a confirmed clinical significance, as it is present in 70–75% of breast cancer cases[7].
Oestrogen receptor (ER) positivity in breast cancer is typically associated with a more favorable prognosis, though this predictive value can be influenced by the histologic grade and stage of the tumor.[7] Therefore, accurately determining ER status is crucial for making informed treatment decisions in breast cancer patients.
The Progesterone receptor (PR), an ER dependent gene product, is a molecular protein expressed in about 75% of ER + breast cancers.[7] Oestrogen and progesterone are closely linked in the development and progression of breast cancer. Oestrogen signaling through its receptor (ER) promotes the expression of progesterone receptors (PR) in breast cancer cells. This interaction increases the cells' responsiveness to progesterone, potentially amplifying its role in cell proliferation.
Conversely, the PR is also implicated in oestrogen signaling by modulating the expression of the ER, effecting the transcriptional activity of the ER and subsequently its impact on cell growth and survival.[8]
To enhance the accuracy and reliability of ER and PR testing, the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) released guidelines in 2010 which state that breast cancer is classified as ER-positive if 1% to 100% of tumor cell nuclei show positivity using immunohistochemistry (IHC).
In 2020, ASCO/CAP revised these guidelines specifically for ER reporting. If 1-10% of tumor nuclei are positive, the sample should now be classified as ER Low Positive. The updated guidelines also recommend ER testing for newly diagnosed ductal carcinoma in situ (DCIS) cases without invasive components, while PR testing is considered optional.[9]
The primary clinical importance of testing for receptors—such as ER, PR, HER2—and the Ki67 index in breast cancer is to identify patients who are likely to benefit from endocrine therapy, whether it is administered in the neoadjuvant, adjuvant, or palliative setting. Additionally, these receptors have predictive and prognostic significance in that ER+/PR+ tumours are associated with better survival rates and a reduced risk of recurrence within the first five years following treatment.[10]

Human Epidermal growth factor Receptor 2 (HER2)

HER2 is a glycoprotein located on the cell membrane with tyrosine kinase activity. It is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. The HER2 protein receptors on breast cells regulate their normal growth, division, and repair. However, if the HER2 gene malfunctions, it can lead to gene amplification, causing excessive replication or HER2 over-expression. This in turn leads to increased cell proliferation and tumorigenesis.
Around 15-20% of breast cancers are HER2-positive, and this subtype is more commonly seen in ER-negative breast cancers.[11] HER2 protein overexpression can be identified using immunohistochemistry (IHC), while HER2 gene amplification can be detected through fluorescence in situ hybridization (FISH).[11]
Possessing HER2 overexpression is considered an adverse tumour characteristic and is associated with higher nuclear grade and mitotic count, more lymph node involvement, increased resistance to endocrine therapy and an overall poorer prognosis. However, this has also facilitated the development of specific treatment targeting Her2 receptors which has significantly improved the clinical course of HER2-positive breast cancer.[12]
Currently, HER2 evaluation is primarily used to predict the response to anti-HER2 therapy in both neoadjuvant and adjuvant settings.

Ki67 Index

Ki67 serves as a marker for cell proliferation, detectable in all phases of the cell cycle except G0 and is measured by the percentage of tumour cells that show antibody staining. This marker is often correlated with tumour grade and biological behaviour, with higher Ki67 levels generally linked to poorer prognosis[13]. While many studies support this association, some have found no significant connection between Ki67 levels and outcomes like disease-free survival (DFS) or overall survival (OS)[14]. Despite its association with prognosis, Ki67 has not been established as a reliable predictor for chemotherapy benefits in the adjuvant setting. However, in the neoadjuvant context, high Ki67 levels might indicate a better response to chemotherapy, whereas lower levels might suggest a greater benefit from endocrine therapy[14]. Currently Ki67 assessment has become standard practice, and tracking its levels at different stages of treatment could potentially help predict how breast cancer patients will respond to specific therapies.

Molecular Classification of Breast Cancer:

Breast cancer is classified into several molecular subtypes based on gene expression profiles. These subtypes are important for determining prognosis and guiding treatment decisions. The main molecular subtypes of breast cancer are:

1. Luminal A:
    - Characteristics: Oestrogen receptor-positive (ER+), progesterone receptor-positive (PR+), HER2-negative, and low levels of Ki-67 (≤20%).
    - Prognosis: Considered to be indolent and slow growing, good response to endocrine therapy
    - Treatment: Often treated with hormone therapy (e.g., tamoxifen, aromatase inhibitors).
2. Luminal B:
    - Characteristics: Oestrogen receptor-positive (ER+), may be progesterone receptor-positive or negative (PR+/−), can be HER2-positive or negative, and higher levels of Ki-67 than Luminal A.(Ki67 >20%)

    - Prognosis: More aggressive than Luminal A but still responsive to hormone therapy.
    - Treatment: Often treated with a combination of hormone therapy, chemotherapy, and HER2-targeted therapy if HER2-positive.
3. HER2-enriched:
    - Characteristics: HER2-positive, oestrogen receptor-negative (ER−), and progesterone receptor-negative (PR−).
    - Prognosis: More aggressive but can respond well to HER2-targeted therapies like Trastuzumab (Herceptin) and Pertuzumab.
    - Treatment: HER2-targeted therapy, chemotherapy, and sometimes hormone therapy if there is low ER expression.
4. Triple-negative (Basal-like):
    - Characteristics: Oestrogen receptor-negative (ER−), progesterone receptor-negative (PR−), HER2-negative.
    - Prognosis: Generally, has the worst prognosis and is the most aggressive subtype. Lacks targeted therapies, making treatment more challenging.
    - Treatment: Primarily treated with chemotherapy, although newer targeted therapies and immunotherapies are being explored.

These molecular subtypes are determined through various methods, including immunohistochemistry (IHC) and gene expression profiling. They help in tailoring treatment approaches to improve outcomes for patients with breast cancer.[15]

Uncommon Subtypes:

- **Oestrogen receptor positive (ER+)/Progesterone receptor negative (PR-) Cancer[17]**

Oestrogen receptor-positive/progesterone receptor-negative (ER+/PR-) breast cancer is a distinct subtype that has been reported to occur in about 10-20% of cases according to various studies[16]. This subtype suggests a functional blockade in the oestrogen receptor (ER) signalling pathway, making these tumours biologically more aggressive than their ER+/PR+ counterparts. Data from the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database (NCDB) highlight that ER+/PR- tumours constitute approximately 11.5-13.7% of all ER+ breast cancers. These tumours often exhibit more aggressive clinicopathologic characteristics, such as HER2 positivity and higher histologic grades, and are more prevalent in older patients and African Americans when compared to other subtypes.[17]
The clinical behaviour of ER+/PR- tumours indicates a worse prognosis compared to ER+/PR+ tumours, but they fare better than ER-/PR- cancers. The reduced progesterone receptor (PR) expression in ER+ tumours is thought to signal a blockade in functional ER signalling, which may contribute to the observed resistance to endocrine therapies, particularly selective oestrogen receptor modulators (SERMs) like Tamoxifen. However, studies have shown that treatment with hormone-blocking agents, particularly aromatase inhibitors, significantly improves overall survival in patients with ER+/PR- tumours, underscoring the importance of effective therapy. Despite this, a notable proportion of patients do not receive optimal endocrine treatment.[17]
Research into the biology of ER+/PR- tumours reveals complex mechanisms behind their aggressiveness and resistance to endocrine therapy. There is evidence of increased growth factor signalling, such as HER2 overexpression, contributing to the resistance observed with SERMs. This has led to a growing consensus that different therapeutic strategies

may be necessary for ER+/PR- tumours compared to ER+/PR+ tumours, highlighting the need for further investigation to develop more targeted and effective treatments.

- **Oestrogen receptor-negative/progesterone receptor-positive breast cancer**[17]

The existence of the ER-/PR+ breast cancer subtype has been a topic of debate due to the fact that PR is typically an ER-dependent gene product. Initially, some studies dismissed this subtype as a technical artifact caused by issues like improper tissue fixation or errors in immunohistochemical testing. However, recent studies adhering to strict ASCO/CAP guidelines have confirmed the presence of this rare subtype, which is now recognized as a distinct entity with unique molecular and clinical features. Its incidence is low, ranging from 1-4% in large cohorts, with some variations observed in specific populations. Patients with ER-/PR+ tumors tend to be younger and include a higher proportion of African Americans compared to other subtypes. Clinically, these tumors are often of a higher grade, which correlates with a more aggressive disease course. Despite the rarity of this subtype, it has been shown to respond to both chemotherapy and endocrine therapy, similar to other hormone receptor-positive tumors. Interestingly, ER-/PR+ tumors have been linked to specific molecular mechanisms, such as mutations in the ER gene's ligand-binding domain, which may explain the presence of PR expression in the absence of ER activity.
Given its distinct biological behavior and response to treatment, the ER-/PR+ phenotype should not be overlooked in clinical practice. Current guidelines, including those from the National Comprehensive Cancer Network (NCCN) and the St. Gallen Consensus, recommend treating these tumors similarly to other hormone receptor-positive subtypes. However, further research is needed to better understand the molecular mechanisms underlying this subtype and to refine treatment strategies accordingly.

- **Estrogen receptor-low-positive breast cancer**

The criteria for determining oestrogen receptor (ER) positivity in breast cancer have undergone significant changes over the past few decades. However, the advent of immunohistochemistry (IHC) in the 1990s, along with the development of sensitive monoclonal antibodies, significantly improved the accuracy and diagnostic value of ER and progesterone receptor (PR) testing. As a result, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommended in 2010 that a 1% cutoff for ER positivity should be used to guide the consideration of endocrine therapy.[18]
Despite the advances in testing, defining an optimal ER expression cutoff to determine which patients will benefit from endocrine therapy remains controversial. The 2020 ASCO/CAP Guideline Update indicated that there was no significant survival benefit from endocrine therapy in patients with ER-low (around 1%) and PR-negative tumours. These findings highlighted the challenges in using low ER expression levels to predict therapeutic outcomes, especially when considering the improvements in chemotherapy and HER2-targeted therapies over recent years. The data suggested that for patients with ER-low tumours, a combination of chemotherapy and endocrine therapy might be more beneficial, prompting calls for further prospective studies to validate these findings and refine treatment strategies.[17]
The ongoing debate underscores the complexity of breast cancer treatment, particularly in cases with low ER expression. While the shift to a 1% cutoff has allowed more patients to be considered for endocrine therapy, the clinical benefits for those with minimal ER expression are still unclear. Further research is needed to establish standardized treatment

protocols for these patients, ensuring that they receive the most effective therapy tailored to their specific tumour biology.

Conclusion

The evolving understanding of hormones and their receptors has fundamentally reshaped the approach to breast cancer treatment and prognosis. The identification and characterization of oestrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) have provided critical insights into the biological behaviour of breast tumours, guiding therapeutic decisions with increasing precision.

The recognition of distinct breast cancer subtypes based on receptor profiles, such as ER+/PR+, ER+/PR-, ER-/PR+, and triple-negative (ER-/PR-/HER2-), underscores the heterogeneity of breast cancer and the necessity for tailored treatment regimens. While ER-positive tumours generally respond well to hormone therapies, emerging evidence suggests that ER-low and ER-/PR+ subtypes may require combined therapeutic approaches, integrating endocrine therapy with chemotherapy or targeted therapies like HER2 inhibitors. Ultimately, the updated understanding of hormones and receptors in breast cancer not only enhances therapeutic outcomes but also fosters a more individualized approach to patient care, paving the way for improved survival and quality of life for breast cancer patients.

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Surgery for nodular colloid goitre, when and how much?

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Abstract: Nodular colloid goitre (NCG) or nodular thyroid disease is common especially in females. Causes of NCG are not limited to iodine deficiency but include genetic predisposition and environmental factors. Presentation of NCG vary and may include hyperthyroidism or mass effect. Management of patients with NCG depends on the functional status, nature of goitre and fitness. Surgery is the mainstay of treatment of NCG and it should be tailored to a patient. Although total thyroidectomy should be the preferred surgical option bilateral subtotal thyroidectomy and the Dunhill procedure including lobectomy for solitary colloid nodule are appropriate (Cirocchi et al., 2015). The choice of surgery balances the risk of surgical complications especially permanent hypoparathyroidism with the likelihood of recurrence and necessity for re-do surgery.
Key words: Colloid goitre, indications, management, surgical options

Introduction

Thyroid nodules are common especially in adult females (Hoang et al., 2015; Fernandes et al., 2022; Jacome et al., 2023). Although over 90% of thyroid nodules are benign malignancy must always be ruled-out. Initial clinical evaluation and diagnostic investigations must prioritize a determination of whether the nodule(s) is/are hyperfunctional as malignancy is less likely if the nodule is/are hyperfunctioning but regardless of functional status a possibility of thyroid malignancy must always be considered (Fernandes et al., 2022). Family history, history of neck irradiation, change of voice and enlarged cervical lymph nodes should be considered suspicious of malignancy, and be subjected to a minimum requisite diagnostic investigation. The minimum diagnostic investigations must include thyroid function test (TFT) and ultrasound (US) with or without fine needle aspiration cytology (FNAC) (Vahdati et al., 2024). A benign result in patients with worrisome history and clinical findings must never be accepted. Should not be accepted. Application of artificial intelligence (AI) has improved preoperative work-up of thyroid nodules (Vahdati et al., 2024).

Majority of thyroid nodules are benign and around 60% of thyroid nodules are follicular nodular thyroid disease due to absolute or relative iodine deficiency, a condition previously erroneously called multinodular goitre (Ghartimagar et al., 2020; Goswami et al., 2024). The term was misleading as goitre due to iodine deficiency may, although rare be unilateral and solitary. Additionally, chronic autoimmune thyroiditis, tuberculosis (Kindie et al., 2024) and thyroid malignancies may present as multinodular goitre. Papillary thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma and primary thyroid lymphoma may present as multinodular goiter (Shahi et al., 2020). Nodular goitre in patients with chronic thyroiditis should not be assumed to be benign as chronic inflammation of the thyroid is among the risk factors of PTC (Bove et al., 2023). Furthermore, a long-standing colloid goitre is predisposing factor for PTC, FTC, poorly differentiated thyroid carcinoma (PDTC) and ATC (Shahi et al., 2020). Often, incidental thyroid malignancies in colloid goitre are missed and only diagnosed histologically following subtotal or total thyroidectomy (Bombil et al., 2014). In some cases, the colloid goitre may concurrently harbour two or more different types of thyroid malignances, the so-called collision tumours (Shahi et al., 2020; Magra et al., 2024). Decision regarding the appropriate management of nodular goitre must follow the standard guidelines and be preceded by minimum requisite clinical evaluation, laboratory and imaging investigations.

Pathogenesis

Traditionally, colloid goitre was thought to be endemic resulting solely from iodine deficiency (Unlu et al., 2022). However, it can result from genetic defects of thyroid hormogenesis pathway or other environmental factors like goitrogens in diet (Singh et al., 2021; Unlu et al., 2022). Once initiated colloid goitre goes through a colloid phase and thereafter a nodular phase. Appearance of nodules marks the period of heterogenous response to activity of thyroid stimulating hormone (TSH) and growth (Unlu et al., 2022). The likelihood of automaticity increases with the duration of nodular goitre, and likely in nodular goitre over 10 years. Additionally, the risk of development of differentiated thyroid cancer like papillary thyroid cancer also increases (SamieeRad & Emami, 2020; Shahi et al., 2020).

Clinical presentation

Colloid goitre may be detected incidentally following imaging with ultrasound (Hoang et al., 2015; Jacome et al., 2023), CT scan (Hoang et al., 2015) or PET/CT. Majority of patients with colloid goitre present due to cosmetic concerns. Other reasons for presenting include thyrotoxic symptoms, respiratory complaints or change of voice (Negro and Greco, 2016). Occasionally, patients with goitre may complain of dysphagia when nodule involves the tubercle of Zuckerkandl (Unlu et al., 2022) or recent onset of pain or dyspnoea due to bleeding leading to sudden expansion of the nodule (Lei et al., 2016). A sudden change in size may sometimes be due to anaplastic thyroid carcinoma originating from a de-differentiated PTC or follicular thyroid carcinoma (FTC) (Shahi et al., 2020). Retrosternal extension and enlarged cervical lymph nodes must be ruled-out.

Diagnostic investigations

No patient presenting with NCG should have management decision instituted before undergoing the standard investigations, which must as mentioned previously include serum TSH, thyroid US and FNAC (Hegedus, 2004). Differential diagnoses of include PTC, MTC and ATC, which sometimes occur concurrently (SamieeRad & Emami, 2020). Worrisome features for malignancy regardless of the size or number of nodules include solid architecture, increased internal vascularity, microcalcifications, tall than wide, irregular border and discontinuous or interrupted ring of calcifications (Yao et al., 2020; Vahdati et al., 2024). Checking serum levels of T4 and T3 should be selective and be added in patients with subclinical hyperthyroidism or hypothyroidism. Testing of s-calcitonin and autoantibodies should not be routine but be based on clinical suspicion (Trimboli et al., 2022). Radioisotope scan is added if serum TSH is low (Hegedus, 2004) and CT scan is mandated for massive goitre or when there is retrosternal extension (Hurley et al., 1996) and for recurrent goitre planned for re-do thyroidectomy.

Management

Management of colloid goitre include serial observation, radioactive iodine treatment (Guo et al., 2024), surgery and other ablative options like thermal ablation with radiofrequency (Shin et al., 2013; Yao et al., 2020) and ethanol injection (Monzani et al., 1997; de Alcantara-Jones et al., 2021). Options for management of patients with colloid goitre include serial observation, surgery or ablative procedures. Serial observation should only be considered in patients without worrisome findings on history, clinical, ultrasound and FNAC evaluation. Serial observation should be 6-monthly in the first two years and yearly thereafter. History taking, s-TSH and neck ultrasound should be repeated at every visit (Unlu et al., 2022). Levothyroxine supplementation or suppression of s-TSH should not be part of treatment of nodular BCG (Knobel, 2016). Similarly, iodine supplementation is not useful once nodular colloid goitre is established. Iodine supplementation is hazardous in nodular colloid goitre in patients above the age of 60 years as some of the hyperplastic nodules are likely to be autonomous (Unlu et al., 2022).
Radioactive iodine (I-131) therapy is another option for treatment of toxic and non-toxic NCG (Guo et al., 2024), The potency of I-131 may be enhanced with prior administration of recombinant TSH (Huo et al., 2021). Complications of I-131 treatment include acute pain and hypothyroidism in majority of patients (Unlu et al., 2022). Regardless, thyroidectomy and other ablative options should be earned and be after minimum appropriate imaging by competent specialists. Thyroid stimulating hormone suppression and iodine supplementation are not effective and may be risky once nodules have developed as levothyroxine therapy may cause significant cardiac side effects, especially in elderly patients (Unlu et al., 2022) while iodine supplementation risks the development of Jod-Basedow's effect (Pokhrel et al., 2022). Thyroxine replacement or supplement is mandatory following surgery or other ablative treatment of NCG.

Surgery for benign colloid goitre

Indications for surgery are hyperthyroidism, fear of malignancy, compression symptoms and retrosternal extension (Makay, 2017; Fernandes et al., 2022). While the standard surgical treatment of multinodular goitre is total thyroidectomy; non-total options are however appropriate and acceptable (Mobayen et al., 2015). The non-total thyroidectomy options include lobectomy (Yetkin et al., 2010), bilateral subtotal (Ciftci et al., 2015) and near total thyroidectomy (Dunhill procedure) (Mobayen et al., 2015; Sewefy et al., 2017).

Lobectomy is adequate if the contralateral lobe was shown to be either normal or minimally involved on pre-operative imaging and no significant lesion is palpated during surgery (Mauriello et al., 2016; Barczynski et al., 2019). The main motivation for choosing bilateral subtotal thyroidectomy is to reduce the rate of occurrence of permanent RLN injury and especially hypoparathyroidism, if total thyroidectomy is performed by an occasional thyroid surgeon (Barczynski et al., 2019; Unlu et al., 2022). However, bilateral subtotal thyroidectomy does not eliminate complications (Ciftci et al., 2015). The rate of transient or permanent injury to the RLN and hypoparathyroidism (Privitera et al., 2023) following bilateral subtotal thyroidectomy are like those following total thyroidectomy and the Dunhill procedure in experienced hands (Barczynski et al., 2010). Additionally, goitre is more likely to recur following bilateral subtotal thyroidectomy and require re-do thyroidectomy in up to 50% of the cases (Mauriello et al., 2016). The Dunhill procedure is meant to reduce the rate of complications following thyroidectomy but around 5% of the goitres may recur (Barczynski et al., 2010). Patients who had bilateral subtotal thyroidectomy or Dunhill procedure require completion thyroidectomy if cancer is diagnosed incidentally following surgery (Barczynski et al., 2010).
Nodulectomy (Divarci et al., 2017; Parikh et al., 2022) and partial thyroidectomy (Makay, 2017) are historical and should be avoided. Lobectomy, which must include ischmusectomy is justified if the nodular colloid goitre is unilateral (Yetkin et al., 2010). The choice of surgery in patients with nodular goitre should only be based on the likelihood of post-operative complications. The wish to maintain normal thyroid function and to prevent recurrence should not be prioritized (Snock et al., 2007). All patients with nodular goitre require thyroid hormone replacement after surgery, regardless of the extent of surgery. Thyroxine is cheap and available worldwide, including in low-income countries. The most feared complications of thyroidectomy are recurrent laryngeal nerve (RLN) injury (Sajid et al., 2016) and permanent hypoparathyroidism. The rate of permanent hypoparathyroidism is higher following total compared to non-total thyroidectomy, regardless of the experience of a surgeon (Makay, 2017).

Conclusion

Benign colloid goitre is common. Thyroidectomy is indicated if the goitre is toxic, malignancy cannot be excluded and for evident or eminent compression symptoms. The ideal surgical option is total thyroidectomy, which should be balanced with the risk of permanent hypoparathyroidism and RLN injury. Lobectomy is appropriate in cases of solitary benign colloid nodule. Regardless of the surgical option, surgery must be earned and only considered following investigations to rule out hyperfunction and thyroid malignancy. There is a need to embrace the use of AI better characterize thyroid nodules pre-operatively to reduce the rate of incidentally diagnosed thyroid cancers. The effectiveness of other non-surgical ablative strategies like RFA need to be thoroughly investigated.

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COMPARISON OF DIFFERENT RISK STRATIFICATIONS FOR DIFFERENTIATED THYROID CANCER, WHICH ONE SHOULD BE THE STANDARD?

UP Controversies 2024

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Introduction

It is important to have a good risk stratification system (RSS) for the following reasons:

1. To provide reliable estimation of risk of recurrence and disease-specific mortality for individual patients, hence allowing clinicians to make evidence-based decisions on appropriate treatment, aggressiveness of adjuvant treatment and intensity of follow-up.
2. To provide accurate patient education and counselling.
3. To allow clinicians around the globe to communicate effectively, providing a common language for medical discussion and research studies.

Disease Mortality Static Risk Stratification Systems
Today, according to MEDLINE search, there are 17 different RSS for DTC predicting mortality [1] (table 1).

Table 1: Risk Stratification systems (Static Systems)

Risk Stratification system	Description
AJCC/ TNM (8th edition)	Tumour-Node-Metastasis system
MACIS (Mayo clinic)	Metastases, Age, Completeness of surgery, Invasion and Size system
AGES	Age, Grade, Extent and Size classification
AMES (Lahey clinic)	Age, Metastases, Extent and Size system
GAMES (MSK cancer centre)	Grade, Age, Metastases, Extent and Size classification
DAMES	DNA, Age, Metastases, Extent and Size system
SAG	Sex, Age and Grade system
EORTC	European Organization for Research on Treatment of Cancer
MDA	University of Alabama
Clinical Class	University of Chicago
Münster	University of Münster system
NTCTCS	National Thyroid Cancer Treatment Cooperative Study
OSU	Ohio State University system
Noguchi	Noguchi thyroid clinic system
Murcia	University of Murcia system
CIH	Cancer Institute Hospital system - Tokyo
Ankara	Ankara Oncology Training and Research Hospital system - Turkey

While none of the staging systems has been shown to be clearly superior to the other systems, several studies have demonstrated that the AJCC/ TNM system and the MACIS system consistently provide the highest proportion of variance explained when applied to a broad range of patient cohorts and they have been validated in retrospective studies as well as prospectively in clinical practice [2]
Currently the AJCC is the most commonly used RSS and should be recommended for all patients with DTC, based on its utility in predicting disease mortality, to enable risk-stratified description of patients for communication among health care professionals, its requirement for tracking by cancer registries and for research purposes.
Unfortunately, none of the disease mortality static RSS are designed to predict mortality accurately. This relative inability to accurately predict the risk of death from thyroid cancer for an individual patient may be related to the failure of these staging systems to adequately integrate the risk associated with other potentially important clinicopathologic features such as the specific histology, molecular profile, size and location of distant metastases, functional status of the metastases, and effectiveness of initial therapy. This led to the development of risk of recurrence static RSS.

Risk of Recurrence (RR) Static Risk Stratifications System

Assuming that the great majority of DTC patients will have a 10-year overall survival above 95% according to the AJCC, in the last decade, the European Thyroid Association (ETA), the American Thyroid Association (ATA) and the Latin American Thyroid Society (LATS) among other societies, adopted the risk of recurrence (RR) classification, released in the 2009 ATA guidelines [4]. After completing initial therapy (thyroid surgery with or without RA), patients with a diagnosis of DTC are classified as having low, intermediate or high RR. In 2016, this 2009 ATA risk stratification system was updated [5]. In this individualized management approach, where postoperative staging is recommended, is not only for assessing risk of recurrence, but also for tailoring decisions regarding both the need for postoperative adjuvant therapy (including need for radioactive iodine [RAI] ablation and degree of thyrotropin [TSH] suppression) as well as the frequency and modality of follow-up studies.

The Modified Stratification System from ATA 2009 guidelines were validated in several cohorts of patients around the world [6]. These studies demonstrated that the percentage of structural incomplete response (evidence of local or distant persistent/recurrent disease) at the end of follow-up was 3–9% for low-risk patients, 13–45% for intermediate-risk patients and 60–80% for high-risk patients [3,6].

While these initial staging systems provide an important starting point for risk assessment, and management of a patient during the first 1-2 years after thyroidectomy, they are static representations of the patient at the time of initial therapy and are not designed to be modified over time based on the clinical course of the disease. Further, none of the commonly used staging systems include adequate variables to address the impact of treatment on subsequent outcomes. Since initial surgery and RAI remnant ablation are likely to have a major impact on risk of recurrence and risk of death in thyroid cancer patients. Therefore, it is not surprising that the risk estimates provided by any of the commonly used clinicopathologic staging systems account for only a small proportion of the observed variance in disease-specific survival. This led to the development of dynamic RSS.

Dynamic Risk Assessment System (DRAS)

This re-stratification of the initial RR based on new clinical data that becomes available during the initial follow-up is called Dynamic Risk Assessment System (DRAS) first suggested by Michael Tuttle from the Memorial Hospital of New York in 2010 [7]. As expected, this strategy would provide a more accurate prediction of the RR and a more individualized approach.

The DRAS approach implies the re-stratification of the initial RR of DTC patients considering the different responses to treatment: excellent, indeterminate, biochemical incomplete and structural incomplete, using specific data obtained during follow-up: Tg and anti-Tg values, results of imaging studies, including neck ultrasound (US), RAI scans, computed tomography (CT) or 18-fluorodeoxyglucose positron emission tomography-CT (18-FDG PET/CT), guided by initial RR assessment.

Tuttle originally suggested this DRAS in 2010 after his retrospective study of 588 patients with DTC who received total thyroidectomy and RA, with a median follow-up of 7 years (range 1–15 years) [7]. After 2 years, he classified patients into having no evidence of disease, having evidence of persistent disease (either biochemically or structural), or having recurrent disease. He correlated these findings with the different stages of AJCC and the RR of ATA.

When Tuttle compared his end points with stages of AJCC. As expected, stage 4 disease had the highest percentage of persistent disease. However, stage 2 had a higher risk of persistent disease than stage 3 and all stages had around the same risk of recurrent disease, concluding that the AJCC system cannot be used for determining RR [7].

When Tuttle compared his DRAS (structural only as the ATA RR only looked at structural) to the RR of the ATA, the RR established by the ATA was verified by Tuttle with low, intermediate and

high-risk groups around 3%,18% and 66% respectively in patients with recurrent or persistent structural disease [4,7].
However, after this initial DRAS assessment, the best response to treatment obtained during the first 2 years after initial therapy was analysed using both structural and biochemical evaluations. After the re-stratification, among patients who had an initial excellent response, the probability of having RR was reduced from 3 to 2% in low-risk patients, from 18 to 2% in intermediate risk patients, and, which was more remarkable, from 66 to 14% in patients with high RR [7]. On the contrary, having an initial incomplete response (structural and or biochemical) increased the RR at the end of follow-up from 3 to 13% in low-risk patients, 18 to 41% in intermediate-risk patients and 66 to 79% in high-risk patients (table 3) [7].
The ability of the ATA RR staging system and Tuttle's DRAS staging system to predict recurrent/ persistent disease was assessed by determining the PVE (which measures the ability of a classification system to predict the final for each system). The ATA RR system was able to account for 34% of the observed variance in predicting recurrent/persistent disease. However, the Tuttle DRAS system was able to account for 84% of the variance observed, making it a superior system.
The ATA in their revised 2015 guidelines acknowledged this system proposed by Tuttle, but did not endorse its use due to the potential challenges in applying this specific system in routine clinical practice which included the lack of validation in specific subgroups of patients (such as those who had less than total thyroidectomy or those not treated with RAI) because Tuttle had only looked at patients with total thyroidectomy and post op RAI. Furthermore, they pointed out on the lack of published prospective data utilizing this system in clinical care, and some inconsistency with other authors in classifying the significance of varying levels of detectable Tg levels or imaging findings.
However, since the ATA guidelines in 2015, the DRAS has been substantially validated in numerous studies in different patient cohorts including 2 prospective trials [8].
Despite the ATA not endorsing Tuttle's DRAS system, they did go on to state that; "given that there is emerging evidence that such a reclassification system has potential to be of great importance in ongoing clinical care of DTC patients after primary treatment" they included the details and provided a table with treatment recommendations based on this.
Now considering the ATA's criticism of Tuttle's DRAS only looking at one subset of patients (Total thyroidectomy plus RAI), many subsequent studies have been performed verifying its use in lobectomies and total thyroidectomies without RIA [8].
In the initial excellent and structurally incomplete response groups in all these studies in patients without RA irrespective if they had lobectomy or total thyroidectomy, they demonstrated that the risk of structural recurrence was more accurate that ATA RR after initial surgery [9,10].
With regards to the initial indeterminant group however, this group was different compared to studies in patients who initially received RA. In the non-RA patients, there was a very low risk of final structural recurrence in patients who were initially stratified into the indeterminate group. Suggesting that in patients who do not receive RA and originally stratified into indeterminate group, nonspecific ultrasonographic findings, slightly elevated Tg values or stable/declining anti-Tg levels would have very little impact on the persistence/recurrence rate [9,10].
With regards to the initial biochemical response group in both Momesso's and Park's studies, an initial biochemical response was associated with a low probability of structural disease in patients with total thyroidectomy without RA, similar to what happens in patients who received RA [9,10].
In contrast, lobectomy patients in both Parks study and Cho's study, of 208 and 619 patients respectively showed that the biochemical response (anti-Tg status, the Tg levels or the changing trend of Tg/anti-Tg levels) were not significantly associated with structural recurrence [10,11]. Therefore, periodic measurements of serum Tg levels in lobectomy patients would not be useful for predicting recurrent disease, and decreased or stable serum Tg levels do not guarantee a lower probability of recurrence in these patients.
Moreover, in Cho's study of patients treated with lobectomy alone, each response to therapy category was not well correlated with the incidence of structural recurrence, and the PVE of the dynamic stratification system in these patients was only 32%, which is similar to what it was

reported for the initial ATA RR assessment in patients who received total thyroidectomy and RA [7,11]. This does confirm that applying Tuttles DRAS to lobectomy patients doesn't outperform the ATA RR assessment.
Furthermore, there is also the question of what cut off value of Tg level on follow up lobectomy patients to act on? In Pitoia's review of all studies a value of >30ng/ml is suggested for lobectomy patients [8]. Reasons for this was in Momesso's study the presence of an initial biochemical incomplete response (non-stimulated Tg level >30ng/mL) was associated with a 50% frequency of structural incomplete response and in Park's study two patients of the cohort who had Tg measurements >30ng/mL had recurrent disease [9,10].

So what Risk Stratification is best then?

Modern risk stratification has moved from a single postoperative static assessment of the risk of disease specific mortality to an all-encompassing evaluation of the patient that is continually modified over time, beginning from the first detection of a suspicious thyroid nodule and continuing throughout the life of the patient through the phases of diagnosis, treatment, adjuvant therapy, and follow-up. [12]. The AJCC should be used post operatively for prognostication, the ATA RR for risk of recurrence and planning future treatments and then the DRAS to assess treatment response and guide further treatment.

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Approach to Adrenal incidentalomas

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Background

An adrenal incidentaloma is defined as an asymptomatic mass discovered on imaging investigations that was originally ordered for any reason other than adrenal disease.(1) The prevalence of adrenal incidentalomas is approximately 2% of the general population.(2) Adrenal incidentalomas are diagnosed up to 7% in patients over the age of 70 and even more rarely in patients <40years.(2, 3) Adrenal incidentalomas are commonly benign adenomas,(1) with the prevalence of malignancy reported between 1.9 to 4.7%.(4) Adrenal incidentalomas may be metastatic disease in 30-70% of patients with a current, or with a previously diagnosed, extra-adrenal malignancy.(5) Adrenal incidentalomas are commonly non-functioning adenomas (80%) and approximately 10-30% are functional.(2, 6) The prevalence of autonomous cortisol secretion is 11.7%, primary aldosteronism at 4.4% and pheochromocytoma at 3.8%.(7)

Diagnosis: Imaging

Noncontrast computerized tomography scan (CT) is the recommended investigation for all adrenal incidentalomas to determine if the tumour is benign, i.e. Hounsfield units (HU) ≤10, smooth borders and homogenous density.(1, 8) Adrenal adenomas are lipid rich resulting in the low attenuation on noncontrast CT, whereas malignant tumours are lipid poor resulting in high attenuation.(9) If the attenuation value is >10 HU, which occurs in approximately 30%, then the incidentaloma is considered suspicious and further imaging is required.(1, 8, 9) Attenuation >10 HU has a sensitivity of 100% and specificity 33% in diagnosing adrenal malignancy.(10)
Contrast-enhanced CT is then performed to assess the contrast enhancement washout. Adrenal adenomas have a rapid take up and rapid washout of contrast (absolute washout >60% and relative washout >40%).(9) Adrenal tumours with a slow washout of contrast are more typical of malignant lesions.(1) Magnetic resonance imaging with chemical-shift analysis can also be used. High risk features on MRI include hyperintensity on T2 weighted images and no loss of signal on chemical-shift analysis. MRI has been reported to have sensitivity of 89-99% and a specificity of 60-93%, but with low number of patients.(11)
When Fluoro-deoxyglucose positron emission tomography/computerized tomography (FDG-PET/CT) scan is performed as part of the workup for a patient with extra-adrenal malignancy, no additional adrenal imaging is then necessary.(1) FDG-PET/CT has a sensitivity of 87% and specificity of 84% in diagnosing malignancy.(10)

Diagnosis: Hormonal work-up

All patients with adrenal incidentalomas should be assessed for signs and symptoms of adrenal hhyperfunctional status and undergo a biochemical work-up.(6) Increase cortisol secretion is the most common functional adrenal disorder, 1-29%, followed by pheochromocytoma, 1.5-14%, and aldosterone-secreting tumours, 1.6-3.3%.(1, 12) For hypercortisolism, one or two tests are first performed as screening tests then, if positive, followed by a different test for confirmation.(6) Autonomous cortisol excess can be assessed with a low dose, i.e. 1mg, overnight dexamethasone suppression test, which is recommended by the Korean Endocrine Society for all incidentalomas regardless of symptoms.(13) In order to exclude an autonomous cortisol secretion, the serum cortisol level should be suppressed ≤50nmol/L (≤1.8µg/dL).(1) Above 50nmol/L is considered a mild autonomous cortisol secretion or definitive depending on clinical symptoms.(1, 8) Cortisol levels can also be assessed with an abnormally raised late night salivary cortisol test or a 24 hour urine cortisol test. Once hypercortisolism has been diagnosed, the clinician has to exclude an adrenocorticotropic hormone (ACTH) dependent cause as 30% can have coincidental adrenal nodules.(14) Pheochromocytomas should be excluded by measuring

plasma-free- or urinary fractionated- metanephrines.(1, 8) Aldosterone hypersecretion, with the aldosterone/renin ratio more than 20, is only investigated if the clinical features of unexplained hypokalemia and hypertension are present.(1) Steroid precursors and sex hormones and are also only investigated if there are clinical features present or imaging is suspicious of an adrenal carcinoma.(1, 8, 13)
Biopsy of adrenal incidentalomas are not commonly performed due to the risk of tumour dissemination if malignancy was present. Biopsy of incidentalomas are only warranted in patients with a history of an extra-adrenal malignancy when the adrenal tumour cannot be conclusively diagnosed as benign and if the management would change with the histology results.(1, 8) Unfortunately differentiating between an adenoma and a carcinoma is not always possible.(2) Hyperfunctioning of the incidentaloma first has to be excluded before the invasive procedure.(1)

Incidentaloma Size

Adrenal masses less than 1cm are not considered as a true adrenal incidentaloma and therefore not considered for further diagnostic work-up, unless there are clinical features of excess adrenal hormone production.(4, 15)
Nonfunctioning adrenal incidentalomas less than 4cm do not require further intervention or follow-up if they are benign on non-contrasted computer tomography (CT) evaluation.(1, 12) Adrenal incidentalomas less than 4cm but with suspicious finding on non-contrasted CT evaluation (Hounsfield units ≤10, irregular borders and heterogeneous density) can either have an additional imaging modality, repeat imaging in 6-12 months or undergo adrenalectomy.(1, 6) Reports have also recommended a repeat computed tomography scan in 3-6 months then annually for 2 years.(16) A radiological study reported the mean diameter of malignant adrenal lesions was 2.3cm with a range of 1cm to 4.1cm.(17) In 2002, the National Institute of Health consensus stated that the prevalence of adrenocortical carcinoma was 2% in tumours up to 4cm, 6% in tumours greater than 4cm to 6cm and 25% in tumours larger than 6cm.(5)(18) The same consensus also stated the limitation of clinical data on the prevalence and natural history of incidentalomas.
Incidentalomas that are 4cm or greater have a higher risk of malignancy and therefore qualifies for surgery as recommended by the 2016 European Society of Endocrinology (ESE) Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT), as well as the 2009 American Association of Clinical Endocrinologists (AACE) and American Association of Endocrine Surgeons (AAES) Medical Guidelines.(1, 6) The Korean Endocrine Society, however, also agrees with a cut-off of 4cm.(13) The panel, from the European Society of Endocrinology Clinical Practice Guidelines, acknowledges the guideline of 4cm is only based on expert opinion and not from documented clinical research.(1) Although majority of adrenocortical carcinomas are greater than 4cm, the majority (60%) of other adrenal malignant tumours (including lymphomas and metastases) are less than 4cm in size with a median of 3cm.(19, 20)
When considering size and hyperfunctioning, an incidentaloma with a diameter of 3cm or greater has a higher risk of hormone secretion.(21) Hormone hypersecretion is usually asymptomatic and has a peak 3 to 4 years after initial detection of the incidentaloma.(21) Therefore it has been recommended that adrenal incidentalomas more than 3cm in diameter should be followed up for a minimum of 5 years.(16)

Management

There are certain indications for adrenalectomy for incidentalomas. Surgical resection is suggested for an indeterminate adrenal mass in children, adolescents, women who are pregnant and < 40 years.(8) Unilateral incidentalomas suspicious of malignancy should have a laparoscopic adrenalectomy up to 6cm in diameter, provided there are no features of local infiltration.(1) Incidentalomas should have an open adrenalectomy in the presence of a diagnosed

adrenocorticoid carcinoma or when there are signs of local invasion in the presence of suspicion of incidentaloma malignancy.(1, 22) The procedure includes adrenalectomy with the surrounding lymphatics and the surrounding tissues such as liver, kidney, inferior vena cava, etc.(6) However, other reports show that even in the presence of adrenocortical carcinoma, excluding stage 4, up to 10cm in diameter can be removed with a laparoscopic adrenalectomy.(23, 24) Other studies even advocates for laparoscopic adrenalectomy up to 12cm.(25, 26) However, those with stage 2 malignancy have shown to have a shorter time for recurrence when laparoscopic resection was performed for a cut-off up to 10cm.(27) Laparoscopic resection has a higher risk of port site seeding, local recurrence and peritoneal dissemination.(28, 29) Laparoscopic adrenalectomy also has a significant shorter time of recurrence, by almost 10 months, and a higher risk of positive resection margins or intraoperative tumour spillage compared to open surgery.(22, 27) Overall survival has also been shown to be longer for open surgery in those with malignant adrenal tumours, specifically stage 2.(27) In contrast, other studies report no change or non-inferiority with laparoscopic adrenalectomy.(23, 30) The larger the diameter of the tumour, the greater the technical challenges associated with adrenalectomy.(25) The size of the adrenal lesion and the decision to perform a laparoscopic adrenalectomy is also influenced by the site. Retroperitoneal laparoscopic adrenalectomy is appropriate up to a diameter of 6cm but with disadvantages of the inability to perform other abdominal procedures or explore the peritoneal cavity.(25) Incidentalomas with clinically significant hormone secretion are recommended for adrenalectomy.(1, 8) Incidentalomas with mild autonomous cortisol secretion may be considered for adrenalectomy with worsening comorbidities, including type 2 diabetes, hypertension, osteoporosis or dyslipidemia.(6, 8)

Follow-up and size

For patients that do not qualify for resection initially, progressive growth of the incidentaloma may be of concern on follow-up investigations. Up to 37% of incidentalomas may demonstrate an increase in size on follow-up investigations.(31) Benign adrenal tumour growth is typically slow and insignificant,(32) 2mm growth over 52.8 months,(33) but significant increase in diameter of 10-20mm over a 3-year period has been reported.(34)
The ESE and ENSAT does not recommend further imaging if the initial investigations demonstrated an incidentaloma less than 4cm with benign findings and biochemically no hormone hypersecretion (refer to Table 1).(1, 8) Patients who decide not to have an adrenalectomy in the presence of an indeterminate incidentaloma should have a follow-up imaging after 6-12 months with a non-contrasted CT or MRI to assess the growth.(6) Adrenal malignancy or metastasis would most likely increase in size during this period.(1) The Korean Endocrine Society recommends a follow-up period of 1 year for benign non-functional incidentalomas less than 2cm. For adrenal incidentalomas less than 4cm and indeterminate, the KES recommends 3-6 months follow-up initially then 1-2 years thereafter for 4-5 years.(13) According to the AACE and AAES, all patients that do not have an adrenalectomy should have follow-up imaging at 3-6 months then annually for the next 1-2 years.(6) The rationale for the frequent follow-up is the cumulative risk of tumour enlargement of 6% at 1 year, 14% at 2 years and 29% at 5years.(21, 35) The AME recommends follow-up imaging at 3-6 months and an increase in size of >1cm as significant for malignancy.(36)

Table 1: Summary of follow up recommendations for adrenal incidentalomas

ESE and ENSAT	AACE and AAES	AME	KES	CUA
<4cm: no follow-up if benign and inactive	<4cm: follow-up imaging at 3-6 months then annually for one to two years	<4cm: follow-up imaging at 3-6 months	<2cm: follow-up period of 1 year	<4cm: no follow-up if benign and inactive
<4cm: follow-up imaging if indeterminate at 6-12 months	<4cm: follow-up if indeterminate at 3-6 months then annually for one to two years		<4cm: follow-up if indeterminate at 3-6 months then annually for one to two years, then 4-5years.	>4cm: follow-up if inactive and initial benign imaging, then 6-12 months

ESE: 2016 European Society of Endocrinology Clinical Practice Guideline; ENSAT: European Network for the Study of Adrenal Tumors; AACE: 2009 American Association of Clinical Endocrinologists; AAES: American Association of Endocrine Surgeons Medical Guidelines; AME: 2011 Italian Association of Clinical Endocrinologists, or Associazione Medici Endocrinologi; KES: 2017 Korean Endocrine Society; CUA: 2011 Canadian Urological Association.

An increase in an incidentaloma's largest diameter by more than 20%, in combination with a 5mm increase in the same diameter, is considered as progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria (refer to Table 2).(37) Although the RECIST 1.1 criteria is used in multiple oncological trails, it has not been validated for adrenal tumours but, according to expert opinion (ESE and ENSAT), can be adapted for incidentalomas.(1) The increase in diameter more than 5mm on follow-up evaluations has also been agreed by other authors (35) and has been reported to occur in 17.4% at 2 years.(38) The AACE, AAES and the Korean Endocrine Society recommend an increase in diameter of more than 1cm, which occurs in 20%, should be for surgery.(6, 13, 21) Another reported recommendation is an increase of more than 8mm which is a predictor of malignancy, with a sensitivity of 72% and a specificity of 81.1%, requiring resection.(16, 39)

Table 2: Significant increase in size on follow-up indicating progressive disease

ESE and ENSAT	CUA	AACE, AAES, AME and KES	Pantalone et.al. Zieger et.al.
Increase in the largest diameter by more than 20%, in combination with a 5mm increase in the same diameter	Increase in diameter more than 5mm	An increase in diameter of more than 1cm	Increase in diameter more than 8mm

ESE: 2016 European Society of Endocrinology Clinical Practice Guideline; ENSAT: European Network for the Study of Adrenal Tumors; CUA: 2011 Canadian Urological Association; AACE: 2009 American Association of Clinical Endocrinologists; AAES: American Association of Endocrine Surgeons Medical Guidelines; AME: 2011 Italian Association of Clinical Endocrinologists, or Associazione Medici Endocrinologi; KES: 2017 Korean Endocrine Society.

The ESE and ENSAT also does not recommend repeating the hormonal investigations when the initial work-up did not demonstrate a hyperfunctioning tumour. The risk of developing Cushing's syndrome is 0.1% regardless if the original hormonal investigations showed an autonomous cortisol secretion or a nonfunctioning adrenal incidentaloma.(33) In patients with worsening of comorbidities, such as hypertension, or clinically have new features of adrenal hypersecretion, then repeating the hormonal work-up is warranted.(1) Patients with no signs of Cushing's syndrome, but biochemically have raised cortisol levels that may be related to co-morbidities,

can have an annual cortisol level assessment.(1) According to the AACE and AAES, the hormonal work-up should be repeated annually for the 5 years in all patients with an incidentaloma.(6) The rationale for the frequent follow-up is the cumulative risk of hormonal changes of 17% at 1 year, 14% at 2 years and 47% at 5 years.(21)

Conclusion

Adrenal incidentalomas need to be investigated for malignancy and functional status. The common diagnostic work-up includes a non-contrasted CT scan and the appropriate hormonal investigations. Management options includes either observation, additional imaging, or adrenalectomy. The clinician should be aware of the differences between the various international endocrine societies when managing a patient with an adrenal incidentaloma.

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Diagnostic work up of Endocrine Hypertension
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Definition
Endocrine hypertension is one of the cause of secondary hypertension that is due to over-secretion of hormones from organs of endocrine system mainly the adrenal gland. This chapter will therefore focus only on adrenal causes of hypertension.

Epidemiology
Essential hypertension is by far the most common cause of hypertension. Endocrine hypertension, although uncommon, is believed to be under-estimated worldwide especially in sub-saharan Africa[1]. The incidence is estimated to be more than 10% but it is much higher (17-23%) in the subgroup of resistant hypertension that requires multiple drugs[1]. The most common etiology of endocrine hypertension is hyperaldosteronism whereas the Cushing syndromes and the catecholamine producing tumours are much more uncommon[1,2,3]. The literature in sub-saharan Africa is scanty with some reported publication from Cape town and Johannesburg in South Africa[4,5].

Clinical presentation
High index of suspicion is important to think of endocrine hypertension. Unfortunately hypertension can remain silent until it manifests with complications like cerebrovascular accident (CVA), myocardial infarction (MI) or it can present with non-specific symptoms. The hyperaldosteronism is the least symptomatic, and its symptoms are mainly related to hypokalemia that manifest mainly with fatigue[1]. The diagnosis can be delayed since hypokalemia is not an early sign and is only present in 30-40% of cases[1]. Eventually the combination of hypertension and hypokalemia can prompt investigation of hyperaldosteronism.
The catecholamines producing tumours are suspected in the presence of hypertension associated with signs and symptoms of sympathetic overstimulation: headache, palpitation, diaphoresis, anxiety, panic attack[1]. Patients can present with complications of hypertension that can manigest as cardiogenic shock, congestive cardiac failure or sudden death.

In Cushing syndrome, hypertension is associated with features of hypercortisolism. In the absence of consumption of exogenous cortisol, Cushing syndrome is suspected when the patient experiences symptoms such as unintentional weight gain, buffalo hump, moon face, truncal obesity, striae, acne, thinning of the skin, bruising of the skin and others[4].

Whom to screen?
Essential hypertension is the most cause of hypertension and it is going to be tedious to screen every hypertensive patient.
Selective screening of hypertension in young patients, the newly diagnosed hypertension and those on three or more anti-hypertensive drugs is beneficial to enable early diagnosis of endocrine hypertension and to mitigate the damage to the target organs.

Investigations
Thorough history is paramount to rule out other causes of secondary hypertension particularly of renal origin[1].

A. Hyperaldosteronism
The screening test for hyperaldosteronism must be highly sensitive to avoid missing patients and includes plasma aldosterone, plasma renin and aldosterone-renin ratio (ARR)[1].
The confirmatory test includes oral sodium loading test, saline infusion test, fludrocortisone suppression test and captopril challenge test[1]. These tests are useful to exclude false positive results. The confirmatory testing is not mandated in hyperaldosteronism with spontaneous hypokalaemia, a plasma aldosterone concentration (PAC) greater than 550 pmol/L and a plasma renin activity (PRA) below assay detection limits[1]. It is worth mentioning that the drugs that

interfere with the renin-angiotensin-aldosterone axis should be discontinued a few weeks prior to the test but not at the expense of worsening hypertension, especially when it is severe[1].

The lateralization studies are needed to determine the subtypes of primary hyperaldosteronism and include:

Anatomical lateralization.
- Computed tomography scan (adrenal protocol)
- Magnetic resonance imaging (MRI)
- NP-59 Iodo-methyl-norcholesterol scintigraphy: Not commonly used. It is beneficial to distinguish between adenoma and hyperplasia.

Functional lateralization.
Adrenal vein sampling (AVS) is indicated when imaging fails to demonstrate the presence of a tumour, raising suspicion of bilateral adrenal hyperplasia, the most common cause of primary hyperaldosteronism[1,6]. The AVS, although being the gold standard, is not indicated in young patients with severe hypertension, unilateral adenoma with normal contralateral adrenal gland on computed tomography scan[1,6]. Moreover, AVS is an invasive procedure with failure rate up to 20% and potential major complication such as infarction of the adrenal, ruptured inferior vena cava (IVC). The AVS required a skilled interventional radiologist and was subjected to challenge in interpretation[1,6]. The AVS is also beneficial to differentiate functioning adrenal adenoma from the non-functioning incidentaloma especially in advanced age (> 40 years) as the incidence of incidentaloma increases with age.

B. Pheochromocytoma/paraganglioma (PCC/PGL)
The diagnosis is confirmed on biochemistry. Plasma-free serum metanephrine has a sensitivity and specificity of 96% and 85% respectively[7] whereas 24-hour urine collection for catecholamines and their byproducts (metanephrine, normetanephrine) is 87.5% sensitive and 99.7% specific[7]. Plasma-free serum metanephrine is the preferred method but it is not readily available. It is beneficial to rule out rather than to rule in catecholamine producing tumours. An elevate catecholamines byproducts in a 24 hour urine collection of more than three times normal is diagnostic. The result is considered ambiguous if the elevation is 2-3 folds and requires a repeat 6 months later. Clonidine test can be considered if the result remains ambiguous. The adrenal origin of catecholamines producing tumour is suggested when both metanephrines and normetanephrines are elevated since the sympathetic chain (source of PGL) lacks the phenylethanolamine N-methyl transferase (PNMT) that converts noradrenaline to adrenaline in the adrenal medulla. Therefore, in PGL, only the normetanephrines can be raised. It is important to have in mind the medications that can cause false positive results[1]
Once the diagnosis is made, localization is often obtained with computed tomography scan that has an accuracy of 85-95%[1]. MRI, with a sensitivity approaching 100%, is preferred in children and in pregnancy[1].
The MIBG Scintigraphy (Meta-Iodo-Benzyl-Guanidine) is indicated when the biochemically confirmed PCC/PGL is not localized by Ct scan or MRI, when metastasis is suspected, in case of larger or multifocal tumours, in extra adrenal manifestation and in syndromic conditions[1,7].
Other functional imaging are FDG PET/CT (18F-Fluorodeoxyglucose) and DOPA PET/CT (18F-Fluorodihydroxyphenylalanine). They are used when the MIBG scan is negative. Their sensitivity in detecting metastasis is higher than the one of MIBG scan[1,7,8].

C. Cushing syndrome
Biochemical test.
The low ACTH differentiate Cushing syndrome (ACTH independent) from Cushing disease (ACTH dependent) which originate mainly from the pituitary[9]. Furthermore, Cushing disease responds to negative feedback with high dose dexamethasone suppression test that helps differentiate Cushing disease from ectopic production of ACTH[9]. A plasma ACTH of < 5pg/ml is suggestive of adrenal origin. An ACTH of > 20pg/ml is in keeping with ACTH dependent Cushing syndrome, whereas a value between 5 and 20 pg/ml is considered equivocal. The diagnosis of Cushing syndrome is confirmed with 24 hour urine free cortisol excretion, low-dose dexamethasone suppression test (overnight) and late night serum and salivary cortisol level[1,9].

The computed tomography scan of the abdomen is the next step to localize the disease. In case of non-localization, AVS is recommended to confirm bilateral adrenal hyperplasia.
In our practice, we had a case of bilateral micronodular adrenal hyperplasia in a 13 years old boy who benefited from laparoscopic transabdominal bilateral adrenalectomy. The histopathological report was in keeping with primary pigmented nodular adrenocortical disease (PPNAD). PPNAD is part of Carney complex.

Our local experience
Our finding at Chris Hani Baragwanath Academic Hospital (CHBAH) report rather a higher incidence of catecholamine producing tumours (65.9%) in contradiction to the literature that is in favor of hyperaldosteronism. Possible explanation is the difficulty to suspect hyperaldosteronism because of paucity of symptoms. We believe hyperaldosteronism is underdiagnosed. Hypercortisolism and hyperaldosteronism represented 18 and 16% respectively.

Conclusion

Awareness of endocrine hypertension needs to be inculcated in the mind of healthcare practitioners and the entire population for early referral. With high index of suspicion, appropriate work up and prompt intervention, surgery can achieve cure in the majority of patients especially if diagnosed early. In the subgroup of patients where the cure is not achieved, the anti-hypertensive requirement will be reduced.

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Indications For Intervention in Acute Pancreatitis

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1. **Introduction**
    a. Diagnosis of acute pancreatitis.
    b. Aetiology of acute pancreatitis.
    c. Severity grading of acute pancreatitis.
    d. Historical context of surgical interventions in acute pancreatitis.

2. **Current roles for intervention in acute pancreatitis.**
    a. Role of ERCP and EUS in biliary pancreatitis.
        i. Management of co-existing biliary obstruction in biliary pancreatitis.
        ii. Definitive role of ERCP in convalescent patients with biliary pancreatitis.
        iii. The emerging role of EUS for gallbladder drainage.
    b. Definitive management of underlying aetiology.
        i. Cholecystectomy.
    c. Role of emergency surgical interventions in acute pancreatitis.
        i. Emergency decompressive laparotomy for abdominal compartment syndrome.
        ii. Endovascular control of hemorrhage as a complication of acute pancreatitis.
        iii. Emergency surgery for intestinal ischemia as a consequence of acute pancreatitis.
    d. Interventions for the management of local complications of acute pancreatitis.

Introduction[1,2,3]

a. Diagnosis of acute pancreatitis.

Acute pancreatitis (AP) is defined as an acute inflammatory disease of the pancreas with a sudden onset of symptoms, which can follow one of two broad paths. The inflammatory response can result in post necrotic damage to the gland often accompanied by organ damage (transient or permanent). Alternatively, with the absence of this effect, there is complete resolution of the symptoms and if the initiating cause is removed there will be no further attacks.

The diagnostic process of AP stipulates the clinical and biochemical criteria to make the diagnosis. Importantly, the role and caution that must be given to the role of contrasted imaging in these patients.

Diagnostic criteria for AP (two of three are required):

1. Characteristic pain (epigastric in location, severe in nature, radiates to the back) often with a suggestive aetiology identifiable on history.

2. Serum amylase and/or lipase levels that are three times or higher than the upper limit of normal.

3. Characteristic features on contrasted imaging or MRI (the indication for the imaging and the type of imaging are tailored to the clinical picture and suspected aetiology). Consider imaging in the following:

a) Cases of diagnostic doubt.

b) Patients that are failing to improve within 48-72 hours of presentation or deteriorating rapidly.

c) Cases where local complications are suspected.

Irrespective of the aetiology, the trigger factors cause supraphysiological intracellular signalling resulting in trypsin activation within the zymogen granules. The resultant acinar cell death causes a localized and systemic inflammatory response

b. Aetiology of acute pancreatitis.

The most common causes of AP are gallstones (40-65% of cases) and alcohol (25-40% of cases). The remaining 10-30% if cases are due to a variety of more rare conditions including autoimmune and genetic risk factors inherent within the patient.

Etiology of pancreatitis
Gallstones
Toxic-metabolic: Alcohol Tobacco smoking Hypercalcemia (hyperparathyroidism) Hypertriglyceridemia
Chronic kidney disease
Medications (tetracycline, isotretinoin, carbimazole, furosemide, isoniazid, metronidazole)
Chemotherapy
Radiation
Porphyria (acute intermittent porphyria; erythropoietic protoporphyria)
Toxins (Scorpion string, adder toxin, viper toxin, hornets)
Chemical (penetrating duodenal or gastric peptic ulcers)
Idiopathic (early onset; late onset)
Obstructive (ampullary stenosis/tumors, main duct strictures, IPMN, pancreatic divisum, ABPU)
Trauma (blunt abdominal trauma; iatrogenic surgical- renal surgery, organ transplantation, partial pancreatectomy; iatrogenic endoscopic- ERCP, EUS biopsy)

Genetic Hereditary pancreatitis (PRSS1 and CPA gene mutation) Cystic fibrosis (CFTR gene mutation) Genetic risk factors (SPINK1, CFTR, CTRC, CEL, CPA1 and PRSS1 gene variations and/or mutations)
Autoimmune (autoimmune pancreatitis- predominantly type II syndromic- SLE, vasculitis)
Infection (Viruses- Coxsackie B, CMV, Covid 19, EBV, Hep B, HIV, HSV, mumps, VZV; Bacteria- legionella, leptospira, mycoplasma, salmonella. Fungi- aspergillus. Parasites- ascaris, cryptosporidium, toxoplasmosis, clonochiasis).
Ischemia and embolism (cardiac surgery, abdominal aorta dissection)

c. Severity grading of acute pancreatitis.

The revised Atlanta classification published in 2012 provides a well-established framework for the stratification of AP patients with precise definitions of complications and severity. Correct identification of the nature of the local complication is important for clinical decision-making.

The Determinant-Based Classification provides an additional Critical Severity Grade defined as a combination of both infected pancreatic necrosis and persistent organ failure but is not as widely used as the revised Atlanta classification.

These two classifications have largely superseded the older systems such as the Ranson's criteria.

Revised Atlanta Classification (RAC) regards organ failure as a dynamic and reversible process, such that the definition of severe AP depends on the duration as well as the presence of organ failure (OF).

In the RAC, severe AP is defined as OF that lasts more than 48 h (persistent OF; POF) whereas patients with OF that resolves within 48 h (transient OF; TOF) are categorized as having moderately severe AP, since TOF was shown previously to have no significant influence on mortality.

The broad definition of 'moderately severe' category under the RAC may describe a heterogeneous group of patients with varying levels of severity.

Local complications such as acute peripancreatic fluid collection, pseudocyst, and necrosis (sterile/infected) may not be all equal contributors to disease severity.

The Determinants Based Classification (DBC) is based on the actual local and systemic determinants of severity, rather than a description of events that are correlated with severity.

The local determinant relates to whether there is (peri)pancreatic necrosis or not, and if present, whether it is sterile or infected.

The systemic determinant relates to whether there is organ failure or not, and if present, whether it is transient or persistent.

The presence of one determinant can modify the effect of another such that the presence of both (peri)pancreatic necrosis and persistent organ failure have greater effect on severity than either determinant alone.

The main difference between the RAC and DBC is the importance given to infected necrosis (IN) in predicting mortality.

What is important is that it creates two categories out of the 'severe' category; those with POF and IN and those with POF and no IN. These groups are strikingly different for morbidity and mortality.

This highlights the importance of including IN as a criteria for severe category and it highlights the problem with the RAC that does not consider IN as a criteria for severe AP.

The DBC had better ability to predict the need for interventions than the RAC, whereas the RAC appeared to predict length of hospital stay better than the DBC.

d. Historical context of surgical interventions in acute pancreatitis.

In the late nineteenth century, exploratory laparotomy became popular for diagnosing AP and drainage of pancreatic abscesses, and necrotic tissue debridement was performed in some cases.

Surgeons such as Mickulicz, Mayo Robson, and Moynihan were encouraged to employ laparotomy to treat the complications of severe AP as anaesthetics developed in the early twentieth century. In the first few decades of the twentieth century, various procedures were performed, such as drainage, resection, and cholecystostomy, but the operative mortality rate remained close to 60%.

Later, as the understanding of pancreatic physiology improved and diagnostic modalities advanced, conservative management of patients gained preference.

With the identification of WON or organized pancreatic necrosis and the advent of advanced antibiotics to curb systemic toxicity and OF, the treatment of pancreatic necrosis has evolved further. Minimally invasive laparoscopic, endoscopic, and percutaneous techniques have been established in recent decades to treat pancreatic necrosis.

However, surgery still serves a critical function in managing AP, and there are specific situations in which minimally invasive or open surgical interventions are necessary.

Role of ERCP(±EUS) in biliary pancreatitis[4,5,6,7,8]

1. Management of co-existing biliary obstruction in biliary pancreatitis.

   Acute biliary pancreatitis (ABP) has remained a challenging condition to diagnose and manage despite over 100 years of research.

   The debate over the role of endoscopic retrograde cholangiopancreatography (ERCP), the timing of cholecystectomy as well as the role of more modern technology such as EUS has raged on for decades.

ERCP in acute biliary pancreatitis (ABP) has historically been investigated from the postulation that it can help to resolve pancreatic duct obstruction as well as eliminating biliary obstruction through the removal of the offending gallstone.

However, conclusively proving cholangitis is difficult in patients with acute biliary pancreatitis (ABP) due to the concurrent pancreatitis and its SIRS effect.

Additionally, ERCP in ABP can be problematic due to its associated complications such as aggravation of the ongoing pancreatitis, perforation, and bleeding. Additionally, it is known that emergency ERCP for ABP is associated with higher procedural difficulty and higher risk.

The most-current literature (the APEC and the APEC-2 study done in 2020 and 2021) is congruent with the 2013 IAP and the 2017 British guidelines. Combined, it was found that that there is no indication to perform an urgent ERCP in patients with acute biliary pancreatitis, regardless of predicted severity.

The only indication for urgent ERCP is (suspected) cholangitis (which can be challenging to ascertain).

It is also suggested due to many biliary stones passing spontaneously, to perform EUS prior to the ERCP to (re)confirm the indication for ERCP with EUS in the same session. Though this was not shown to improve the indications for ERCP in these patients.

2. Definitive role of ERCP in convalescent patients with biliary pancreatitis.

   Cholecystectomy is the recommended definitive management for acute biliary pancreatitis. However, in an ageing population with increased comorbidities, this is not always possible.

   In these frail patients with prohibitive factors for surgical management, ERCP and sphincterotomy alone is an option for definitive management. This strategy has been shown to be effective in the prevention of recurrent attacks of gallstone pancreatitis.

   However, ERCP and sphincterotomy do not protect against the risk of other biliary disease such as acute cholecystitis (1-5.6%) and cholangitis (0.8-7%).

3. The emerging role of EUS for gallbladder drainage.

   The data for EUS-guided gallbladder drainage has started to emerge for acute cholecystitis than for ABP.

   In the setting of acute cholecystitis in patients who are unfit for surgery or unlikely to ever reach surgery, EUS guided gallbladder drainage is becoming a more frequently utilized option. However, this option does have some unanswered questions around patients who subsequently recover and then require a laparoscopic cholecystectomy- what should be done about the fistula? What is the effect on peri-operative outcomes and risks? What is the optimal duration for leaving lumen apposing metal stent (LAMS) in place?

   These questions still need more investigation.

   In biliary pancreatitis, ERCP and sphincterotomy as definitive therapy in patients who cannot tolerate surgical intervention is established but these modalities do not protect against the risk of other biliary disease such as acute cholecystitis (1-5.6%) and cholangitis (0.8-7%).

Is this a possible point to consider EUS interventions? This postulation also requires more investigation but is an exciting avenue for a new type of management for this challenging condition.

Definitive Management of Underlying Etiology: Cholecystectomy[9]

Laparoscopic cholecystectomy is one of the most frequently performed procedures worldwide. It is associated with a morbidity rate of 3.6% and a mortality rate of 0.2%. The most worrisome morbidity of laparoscopic cholecystectomy is a bile duct injury which occurs at a rate of 0.03%.

For biliary pancreatitis, the timing of laparoscopic cholecystectomy depends on the severity of the pancreatitis attack:

- Mild attack: same admission cholecystectomy is recommended.
- Moderate attack: Delayed lap chole until attack is resolved clinically and all transient organ dysfunction is resolved.
- Severe attack: Delayed lap chole; 4-6 weeks after resolution of attack to allow the inflammatory mass and reaction within the abdomen to settle and facilitate safe dissection during the procedure.

The data for these recommendations comes from the PONCHO trial (2012) and the MANCTRA-1 study (2024).

Role of emergency surgical interventions in acute pancreatitis.[10,11,12,13]

1. Emergency decompressive laparotomy for abdominal compartment syndrome.

   Abdominal compartment syndrome (ACS) is defined by a sustained increase in intra-abdominal pressure above 20 mmHg that is associated with the appearance of new organ dysfunction, further increasing morbidity and mortality.

   Acute pancreatitis represents a risk factor for intra-abdominal hypertension (IAH) and ACS, with an incidence of 50–60% for IAH and 15–30% for abdominal compartment syndrome.

   The mortality rate for ACS in severe acute pancreatitis is between 25% and 83%.

   In acute pancreatitis, the abdominal wall compliance is reduced by abdominal pain and abdominal wall oedema. Additionally, there are often fluid collections and visceral oedema secondary to the pancreatitis. The aggressive fluid resuscitation needed for acute pancreatitis combined with the fluid sequestration that occurs due to the inflammatory process also contributes to the development of ACS.

   ACS in AP can often be overlooked due to the many critical issues that occur in these patients. Hence, the recommendation is that patients with severe AP require frequent or scheduled monitoring of intra-abdominal pressure and evaluation of organ function for rapid diagnosis of ACS and prompt initiation of treatment.

   The first stage of treatment in the management of ACS involves non-surgical measures that can be definitive in some patients.

   Due to numerous factors, the mortality rate among patients who benefit from decompressive laparotomy remains high.

The most common technique for abdominal decompression is the median xipho-pubic laparotomy, which permits a thorough exploration of the abdomen. A further method of decompression is the bilateral subcostal transverse incision, which allows for a quicker primary closure and an easier access to the pancreatic region if subsequent pancreatic surgery is anticipated. Minimally invasive options have been investigated but are not widely accepted as standard of care.

Temporary abdominal wall closure (TAC) is used to keep the abdomen open outside of the theatre and can be accomplished by using a variety of techniques, including the Bogota bag, Marlex zipper, Velcro adhesive sheets, absorbable and non-absorbable mesh, and sandwich technique; however, the gold standard is the vacuum-assisted closure therapy techniques.

2. Endovascular control of hemorrhage as a complication of acute pancreatitis.

   Pancreatic fistula and necrosis can erode blood vessels involved in the collection causing major bleeding and occurs in 11–17% of cases and pseudo-aneurysm in around 4%. These hemorrhage events can also be a consequence of surgical intervention in AP such as secondary to necrosectomy procedures.

   The mortality rates of these hemorrhage complications are very high. The splenic artery, portal vein, spleen, and unspecified peripancreatic vessels were the most involved sources of bleeding, with associated mortality rates of 33.3%, 50.0%, 30%, and 28.5%, respectively. Massive hemorrhage was more frequently associated with severe necrosis, with a mortality rate of 37.9%.

   Majority of cases are due to localized causes of the bleed such as pseudoaneurysms which can be effectively treated with endovascular intervention. Failure of endovascular intervention for any reason warrants surgical control (including packing) which can be very challenging because of the necrosum as well as the poor physiological condition of the patient.

   There remain some cases where the bleeding cannot be localized. If the bleed in these cases is major, then there are very limited surgical options, and a high mortality rate ensues.

3. Emergency surgery for intestinal ischemia as a consequence of acute pancreatitis

   Enteric and especially colonic necrosis, ischemia, and hemorrhage in the context of severe AP are usually caused by the spread of pancreatic enzymes and pancreatic/peripancreatic necrosis. If suspected, colonic resection is essential.

   Often there are subtle warning signs that should alert the clinician of early suspicion of NOMI, such as the increasing norepinephrine doses, biological signs suggestive of mesenteric ischemia such as worsening metabolic acidosis, and the occurrence of intraabdominal hypertension. The challenge, as always, is that all these clinical features are often seen in SAP, and it can be difficult to differentiate a new complication or worsening of the existing severe disease. A sudden deterioration should alert the clinician to the possibility of this event.

   The intestinal ischemia can be secondary to a low splanchnic blood flow due to a superior mesenteric artery vasoconstriction and/or a low cardiac output causing non-occlusive mesenteric ischemia. The inflammatory process can also thrombose arterial vessels to the colon and that will also result in colonic ischemia.

   The mesenteric arteries have no properties of autoregulation, meaning that flow is directly proportional to pressure. Cardiac output should then be optimized mainly with fluid resuscitation and the administration of vasopressors (though it should be noted

that most inotropes will increase the mesenteric vasoconstriction). Management also involves resection of necrotic segments of the affected bowel. Stoma creation can be considered for colonic necrosis. However, due to the poor physiology of these patients, clip-and-drop type staged procedures are often necessary.

Interventions for the management of local complications of acute pancreatitis. [14,15]

Terminology of local complications of AP:

In clinical practice, local complications should be suspected when:

- There is persistent or recurring abdominal pain.
- Worsening clinical signs of sepsis, such as fever and leucocytosis.
- Worsening organ dysfunction.
- Clinical failure to improve after 7–10 days of hospitalization.

In such cases, prompt contrast-enhanced abdominal CT and/or MRI should be performed to confirm the diagnosis of local complications and infection.

Decisions regarding indication for intervention, timing of intervention and modality of intervention are some of the most complex decisions in the management of SAP.

Considerations must be made for:

· Type of local complication.

· The presence/evidence of infection.

· The location of the complication.

· The options for interventions available and decision making to choose the most ideal option.

· The timing for intervention.

Management of pancreatic pseudocysts[16]

1. Indication of Intervention for Pancreatic Pseudocysts

   The drainage of pseudocysts is indicated in patients with:

   - Symptoms (persistent abdominal pain, nausea, early satiety, anorexia, weight loss, or jaundice).
   - Complications (infection, bleeding, or obstruction (gastric, duodenal, or biliary obstruction).

   This is regardless of pseudocyst size.

2. Methods of Intervention for Pancreatic Pseudocysts

   The options for drainage of pancreatic pseudocysts are:

   · Open surgical cyst-gastrostomy.

   · Minimally invasive cyst-gastrostomy.

- Endoscopic cyst-gastrostomy.
- Percutaneous drainage of pancreatic pseudocyst.

Open surgical cyst-gastrostomy and percutaneous drainage of the pseudocyst are some of the least favourable options due to the morbidity conferred by these approaches. The minimally invasive option has mostly replaced the open surgical approach but the endoscopic approach has taken the foreground since the widespread use of endoscopic ultrasound scopes (EUS) and lumen-apposing metallic stents (LAMS).

EUS-guided transmural drainage has been shown to be effective in resolving pseudocysts, with a lower incidence than surgery and without the need for external drains.

Management of Necrotizing Pancreatitis[17,18,19,20]

Pancreatic necrosis is often noted as non-enhancement of the pancreatic parenchyma on contrast-enhanced CT. Accurate classification of local fluid collections is important because the management and prognosis of necrotizing pancreatitis are significantly more challenging and unfavourable.

Infected Necrosis

Infected necrosis occurs as a complication in approximately one-third of patients with necrotizing pancreatitis.

Both acute necrotic collection and WON are initially sterile but can become infected over time. This is due to the bacterial translocation from the gut to the adjacent necrotic pancreatic parenchyma.

Infected necrosis has a high mortality rate of 30% and is a leading cause of morbidity and mortality in necrotizing pancreatitis.

Therefore, when infection is strongly suspected (e.g., gas in necrosis, bacteraemia, sepsis, or clinical deterioration), empiric antibiotic therapy is promptly initiated.

Broad-spectrum intravenous antibiotics known to penetrate pancreatic necrosis should be favoured.

Strong consideration should be given to interventional strategy and timing of this intervention when infected necrosis is identified.

Diagnosis of infected necrosis

Abdominal computed tomography (CT) images showing the presence of an extraluminal gas configuration within the area of necrosis were regarded as pathognomonic. However, it is only found in approximately half of patients with infected necrosis, and the absence of gas does not signify the absence of infection.

EUS- or CT-guided fine-needle aspiration (FNA) of the necrotic collection for Gram staining and culture can be performed to confirm the presence of infection. However, this diagnostic procedure is unnecessary in most cases, and recent guidelines do not recommend the routine use of FNA.

In current practice, therapeutic interventions are postponed whenever clinically feasible until necrosis becomes encapsulated.The guiding principle is often referred to as the DDD strategy i.e. Delay, Delay, Delay (for as long as possible).

Treatment Approach for Necrotizing Pancreatitis

Historical approach: Since the 1980s, necrotizing pancreatitis was mainly treated by surgeons performing surgical necrosectomy within 1–3 days of onset.

The current approach has been shaped by some landmark trials:

1. The PANTER trial.
2. The POINTER trial.

#The landmark PANTER trial: Minimally invasive step up approach versus maximal necrosectomy in patients with acute necrotising pancreatitis: a randomised controlled trial by the Dutch Acute Pancreatitis Study Group; 2010.

- Clinical question: Among patients with necrotizing pancreatitis with infected necrosis, what are the differences in outcomes between a minimally invasive step-up approach and primary open necrosectomy?
- Bottom line: A minimally invasive step-up approach reduced complications or death by 43% compared with primary open necrosectomy, among patients with necrotizing pancreatitis and infected necrosis.
- The step-up approach in the PANTER trial consisted of percutaneous drainage followed, if needed, via minimally invasive retroperitoneal necrosectomy (usually after 4 weeks).
- This randomized controlled trial (n=88) demonstrated that a minimally invasive 'step-up' approach is better than an open necrosectomy with:
    - A significant decrease in the rate of new-onset multiple organ failure (12% vs. 40%).
    - A decrease in incisional hernia (6% vs. 19%).
    - A decrease in new-onset diabetes (16% vs. 38%).

Hence, the traditional management of infected necrosis with upfront surgical debridement has been almost completely replaced by minimally invasive surgical and endoscopic step-up approaches.

#The POINTER trial: Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. The Dutch Acute Pancreatitis Study Group; 2021

1. Question= In patients with infected necrosis, is routine immediate drainage (within 4 weeks) superior to delayed drainage (>4 weeks)?
2. Multicentre, RCT.

Conducted in 2021 (11 years after PANTER).

104 patients in total, split between the 2 groups.

3. Result= Immediate drainage is not superior to delayed drainage.

    - Routine immediate drainage, even when infected necrosis was diagnosed within the first 4 weeks, did not improve clinical outcomes

    - And immediate drainage led to more invasive interventions (catheter drainage and necrosectomy) compared with the postponed drainage group.

    - 39% of infected necrosis cases improved with antibiotics only.

    - Thus, initial conservative management with antibiotics and a postponed drainage strategy are justified when infected necrosis is diagnosed, and help prevent unnecessary procedures, especially in the early phase of AP.

Current treatment approach for necrotizing pancreatitis based on the recent data discussed above:

Indications for intervention

- Both infected necrosis and symptomatic sterile necrosis are accepted indications for therapeutic interventions.

- If the signs of infection continue despite receiving antibiotics for 48 to 72 h, it is necessary to consider interventional techniques for draining the collection as the next step.

Timing of intervention

Pancreatic intervention should be optimally delayed for 4 weeks until pancreatic necrosis has become encapsulated.

During the first few weeks of the AP phase (<3 to 4 weeks), most institutions attempt to postpone the procedure by continuing antibiotics.

- This allows reserving of catheter drainage in patients who are experiencing clinically ongoing deterioration.

Anatomical considerations for intervention

1. The location of the pancreatic necrosis:

    - As assessed with preprocedural cross-sectional imaging, is a key factor in guiding approaches to pancreatic intervention.

    - Central collections located within the lesser sac abutting the posterior gastric wall can be accessed through the trans-gastric route.

    - Retro-gastric collections that extend deep into the left paracolic gutter can be drained endoscopically, percutaneously or via a left retroperitoneal approach, due to the dependent component.

    - Collections located in the root of the mesentery or to the right of the mesenteric vessels are challenging to access thus, laparoscopic transperitoneal or traditional open approaches may be necessary.

2. Endoscopic approaches are generally preferred because it is associated with fewer complications than surgical approaches.

Options for intervention available for necrotizing pancreatitis[21, 22, 23, 24, 25]

The different treatment options available for necrotizing pancreatitis are:

1. Percutaneous drainage.
2. Endoscopic drainage and necrosectomy.
    a. Multi-gated technique.
3. Surgical debridement
    a. MIRP and VARD techniques.
    b. Open surgical debridement.

Percutaneous drainage

Endoscopic drainage is preferred as a much lower rate of pancreatic fistula than percutaneous drainage.

Percutaneous drainage is usually reserved for salvage management when endoscopic drainage is unsuccessful or not technically feasible.

In general, the retroperitoneal route is preferred because it avoids enteric leaks and peritoneal contamination and can be used later for VARD, MIRP, or percutaneous endoscopic necrosectomy.

After the placement of single or multiple catheters, the catheters undergo vigorous manual irrigation with isotonic saline and was serially upsized to larger-bore catheters and repositioned to easily remove necrotic debris.

An overall success rate of 56% is achieved when percutaneous drainage was used as the primary drainage for necrotizing pancreatitis. However, adverse events such as external fistulae occur in up to 27% of the patients who had percutaneous drainage.

Endoscopic options:

1. Endoscopic drainage

Endoscopic transmural drainage involves the creation of a fistula into necrotic cavities using EUS rather than direct puncture under endoscopic vision.

EUS was associated with higher technical success (95% vs. 35–66%) and a trend toward lower adverse event rates (0–4% vs. 13–15%) than the conventional direct puncture technique.

Lumen apposing metallic stents (LAMS), have larger diameter compared to plastic stents, theoretically offers superior drainage and facilitates sequential direct endoscopic necrosectomy (DEN), potentially aiding in managing WON.

- The use of anchoring coaxial double-pigtail plastic stents within a LAMS has been shown to decrease the incidence of adverse events, including stent occlusion and bleeding.

2. Endoscopic necrosectomy

Endoscopists have increasingly attempted to perform direct endoscopic necrosectomy (DEN) in patients with WON in addition to transmural drainage alone.

DEN can be performed at the index procedure but is generally performed as subsequent procedures after the liquid component has been drained.

Endoscopic drainage with necrosectomy achieves a clinical success rate of 81%, with an average of four endoscopic interventions per patient.

The overall complication rate is estimated to be 36%, with a procedure-related mortality rate of 6%.

3. Multi-Gated Endoscopic Technique

- A new EUS-based approach has been devised to manage pancreatic necrosis by creating multiple transluminal gateways to facilitate effective drainage of the necrotic contents- this is the multi-gated technique (MTGT).

- In MTGT, 2 or 3 transmural tracts are created by using EUS guidance between the necrotic cavity and the GI lumen.

- While one tract is used to flush normal saline solution via a nasocystic catheter, multiple stents were deployed in others to facilitate drainage of necrotic contents.

- The EUS-guided MTGT seems to be an effective treatment option for the management of symptomatic walled-off pancreatic necrosis because it might decrease the need for surgery and endoscopic necrosectomy and its attendant procedure-related morbidity.

- Prospective studies are required to confirm these preliminary but promising data.

Surgical options:

1. Minimally invasive surgical debridement

Surgical pancreatic debridement can be performed using either minimally invasive or open techniques.

Minimally invasive approaches are associated with less severe inflammatory response and lower physiologic stress than open surgery.

Video Assisted Retroperitoneal Debridement (VARD) and Minimally Invasive Retroperitoneal Pancreatic necrosectomy (MIRP) are the most used minimally invasive techniques as retroperitoneal approaches for draining retro-gastric collections that extend to the paracolic gutter.

- Laparoscopic trans-gastric debridement.

- VARD and MIRP technique

These patients require preoperative percutaneous access to the retroperitoneal space. Long grasping forceps under direct vision of a videoscope via an incision (5–7 cm) during VARD or two–three 30 Fr nephroscope with forceps in the working channel without an incision during MIRP are used for debridement.Debridement is typically repeated every 7–10 days until the necrotic cavity is free of debris and lined with healthy granulation tissue.

A meta-analysis of VARD demonstrated a 64% success rate, 47% morbidity rate, and 14% mortality rate.

2. Open surgical debridement

Open surgery is infrequently performed in patients with extensive necrosis inaccessible to both percutaneous and endoscopic drainage, in whom the step-up approach has failed, or in those with rare life-threatening complications.

Current treatment strategy selection for necrotizing pancreatitis: step-up endoscopic vs step-up surgical? Which one is preferred

Both endoscopic and surgical 'step-up' approaches have been proven effective in managing infected necrosis. The choice between the two approached are based on data from certain landmark trials:

1. The PENGUIN trial (2012)

2. The TENSION trial (2018) and the ExTENSION study (2022).

3. The MISER trial (2019).

The PENGUIN trial (Endoscopic Trans-gastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis; Dutch Acute Pancreatitis Study Group) compared endoscopic transluminal necrosectomy (n = 10) and various surgical necrosectomy techniques (n = 10).The results revealed a significant decrease in the inflammatory response (measured by interleukin-6) and the development of new-onset multi-organ failure in the endoscopic arm.

#The TENSION trial (Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial; Dutch Acute Pancreatitis Study Group) compared endoscopic catheter drainage followed by endoscopic necrosectomy (if necessary) (n = 51) and percutaneous catheter drainage followed by VARD (if necessary) (n = 47).

- This study found no significant difference between the two approaches.
    - Including mortality and major morbidity at the 6-month follow-up (43% vs. 45%, p = 0.88).
- The endoscopic approach resulted in a shorter hospital stay and significantly fewer pancreatic fistulae (5% vs. 32%, p = 0.001).

#The results of the long-term follow-up of the TENSION trial- reported in the ExTension study- showed that the endoscopy group needed fewer reinterventions at the 7 year follow up (7% vs. 24%, p = 0.038).The results of both these papers directed management to begin at endoscopic step-up strategies as far as possible to mainly provide the benefit of decreased morbidity.

The MISER trial (An Endoscopic Transluminal Approach, Compared With Minimally Invasive Surgery, Reduces Complications and Costs for Patients With Necrotizing Pancreatitis; USA) compared step-up minimally invasive surgical approaches (laparoscopic or VARD) (n = 32) with the endoscopic step-up approach (n = 34).

- Single centre, randomized trial. N=66. Led by medical gastroenterology teams.
    - At six months, fewer patients in the endoscopic group had major complications or death (12% vs. 41%, p = 0.007) or fistulas (0% vs. 28%, p = 0.001) than those in the surgery group.
    - Unlike the TENSION trial, the MISER trial considered enteral and pancreatic fistula as major endpoints (TENSION only looked at pancreatic fistulae), explaining the primary difference in the conclusions between the two studies.

In conclusion, while not superior in reducing death or major complications except pancreatic fistula, the endoscopic step-up approach seems to be the preferred treatment for infected necrotizing pancreatitis compared to the step-up minimally invasive surgical approach

Conclusion

The indications for interventions for acute pancreatitis are diverse and range based on aetiology and severity of the disease. From the historical ideas of universal laparotomy even for diagnosis to the current strategy of mainly conservative approaches with a step-up approach to intervention- the understanding of the disease and development of endoscopic technology has revolutionized management.

The main triggers for intervention are the effects and consequences of severe acute pancreatitis, a deadly form of the disease that still carries a mortality rate of up to 30%. Emergency complications and surgical interventions needed for them are often associated with poor outcomes.

The interventions for local complications of severe acute pancreatitis are multiple and the strategies complex. High volume centres with expertise in both endoscopy and HPB surgery as well as a multi-disciplinary approach are essential to improving outcomes. The quality of data to guide these decisions has also improved and slowly, after almost a century of investigation, a direction of approach has started to emerge.

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Carotid Body Tumours.

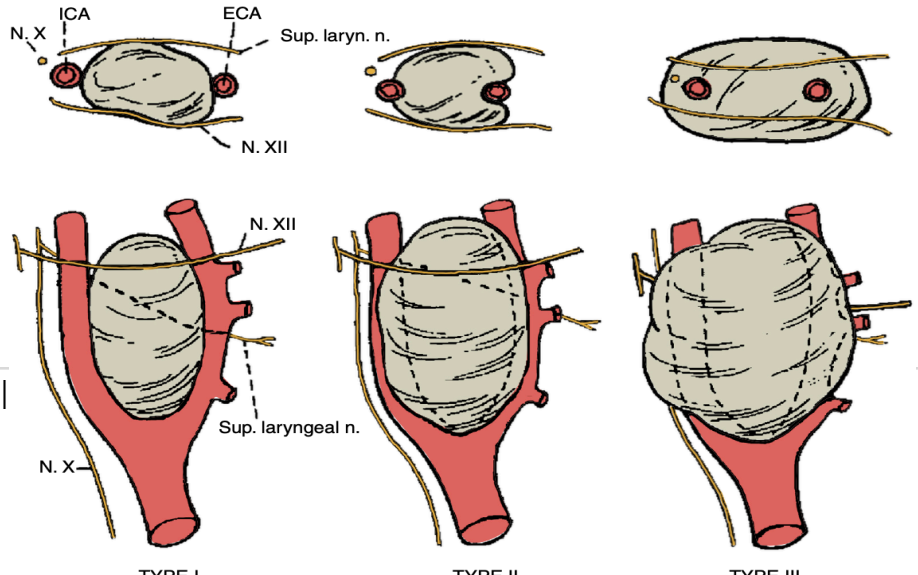
Dr SE Morrison

The carotid body is a small chemoreceptor organ located within the periadventitia of the posteromedial aspect of the carotid bifurcation. They are most common in females in the third to fifth decade of life. Its physiological role relates to homeostasis of pH, pO2, and pCO2, which it controls through modulation of cardiovascular and respiratory function with the release of neuro-transmitters as necessary. It is a highly vascular organ, receiving a rich arterial blood supply originating from branches mainly derived from the external carotid artery (ECA), most commonly the ascending pharyngeal branch. Carotid body tumours (CBTs), which are also termed chemodectomas, are rare neoplasms with a reported incidence of one in 30,000. However, they make up 65% of all head and neck paragangliomas. Other cervical paragangliomas include glomus vagale, glomus jugulare and glomus tympanicum.

The embryologic origins of the carotid body are both neural crest ectoderm and mesodermal tissue from the third branchial arch. The neural crest cells migrate in close association with autonomic ganglion cells; thus, they are often referred to as paraganglioma cells. These cells differentiate into the chemo-receptors, also known as type I glomus cells. The mesoderm forms the rich vascular stroma, made up of type II glomus cells, which support the chemoreceptor cells.

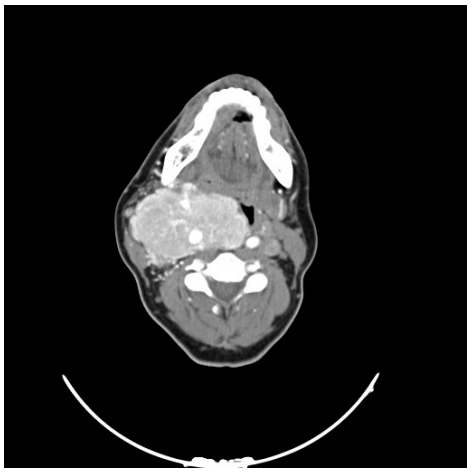
These tumours can be classified by aetiology or anatomy. The three recognised aetiological types are sporadic (the most common), familial, and hyperplastic. Hyperplastic CBTs are most commonly diagnosed in the context of chronic hypoxia, for example in patients living at high altitude or with chronic lung disease. Microscopically, CBTs tend to resemble normal carotid body architecture with a well- differentiated benign appearance. Only very rarely does histology demonstrate degenerative malignant characteristics, such as nuclear polymorphism, vascular invasion, increased mitotic activity, and necrosis.

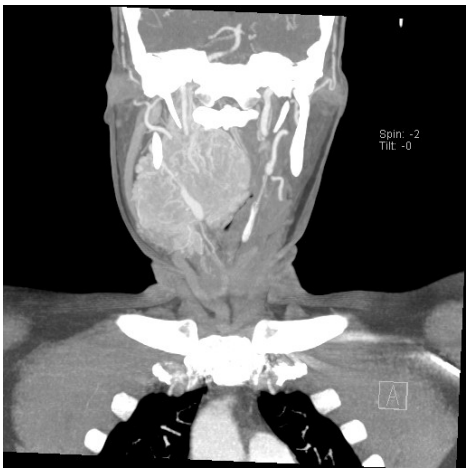
The anatomical classification described by Shamblin et al. is the most clinically useful as it describes the extent to which the CBT envelopes the common carotid artery (CCA), the internal carotid artery (ICA), and the ECA and was designed to be a predictor of intra- operative technical difficulty



The majority of CBT's present as asymptomatic neck masses occurring below the angle of the mandible. They may also present with localized tenderness, fullness, numbness, dysphagia, hoarseness, chronic cough, tinnitus or nerve involvement.

Radiographic imaging is a critically important modality in the diagnostic confirmation and preoperative evaluation. Duplex ultrasound is an important non-invasive method of imaging, providing good anatomic detail, allowing assessment of tumour vascularity via doppler, and allowing us to assess vessel encasement. The current gold standard is CT angiography, which provides good anatomic and vascular detail, as well as assessing





extent in both cephalic and caudal directions. Conventional angiography is reserved for use when pre-operative embolisation is planned.

Vascular surgeons have only a limited experience of treating CBTs, which can be associated with a not insignificant morbidity and mortality, especially peri-operative stroke and cranial nerve injury (CNI). To date, there has been no large scale systematic review and meta-analysis of outcome data to guide practice. Surgical resection remains the mainstay of management for CBT, with radiation therapy being reserved for suppression, poor operative candidates, bulky, unresectable or recurrent tumours.

Cerebral protection and monitoring may be used due to potential or planned internal carotid artery occlusion or reconstruction. Monitoring may be done with intra-operative EEG, carotid stump pressure measurement, SSEP, TCD or transcranial oximetry. The patient is supine with the head rotated to the contralateral side. Depending on the patient's body habitus, a shoulder roll may be placed to extend the neck. The head of the table can be elevated 10 to 15 degrees.

Incision is made through the skin and sub-cutaneous tissues along the anterior border of the sternocleidomastoid muscle.The carotid bifurcation is then exposed by ligating the common facial vein and then reflecting the IJV laterally. The CC should then be circumferentially mobilised. The. Dissection is

carried on in the perivascular plane until the superior extent of the tumour at the ICA is reached and the ICA can be mobilised. The tumour can then be separated from the ICA by following the same perivascular plane toward the bifurcation. The ECA can then be mobilised, and the branches feeding the tumour ligated. The mass can then be mobile on all surfaces and removed.

The overall cranial nerve injury rate is 25%. The commonest CNI involved the hypoglossal nerve (10%), while the vagus nerve is affected in 8%. A Horner's syndrome complicated 3% of tumour excisions; the mandibular branch of the facial nerve was affected in 3%, the glossopharyngeal nerve in 2%, and the accessory nerve in 1%.

The prevalence of neck haematomas requiring re exploration is 5%. The literature shows that preoperative embolisation does not improve peri-operative bleeding as compared with patients who undergo CBT excision without pre-operative embolisation, however there are no randomised trials proving this. Surgery is associated with significant intra-operative bleeding, cell salvage and cross-match is advised for large tumours.

The mean 30 day mortality is 2%, and the mean proportion of patients developing a stroke at 30 days is 4%.

When relating the stroke rate to the Shamblin classification, Shamblin I CBT incurs a 2% stroke rate at 30 days, compared with 3% in patients with Shamblin II tumours and 4% in patients with Shamblin III tumours.

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Pathophysiology of reperfusion syndrome and current management approach

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Introduction

Ischaemia-Reperfusion injury (IRI) is defined as the paradoxical exacerbation of cellular dysfunction and death, following restoration of blood flow to previously ischaemic tissues. Re-establishment of blood flow is essential to salvage ischaemic tissues. However, reperfusion itself paradoxically causes further damage, threatening function and viability of the organ. IRI occurs in a wide range of organs including the heart, lung, kidney, gut, skeletal muscle and brain and may involve not only the ischaemic organ itself but may also induce systemic damage to distant organs, potentially leading to multi-system organ failure. Reperfusion injury is a multi-factorial process resulting in extensive tissue destruction.

Reperfusion syndrome is the umbrella term for complications of I-R injury. The currently accepted definition of reperfusion syndrome was provided by F. William Blaisdell: “complex syndrome with local and systemic consequences developing after a major I-R injury affecting a large amount of tissues

Ischaemia

ATP and mitochondrial function

Ischaemia occurs when the blood supply is less than the demand required for normal function, resulting in deficiencies in oxygen, glucose and other substances required for metabolism. Derangements in metabolic function begin during this ischaemic phase. Initially, glycogen breakdown by mitochondrial anaerobic glycolysis produces two molecules of adenosine triphosphate (ATP) along with lactic acid, resulting in a decrease in tissue pH, which then acts by negative feedback to inhibit further ATP production. ATP is then sequentially broken down into adenosine diphosphate (ADP), adenosine monophosphate (AMP) and inosine monophosphate (IMP) and then further into adenosine, inosine, hypoxanthine and xanthine.

At the cellular level, a lack of ATP production causes ATP-dependent ionic pumps, including the Na+/K+ and Ca^{2}+ pumps, to fail and the transmembrane ionic gradients are lost. Consequently, cytosolic sodium content rises, drawing with it, a volume of water to attempt to maintain the osmotic equilibrium and resulting in hydroponic swelling of the cells. To maintain the ionic balance, potassium ions escape from the cell into the interstitium. Calcium is released from the mitochondria into the cytoplasm and into extracellular spaces, thereby activating mitochondrial calcium-dependent cytosolic proteases including calpain, which then converts the cellular enzyme xanthine dehydrogenase to xanthine oxidase. Phospholipases are also activated during ischaemia, degrading membrane lipids and increasing the levels of circulating fatty acids.

Gene expression during ischaemia

As well as metabolic derangements, ischaemia induces expression of many genes, which play a major role in the tissue's response to ischaemic damage. Hypoxia itself also activates several genes, particularly transcription factors, including activating protein-1 (AP-1), hypoxia-inducible factor-1 (HIF-1) and nuclear factor-kappab (NF-kb). HIF-1 then activates transcription of other genes such as vascular endothelial growth factor (VEGF), erythropoietin and glucose transporter-1, which all play an important role in the cells' adaptive responses to hypoxia

Reperfusion

Reactive oxygen species

Reactive oxygen species have a destructive role in mediating tissue damage during IRI. During ischaemia, the degradation of ATP produces hypoxan. Once the ischaemic tissue is reperfused, an influx of molecular oxygen catalyses xanthine oxidase to degrade hypoxanthine to uric acid and thereby liberating the highly reactive superoxide anion (O_2^-). Superoxide is subsequently converted to hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^\bullet$). The major consequence of hydroxyl radical production is peroxidation of the lipid structures of cell membranes resulting in the production and systemic release of proinflammatory eicosanoids, disruption of cell permeability and cell death. During IRI, ROS also activate endothelial cells, elevating the activity of the transcription factor, NF-κB. Once activated, the endothelial cell produces E-selectin, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), endothelial-leukocyte adhesion molecule (EMLMl Am -1) plasminogen activator inhibitor-1 (PAi-1), tissue factor and interleukin-8 (il-8). These adhesion molecules contribute to important interactions between the neutrophil and the endothelium and will be discussed in more detail later.

Eicosanoids

ROS initiate lipid peroxidation of cellular membranes, releasing arachidonic acid, the main substrate to produce prostaglandins, thromboxanes and leukotrienes. These derivatives of arachidonic acid are collectively known as the eicosanoids and play a major role in the pathophysiology of IRI.

Prostaglandins, synthesised from arachidonic acid via the cyclo-oxygenase pathway, have a protective vasodilatory effect in IRI. However, since prostaglandins are short-lived molecules, their rapid depletion subsequently leads to uninhibited vasoconstriction, reduced local blood flow and exacerbation of ischaemia.

Plasma thromboxane $A_{2,}$ also synthesised from arachidonic acid, increases within minutes following skeletal muscle IRI, thus promoting vasoconstriction and platelet aggregation. These events coincide with a rapid rise in pulmonary artery pressure and a subsequent increase in pulmonary microvascular permeability, which correlates with sequestration of polymorphonuclear cells in the lungs

Leukotrienes are also synthesised from arachidonic acid through the activation of 5-lipoxygenase and participate in the inflammatory cascade of IRI. Leukotrienes lead to local and systemic injury by their direct proinflammatory action on endothelial and smooth muscle cells and indirectly by their effects on neutrophils.

The leukotrienes C_4, D_4, and E_4 modify the endothelial cytoskeleton, leading to increased vascular permeability and enhance smooth muscle contraction, resulting in vasoconstriction. The lung produces leukotrienes following remote IRI. The direct effects of leukotrienes on pulmonary micro vessels lead to increased permeability, transient pulmonary hypertension and the activation of the endothelium to produce thromboxane, resulting in additional vaso-constriction. The leukotriene B_4, released by activated neutrophils, leads to further pulmonary neutrophil accumulation.

Nitric oxide

Nitric oxide (NO) is a signalling molecule synthesised from L-arginine by the nitric oxide synthase enzyme (NOS) of which there are three types, constitutive (CNOS), inducible (INO S) and endothelial (ENO S).

The pathophysiological role of nitric oxide in reperfusion injury is variable, being dependent on the nature of its generation and appears to be tissue specific. In some instances, NO acts as an antioxidant and, in others, combines with the superoxide anion to form the peroxynitrite radical, a potent promoter of lipid peroxidation and hence cellular membrane disruption.

Endothelin

Endothelins are potent peptide vasoconstrictors produced by the vascular endothelium. Hypoxia, growth factors, angiotensin II and noradrenaline all stimulate their production resulting in Ca^{2+}-mediated vasoconstriction. Endothelin-1 is elevated following skeletal muscle IRI during both the ischaemic and reperfusion phases and mediates capillary vasoconstriction, neutrophil aggregation and neutrophil-endothelial interactions.

Cytokines

Hypoxia and IRI both induce the expression of numerous cytokines, including tumour necrosis factor-alpha (TNF- α,) interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and platelet activating factor (PAF), in association with elevations in activity of the transcription factor, NF-kB. These cytokines are released systemically and are thus important in the development of systemic inflammatory response syndrome and ultimately multi-system organ failure.

Neutrophil and endothelial interactions

Neutrophils play a major role in tissue damage incurred during IRI. Activated neutrophils are a major source of ROS, which are generated through the activity of the membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Whilst oxidizing NADPH to NADP+, NADPH oxidase also reduces molecular oxygen to form the superoxide anion. Myeloperoxidase, stored in the azurophilic granules of neutrophils, converts hydrogen peroxide to toxic hypochlorous acid, which, in addition to its direct effects, is also capable of activating proteases. The activated neutrophils also secrete several proteases, including matrix metalloproteinases, which will degrade basement membrane and other tissue structures, contributing to the severity of tissue destruction.

Selectins are a family of transmembrane molecules, expressed on the surface of leukocytes, activated endothelial cells and in platelets. Selectins mediate the

initial phase of neutrophil–endothelial cell interactions, often termed rolling, which is essential for their subsequent adhesion and extravasation.

The integrin and immunoglobulin supergene families of adhesion molecules mediate the strong adhesion of activated neutrophils to the endothelium and hence allow their subsequent extravasation during IRI. The integrins form a large family of cell surface adhesion molecules that mediate intercellular recognition and cellular binding to the extracellular matrix.

The immunoglobulin supergene family (ligands for integrins) contains many molecules with multiple immunoglobulin-G-like domains. Several members of this family are involved in leukocyte-endothelial cell interactions including ICAM-1, VCAM-1 and platelet-endothelial cell adhesion molecule-1 (PECAM-1

Complement activation.

Complement activation and deposition also contribute significantly to the pathogenesis of IRI.

Tissue Destruction

Proteases and metalloproteinases

The matrix metalloproteinases (MMPs) are a family of zinc dependent enzymes that can degrade components of the extracellular matrix. Together with their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), they are the major physiological regulators of the extracellular matrix. MMPs are intimately involved in all processes that necessitate degradation or synthesis of the extracellular matrix and important roles for these enzymes have been identified in wound healing, periodontal disease, cancer metastasis and, of relevance, vascular disease including the development of aneurysms, atherosclerotic plaques and reperfusion injury.

Apoptotic cell death during ischaemia-reperfusion injury

Tissue destruction resulting from IRI can be due to either necrotic or apoptotic cell death. Apoptosis or programmed cell death is an active process characterized by a series of gene-directed events leading to a characteristic cell morphology, controlled DNA fragmentation and eventually death of the cell.

No reflow phenomenon.

No reflow is the failure of microvascular perfusion, following restoration of flow to previously ischaemic tissue. The cause of this phenomenon has not been fully elucidated but is certainly multifactorial. Cytokines and activated neutrophils act synergistically to produce microvascular barrier dysfunction.

Clinical Manifestations of Reperfusion Injury

The clinical manifestations of I/R are diverse and may include myocardial hibernation/stunning, reperfusion arrhythmias, impaired cerebral function, breakdown of the gastrointestinal barrier, systemic inflammatory response syndrome (SIRS) and most devastating, multiorgan dysfunction syndrome (MODS).

However, for the purpose of this review, we have turned our focus towards the local injury of skeletal muscle. The ability of skeletal muscle to anaerobically synthesize ATP confers a relative tolerance to ischemic injury but once energy stores are depleted, reperfusion following ischemia may be complicated by muscle edema, compartment syndrome, muscle necrosis and impaired function. The underlying pathologies include vascular thrombosis and embolism as well as vascular surgical procedures and most importantly, limb trauma and are endowed with a 10–20% rate of amputation. The cytotoxic mediators in concert induce endothelial dysfunction and more important, disruption of endothelial integrity, which is associated with increased microvascular permeability and fluid loss into the interstitial space with the result of oedema formation. This is devastating as the skeletal muscles are limited in expansion and the rise in interstitial fluid pressure can produce extravascular compression and compartment syndrome. While the local injury reflects microcirculatory failure, release of mediators from the limb may promote remote organ injury contributing to the high mortality seen in these patients. Early work has shown that revascularization of ischemic limbs released K+, H+ and myoglobin into the circulation and resulted in impaired renal and pulmonary function and subsequently, a wide array of inflammatory mediators including LTB4, TXA2, TNF-a, IL-1b, IL-6 and activated complement components have been identified.

The most devastating effects of IRI incur through MODS, the leading cause of death in critically ill patients and acute respiratory insufficiency (ARDS) due to increased permeability in lung vasculature that often is the first clinical sign. The pulmonary injury (ARDS) is mediated by neutrophil sequestration where neutrophils are abundantly present in the pulmonary bed when compared to the normal circulating pool and are activated directly by metabolites produced by the ischemic tissue (e.g. C5a, LTB4, Thromboxan A2). Besides the lung, MODS can involve renal, hepatic, myocardial and CNS dysfunction and neutrophil granulocytes and complement activation in concert with cytokine release (TNF-a, IL-6) have been implicated as the primary mediators of remote organ damage. In this context, PMN immunodepletion was shown to moderate both local and remote organ injury and blockage of complement activation (sCR1) was demonstrated to prevent.

Therapeutic Approaches to IRI

Unfortunately, there are very limited therapeutic options in preventing the progression of reperfusion syndrome. Supportive intense therapy, hemodyalysis, plasma exchange, or ultrafiltration with the elimination of toxic products from the circulation might reduce the degree of multiple organ injury. The prevention of complications of reperfusion consist of re-establishing circulation within the golden period before irreversible muscle damage occurs. Early recognition and surgical treatment of compartment syndromes, together with timely limb amputations can be lifesaving.

Experimental concepts

1. Ischaemic preconditioning consists of brief and repetitive episodes of IRI before the induction of sustained organ ischaemia and is effective in reducing the severity of tissue damage.
2. Pharmacological interventions (methylprednisolone, multi-vitamin antioxidant infusion, vitamin E infusion, amrinone, prostaglandin E1,

pentoxifylline, mannitol, trimetazidine, dextrose, allopurinol and a thromboxane A2 synthetase inhibitor).

3. Among patients with myocardial infarction, the use of mesenchymal stem cells has garnered increased attention.
4. Techniques for preservation of organs in transplantation may serve to improve outcomes in I/R injury. Hypothermic machine perfusion with pulsatile flow in deceased donors may reduce the rates of delayed graft function following renal transplantation, highlighting the potential role for mechanical mechanisms to reduce tissue damage in I/R injury

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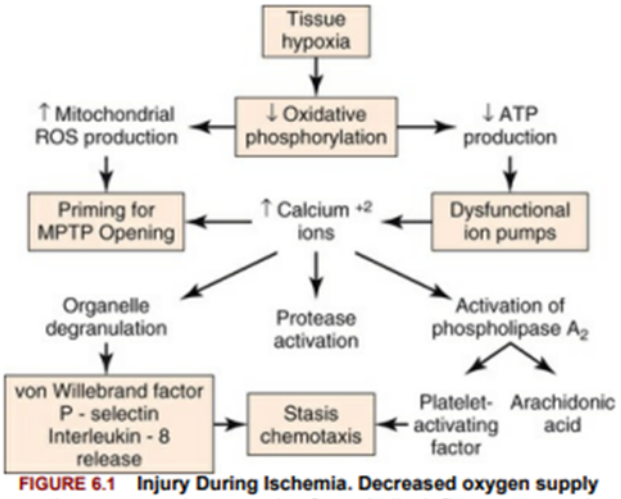


FIGURE 6.1 Injury During Ischemia. Decreased oxygen supply activates a complex cascade of metabolic, inflammatory, and

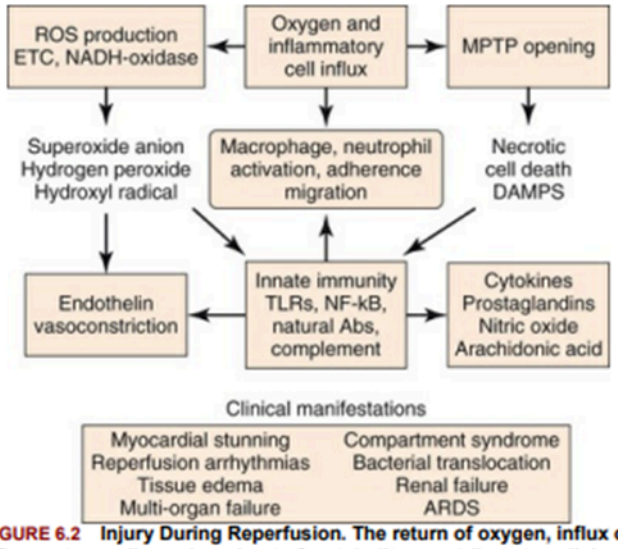
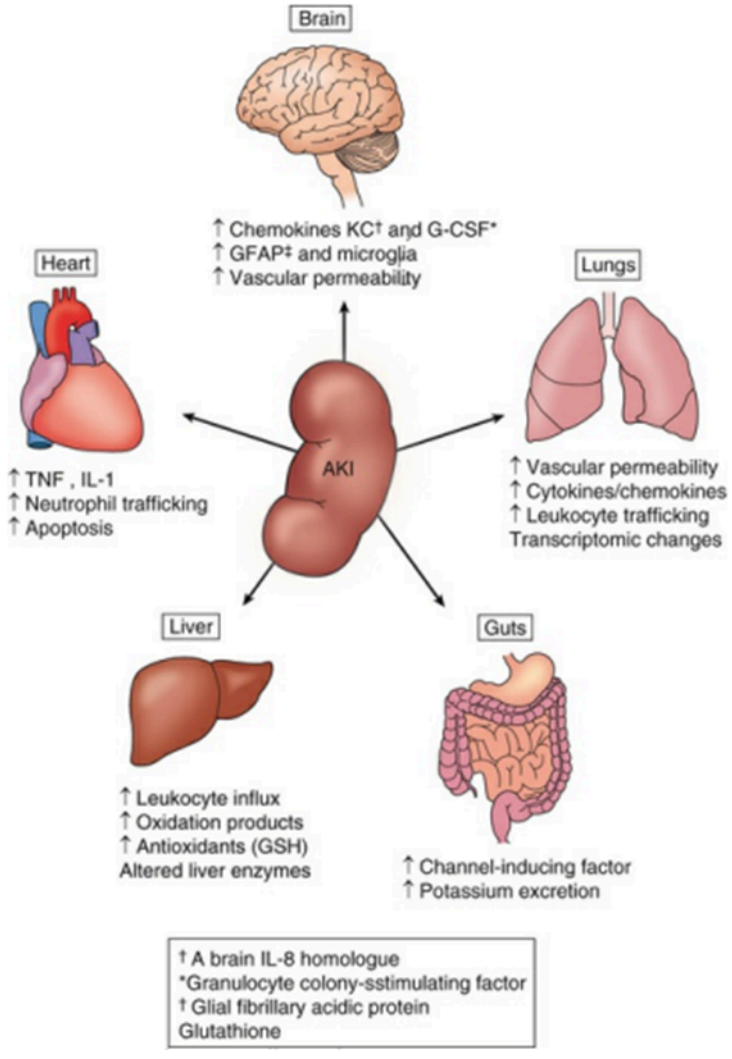


FIGURE 6.2 Injury During Reperfusion. The return of oxygen, influx of inflammatory cells, and washout of metabolites contribute to cell death and an inflammatory, prothrombotic milieu that exacerbates tissue



Are there any indications for definitive surgery in peptic ulcer disease?

Martin Phakula

Introduction

Peptic ulcer is a cause of significant morbidity and mortality and can impairs the quality of life. For decades surgical treatment was the mainstay of treatment for ulcers. However, in the past decades there has been a significant decline in the number of surgeries performed for peptic ulcers disease (PUD). The decline has been attributed to the introduction of H2 receptor blockers and Proton pump inhibitors (PPIs) as treatment for ulcers. Also, a better understanding of *Helicobacter pylori* in the pathogenesis of ulcers and the effectiveness of eradication therapy has played a significant role in the decline of surgery as a preferred mode of treatment for PUD. Despite the reported improvement in the management of ulcers, complication related to the condition still occur and may be the indication for surgery.

Definitive ulcer surgery.

Acid production in the stomach is a response to the cholinergic pathway, histamine pathway, and the gastrin pathway. Definitive ulcer surgery is aimed at disrupting these pathways, resulting a reduction in acid production as the intended outcome.
Indications for surgical intervention are.

- Protracted bleeding despite endoscopic therapy'
- Ulcer perforation
- Obstruction because of scarring following healing of prepyloric and/or duodenal ulcers.
- Intractability despite maximum medical therapy
- Inability to rule out cancer when an ulcer remains despite treatment and negative endoscopic biopsies.

Various surgical procedures have been used in these settings with different outcomes and some with long term morbidities. Therefore, patient selection is important to ensure that the patient receives an appropriate operation from which they can get the maximum benefit with fewer long-term complications.
The goals of surgical procedures are to

- Permit ulcer healing.
- Prevent or treat ulcer complications.
- Address the underlying ulcer aetiology.
- Minimize postoperative digestive consequences.

Vagotomy is the transection of the vagus nerve or its branches with the aim of inhibiting cholinergic stimulation of the parietal cells. The effect is a reduction in acid production. The vagus nerve is responsible for the motor function of the stomach; therefore, transection of the nerve has an impact on the function of the antrum and pylorus. This causes delayed gastric emptying and stasis. It is for this reason that a drainage procedure may be necessary following a vagotomy. While the primary procedure is chosen to treat the complication, vagotomy is typically added to prevent ulcer recurrence, especially in patients who are refractory to, or intolerant of maximal medical therapy.

Truncal Vagotomy

Truncal vagotomy (TV) involves division of the anterior and posterior vagal trunks after they emerge below the diaphragm. Because TV causes total denervation of the stomach a drainage procedure is required (Fig. 1).

Selective vagotomy
Because of the significant delayed gastric emptying seen with TV, a more selective procedure was sought to decrease post-vagotomy side effects. The vagal fibres are divided distal to the take-off of the hepatic branch(es) from the anterior vagus and the celiac branch(es) from the posterior vagus. This technique spares vagal innervation to the gallbladder and intestine while completely denervating the stomach. A drainage procedure is required.

Highly selective vagotomy
Also known as proximal gastric vagotomy and parietal cell vagotomy, it aims to eliminate the vagal stimulation to the acid-secreting portion of the stomach without interrupting motor innervation to the antrum and pylorus. This procedure involves the division of all branches of vessels and nerves to within 6 cm of the pylorus on the lesser curve to denervate nearly all the parietal cells. A concurrent drainage procedure is not required.

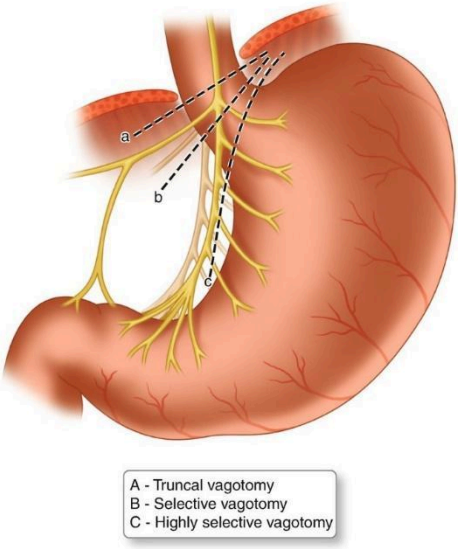


Fig. 1

Pyloroplasty is a drainage procedure which may be added to vagotomy to overcome the complications of gastric stasis, or it may be done as a surgical procedure to relieve gastric outlet obstruction. Gastric drainage procedures divide or bypass the pyloric sphincter mechanism to facilitate gastric emptying. The techniques described for pyloroplasty are the Heineke-Mikulicz, Jaboulay, and Finney.
A Heineke-Mikulicz pyloroplasty involves a longitudinal incision of the pyloric sphincter followed by a transverse closure. The Finney pyloroplasty is performed as a gastroduodenostomy with division of the pylorus. The Jaboulay pyloroplasty differs from the Finney procedure in that the pylorus is not transected (Fig. 2)

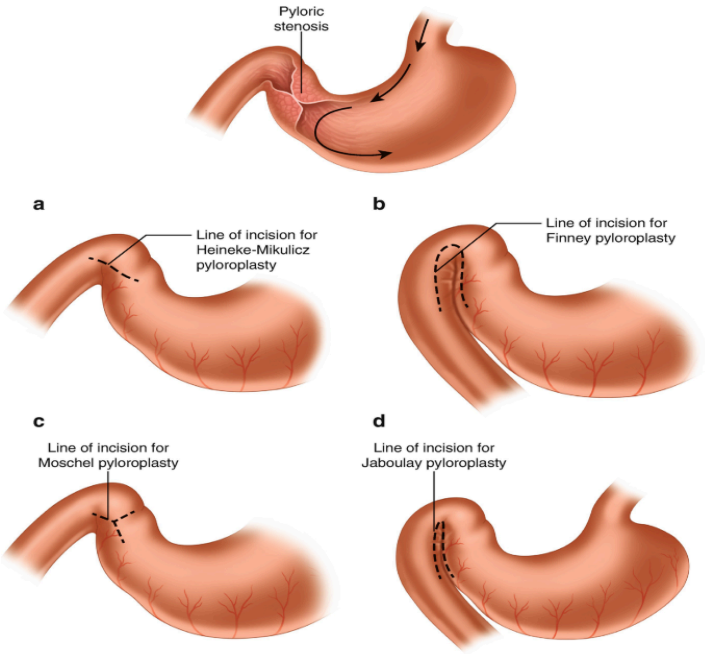


Fig.2

A gastrojejunostomy has been described as a drainage procedure in a select group of patients. It is reserved for patients with severe scaring of the duodenal bulb such that a pyloroplasty would not be possible.

Partial gastrectomy (e.g., antrectomy, subtotal gastrectomy) removes the gastrin-producing cells that stimulate acid secretion and a variable number of acid-producing parietal cells, depending upon the extent of the resection. For a gastric ulcer, the portion of the stomach containing the ulcer should also be removed. Although subtotal gastrectomy was used for the treatment of duodenal ulcer disease in the past, currently it is most used for gastric ulcer and distal gastric malignancies. A more common gastric resection performed for intractable duodenal ulcer is antrectomy that is combined with a vagotomy.

Reconstruction. There are primarily three reconstruction techniques to resume continuity of the gastrointestinal tract after antrectomy each with its own advantages and disadvantages.

Billroth I

If the duodenum is not extremely inflamed, a Billroth I procedure is the preferred method of reconstruction as it allows anatomic continuity and has a lower incidence of post procedural gastrointestinal symptoms (Fig. 3).

Billroth II

If the duodenum is too inflamed for an anastomosis, however, the second reconstruction procedure of choice would be the Billroth II. If a Billroth II is selected, the gastrojejunostomy should be created to allow gravity to aid drainage. This usually requires the anastomosis to be placed in a dependent area on the posterior wall of the stomach on the greater curvature.

Roux-en-Y gastrojejunostomy

Is another option for gastric reconstruction after antrectomy/vagotomy for peptic ulcer disease. The Roux-en-Y reconstruction is used in other surgical indications other than PUD surgery including relief of biliary obstruction, total gastrectomy, and bariatric surgery. Advantages of the Roux-en-Y reconstruction are that it is associated with a significantly lower incidence of reflux gastritis and esophagitis. The disadvantage is that it exacerbates problems with gastric emptying in patients with gastric outlet obstruction, and motility problems tend to develop over time.

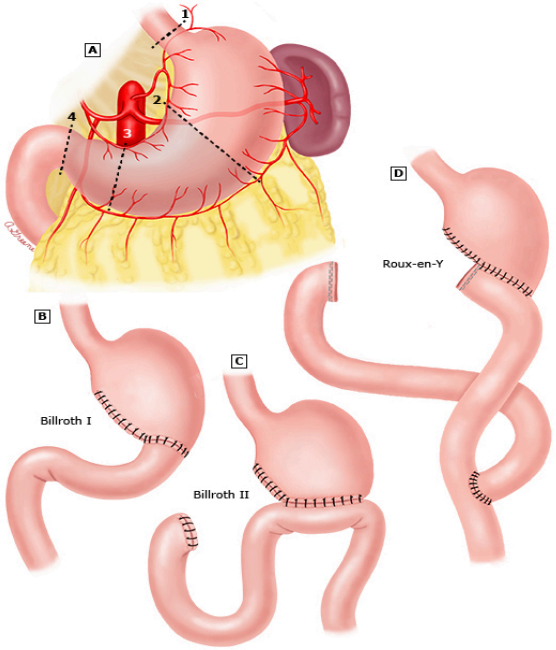
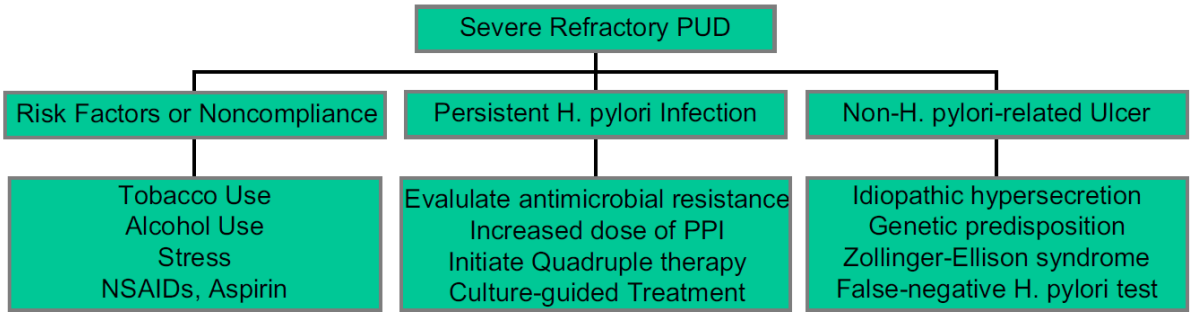


Fig. 3

Elective Ulcer Surgery

Refractory PUD is defined as a disease that fails to heal after 8 to 12 weeks of therapy or one that is associated with complications. Potential aetiologies of persistent or worsening PUD include the following: patient risk factors and noncompliance, persistent *H pylori* infection, and non–*H pylori*–related infection, related to underlying idiopathic gastric hypersecretion, or ZES and gastrinoma.



Surgery is indicated in patients who are intolerant of medications or do not comply with medication regimes, and those at high risk for complications (e.g., transplant recipients, patients dependent on steroids or NSAIDs, those with giant gastric or duodenal ulcer, and those with ulcers that fail to heal with adequate medical treatment). Surgery should also be considered for patients who have a relapse during maintenance treatment or who have had multiple courses of medications.

Gastric Ulcer

Because gastric ulcers may harbour malignancy, the ulcer bed must be either extensively biopsied or, preferably, excised. The extent of excision will depend on the location of the ulcer.

Modified Johnson Classification of Gastric Ulcers		
Type	Location	Acid Secretion
I	Lesser curvature (incisura)	Low
II	Body of stomach and duodenum	High
III	Prepyloric (within 2-3 cm of the pylorus)	High
IV	High in the lesser curvature (cardia)	Low
V	Anywhere (Induced by NSAIDS)	Low

Preferred form of surgery for gastric ulcers is an antrectomy and a Billroth I or Billroth II anastomosis. In conditions associated with high acid production such as Type II and Type III ulcers, a vagotomy is recommended. In this setting the vagotomy of choice is the truncal vagotomy. Addition of a vagotomy in ulcers which are not associated with high acid output has not been shown to offer any advantage. A simple vagotomy and a drainage procedure has been described in this setting but has been shown to be associated with high ulcer recurrence. It is for this reason that it is not preferred.

Duodenal Ulcer
Resection does not offer any advantage over vagotomy in the treatment of duodenal ulcers. When choosing a procedure in the setting of intractable duodenal ulcers, recurrence, and the post op complications such as dumping, and diarrhoea should be considered. The preferred procedure is the TV with a drainage procedure, though it is associated with complications such as dumping and diarrhoea. Highly selective vagotomy is technically challenging and is associated with a high recurrence rate.

Gastric outlet obstruction (GOO): Gastric outlet obstruction is the least common complication of PUD. Malignancy is the most common cause of GOO. Surgery for GOO cause by ulcers is indicated in patients who have failed medical therapy as well as endoscopic intervention such as balloon dilatation or have complications of endoscopic procedures. In most cases, a truncal vagotomy is required to prevent recurrence. The gastric outlet obstruction requires treatment with an antrectomy and reconstruction of the duodenum, if possible. If there is extensive scarring of the duodenum in this setting a Finney pyloroplasty may be the preferred option, alternatively a gastrojejunostomy.
Emergency surgery

Bleeding is said to be the most common indication for ulcer surgery, however, in sub-Saharan Africa it is the least common indication. More than 80% of bleeding ulcers will stop with medical or endoscopic treatment.
Indications for surgery for bleeding ulcers are:

1. Hemodynamic instability despite vigorous resuscitation (>4 units or >6 units taking into consideration the patient's age, with more transfusion tolerated for the younger patient)
2. Failure of endoscopic techniques to arrest haemorrhage
3. Recurrent haemorrhage after initial stabilization (with up to two attempts at obtaining endoscopic haemostasis)
4. Shock associated with recurrent haemorrhage.
5. Continued slow bleeding with a transfusion requirement exceeding 3 units per day.

In the emergency setting, many surgeons will opt for a less aggressive procedure to minimise complications and the operating time.
Duodenal bleeding
In duodenal ulcers the aim of surgery is to control bleeding on the ulcer bed. The duodenum is opened longitudinally and closed transversely as a pyloroplasty. If the patient is stable a vagotomy may be performed. In case of hemodynamic instability, a vagotomy may be omitted and the patient placed on long term PPIs.

Gastric bleeding
For bleeding gastric ulcers, resection in the form of a partial gastrectomy with a Billroth I or II anastomosis is recommended. For patients with medical comorbidities, ulcer excision combined with TV and pyloroplasty is an option. Ulcer excision alone is associated with a high rebleeding rate.

Perforation typically manifests as acute upper abdominal pain followed by development of either local or diffuse peritonitis with a risk for development of sepsis. The goal of operative management in all intra-abdominal infections is source control. Operative strategies vary with respect to ulcer location, malignancy risk, and size of the defect.

Major gastric resections and classically described acid reduction/drainage procedures have been largely abandoned in the acute setting. The only exception is for H. pylori negative individuals who have failed PPI while compliant and are stable enough for additional surgery. The outcome of patients presenting with a perforated ulcer depends on the following:

1. Time delay to presentation and treatment data suggest increasing delays for surgical treatment, in part as a consequence of more extensive diagnostic work-up.
2. Site of perforation - gastric perforation is associated with a poorer prognosis.
3. Patient's age - older patients who often have associated comorbidities have a worse outcome.
4. Presence of hypotension at presentation (systolic blood pressure <100 mm Hg)

Duodenal Perforation

In general, simple patch closure is appropriate for patients with

1. Acute NSAID-related perforation (provided that the drugs can be discontinued postoperatively) and for patients who have never been treated for PUD but who can be treated with PPIs and H. pylori eradication.
2. Perforation in the setting of ongoing shock, delayed presentation, considerable comorbid disease, or marked peritoneal contamination.

Defects larger than 2 cm have an increased risk of omental patch failure. There is no standardized approach in this setting. Options include pedicled omental patch repair, triple tube duodenostomy, jejunal pedicled graft, jejunal serosal patch, partial gastrectomy with reconstruction, omental plug, and pyloric exclusion/gastric disconnection. Pedicled omental repair is preferred to patch for larger defects, while omental plug placed over an NG tube may have benefit for very large defects (> 2 cm). If a duodenal repair is thought to be high risk for complication, pyloric exclusion and gastrojejunostomy can be employed to decrease the leak risk. Resection with Billroth I reconstruction is a viable salvage procedure for anatomically difficult cases or postoperative leaks when feasible.

Gastric Perforation

Because patients with perforated gastric ulcer tend to be older adults and have comorbidities, surgery is associated with high overall mortality regardless of treatment. Partial gastrectomy is the preferred approach unless the patient is at unacceptably high risk because of advanced age, comorbid disease, intraoperative instability, or severe peritoneal soilage.

In unstable patients patch closure of the defect is adequate. The ulcer must be adequately biopsied to rule out malignancy.

Conclusion

The prevalence of peptic ulcer disease has changed significantly in the past decades. The discovery of H2 receptor blockers and PPIs has improved the medical management of ulcers. As a result, fewer patients develop complications from ulcer requiring hospitalisation and intervention. The improvement in endoscopic intervention and technology has also influenced the success of this modality in the management of peptic ulcer complications.

Currently surgery is reserved for a few, carefully selected patients. In those who undergo surgery for peptic ulcer a less aggressive approach is adopted in many units, which has resulted in a few patients undergoing definitive surgery for their disease.

Even though lesser definitive procedures are performed, it is still vital for the modern surgeon to familiarise themselves as much as possible with the available options for managing the condition should they encounter a patient who will benefit from such.

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Non- operative management of esophageal cancer

Introduction

According to the latest global cancer statistics GLOBOCAN 2022, esophageal cancer is ranked the 11th most common cancer but is the 7th leading cause of cancer death globally. The highest incidence is seen in Asia with eastern Africa and southern Africa constituting the second and third highest age adjusted incidence rate, respectively. There are two major histological subtypes namely squamous cell carcinoma and adenocarcinoma, with variable geographic distribution. Adenocarcinoma predominates in the Western world while SCC predominates in Asia and Africa.(Bray et al., 2024). Esophageal cancer is associated with poor prognosis mainly due to its late presentation with incurable disease. However over past 3 decades mortality rates from this cancer have improved and 5yr overall survival doubled between late 1999 and 2014, particularly in high income regions. The improvements can be attributed to increase early detection through screening, use of combination therapies , increased understanding of genomics and molecular biology of the tumor allowing development of novel approaches to treatment including targeted therapy and immunotherapy (Bolger et al., 2022).
Research has shown that following neoadjuvant chemoradiotherapy complete pathological response is seen in approximately 50% of ESCC and approximately 25% of adenocarcinoma, which raises the question of need for esophagectomy in these patients. (Noordman et al., 2018).

Very early lesions

With increasing screening and general access to endoscopy associated technological improvements in endoscopy machinery, there has been an accompanying increase in detection of dysplastic lesions.
Current treatment recommendations for lesions with high grade dysplasia up to T1b sm1 lesion can be safely offered endoscopic therapy. The Paris endoscopic classification of lesions can be used to risk stratify lesions and identify those that have high risk feature and therefore helps guide proper lesion selection. See figures 1 and 2 below
Endoscopic mucosal resection (EMR) and Endoscopic submucosal dissection (ESD) are preferred definitive treatment techniques for appropriately selected lesions in patients with adenocarcinoma. The criteria for histological features that are used to confirm curative endoscopic resection include negative lateral and deep margins (R0), absent lymphatic or vascular invasion (LVI), G1 or G2 grade, well or moderately well differentiated, and absent penetration beyond the first (SM1) layer of the submucosa, approximating to <500 μm depth. Ablative techniques such as radiofrequency ablation cryotherapy and photodynamic therapy are used to treat the surrounding mucosa after resection. The recurrence rate following endoscopic therapy ranges between 4.5% and 14.5%, with a median time to recurrence of approximately 2 years, which supports regular endoscopic surveillance typically at 3, 6 and 12 months (Bolger et al., 2022).

Figure 1: Very early lesion staging. source(Bolger et al., 2022)

Figure 2: Paris endoscopic lesion classification. Source (Bolger et al., 2022)
Endoscopic resection (ER) therapy is also successfully employed in ESCC for T1a and shallow submucosal (T1b:SM1–2). ER not only removes the primary tumor but as well has the advantage of being able to evaluate the actual depth of tumor invasion and the presence or absence of lymphovascular invasion (LVI) using the resected specimen. T1a

lesions confirmed on pathology can be followed up without further treatment. However shallow pT1a with LVI and pT1b lesion need further treatment modalities because of their increased risk of lymph node metastasis. Further treatment of these lesions involved chemoradiation. Lesions with positive margins should be offered surgery or definitive chemoradiotherapy (Minashi et al., 2019). Minash and colleques conducted a trial evaluating the efficacy of endoscopic resection followed by CRT or definitive CRT as appropriately indicated in comparison to oesophagetomy. Their study found 3-year OS rate among the 87 patients in group B was 90.7% and the key secondary end point of 3-year OS among all of the enrolled patients was 92.6%. (See figure 3 below patient grouping). This study taken together with other previous studies demonstrated that the OS from ER followed by CRT has the potential to be equivalent to that of surgery and the relapse-free survival rate is better than that of definitive CRT. Furthermore, they concluded that ER might be a standard treatment option for clinically suspected T1b (SM1–2) N0M0 ESCC as a minimally invasive approach

Figure 3 – Minashi patient groupings and treatment arms.

Locoregional disease

The CROSS trial established neoadjuvant chemoradiotherapy followed by surgery as standard of care for patients with resectable esophageal and junctional cancer (Hagen et al., 2012). However, more than 40% of patients with esophageal squamous cell carcinoma (ESCC) exhibit pathological complete responses (pCR) after neoadjuvant chemoradiotherapy (nCRT), and theoretically, these patients may be cured by CRT and omit surgery. (49 % in the CROSS trial and 43 % in the 5010 trial) (Qian et al., 2022). And approximately a quarter of adenocarcinomas achieve pCR after neoadjuvant therapy. If we are to adopt a surveillance strategy for these patients, they would be subjected to regular clinical evaluations after neoadjuvant chemoradiotherapy, and esophagectomy would be offered only to those with proven locoregional recurrence and no evidence of distant metastases. However, an active surveillance approach would only be justified if the associated oncological outcomes were non-inferior to those achieved with standard surgery. The preSANO study demonstrated that an reasonable accurate approach for evaluating the clinical response to nCRT for EC involved using endoscopic ultrasonography with fine-needle aspiration biopsy of suspicious lymph nodes in conjunction with bite-on-bite biopsy via endoscopy for the detection of locoregional residual disease and PET-computed tomography (CT) for the detection of interval metastases. Furthermore, the median overall survival in complete responders to neoadjuvant chemoradiotherapy managed with active surveillance is similar to that of patients with a complete clinical response who undergo surgery after neoadjuvant chemoradiotherapy, therefore the additional time during active surveillance should not have a significant negative impact (Noordman et al., 2018).

The typical radiation dose of nCRT is 40–41.4 Gy accompanied by 4 cycles of chemo may be enough for tumors with high sensitivity to CRT, whereas DCRT radiation dose is 50 – 60 Gy with 5 -6 cycles of chemo. Qian colleques conducted a pilot study evaluating patients with stage II – IVa ESCC who showed complete clinical response (cCR) immediately following neoadjuvant CRT (nCRT) , they randomized them into group A which proceeded to surgery (n=36) and group B (n=35) who continued with CRT up to dCRT dose without surgery. They followed up the patients for median of 35.7 months and found that the 3-year DFS rate was 56.43 % in arm A versus 54.73 % in arm B, the 3-year overall survival (OS) rates in arms A and B were 69.5 % and 62.3 %, respectively. Interestingly, as well they found that cCR predicted pCR in surgical specimens with high

overall accuracy of 86.1%. Furthermore, their findings illustrated that patients without cCR would receive significant DFS and OS benefits from surgery after nCRT compared with the effects of dCRT (Qian et al., 2022).
A study by Kamarajah et al conducted a population-based cohort study comparing survival rates in patients with nonmetastatic esophageal cancer (including both OAC and ESCC) treated with definitive CRT (DCR) versus neoadjuvant CRT followed by planned surgery (NCRS). The study analyzed 19,532 patients with locoregional esophageal cancer, of which 5977 received DCR and 13,555 received NCRS. They found that compared to DCR, patients in the NCRS group had significantly longer survivals for both adenocarcinoma and SCC, at 32.4 vs 18.6 months and 36.5 vs 18.0 months, respectively. Furthermore, they found that there was no significant survival difference between patients in the NCRS group and those who were offered salvage esophagectomy due to residual disease or recurrence following DCR (Kamarajah et al., 2022) See figures 4 to 6 below.

Figure 4 Overall survival of patients with definitive chemoradiotherapy and oesophagectomy after neoadjuvant chemoradiotherapy for esophageal adenocarcinoma in (A) unmatched and (B) matched cohorts. Source (Kamarajah et al., 2022)

Figure 5: Overall survival of patients with definitive chemoradiotherapy and esophagectomy after neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma in (A) unmatched and (B) matched cohorts. Source (Kamarajah et al., 2022)

Figure 6. Overall survival of patients with definitive chemoradiotherapy with salvage esophagectomy and esophagectomy after neoadjuvant chemoradiotherapy in (A) unmatched and (B) matched cohorts.
Ronald Chow conducted a systemic review and metanalysis looking studies that compared definitive CRT with neoadjuvant CRT followed by surgery. In the final analysis they included study reports on eight studies, with 16,647 patients. They concluded that “patients with esophageal carcinoma receiving neoadjuvant chemoradiotherapy and esophagectomy have better survival than patients receiving definitive chemoradiotherapy. However, given the paucity of data and lack of uniform reporting of endpoints, further studies should be conducted”(Chow et al., 2021).
Despite the variable complete pathological response rates between adenocarcinoma and squamous cell carcinoma, in patients with a clinical complete response based on endoscopy with bite-on-bite biopsies and fine-needle aspiration, the risk that there is any residual disease left seems similar in both subgroups of patients (Noordman et al., 2018).

Conclusion
Given that esophagectomy is associated with significant mortality rates, high morbidity rate even in high volume centers, an altered patient quality of life, adopting an active surveillance approach seems reasonable in appropriately selected patients with complete clinical response, provided adequate resources are available. Moreover, active surveillance may also detect patients with initial subclinical distant metastases who would not have any survival benefit from esophagectomy noting that close to 50% of patients still develop distant metastases despite radical surgery of which 75% occur within 2 years after esophagectomy. Additionally, studies have demonstrated that

delayed radical resection in patients undergoing active surveillance was associated with good survival outcomes that approximate those of standard surgery (van der Zijden et al., 2023). The results from SANO trial and SANO-2 trials will undoubtedly shed more light on the safety and feasibility of active surveillance approaches.

"The Surgery As Needed for Oesophageal cancer (SANO) trial is an ongoing phase-III trial that compares active surveillance with standard oesophagectomy for patients with a clinically complete response (cCR; i.e. no evidence of residual disease on diagnostics) to neoadjuvant chemoradiotherapy for oesophageal or oesophagogastric junctional cancer"

The SANO – 2 Trial has "Primary endpoint is the number and severity of adverse events in patients with cCR undergoing active surveillance, defined as complications from response evaluations, delayed surgery and the development of distant metastases. Secondary endpoints include timing and quality of diagnostic modalities, overall survival, progression-free survival, fear of cancer recurrence and decisional regret."(van der Zijden et al., 2023)

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COMPARISON OF CONVENTIONAL AND COMPLETE MESOCOLIC EXCISION FOR RIGHT COLON CANCER

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INTRODUCTION

Colorectal cancer is the third most common cancer and the second cause of cancer deaths. Approximately 95% can be resected without residual tumour. About 3-5% of patients, resection is palliative.

TME, introduced by heald et al in 1982 significantly modified rectal cancer surgery, defined association between quality of surgical resection and oncological outcomes. This resulted in lower local recurrence rate and better 5-year cancer related survival.

Hohenberger in 2009 transferral philosophy of TME to colonic surgery, the concept called complete mesocolic excision.

CME consists in the surgical dissection along embryological fascial planes around mesentery, with intact removal of the mesocolon and its lymphatics, central vascular ligation which allows removal of central lymph nodes and removal of other distant lymph nodes.

In Hohenberger's experience local recurrence was reduced from 6.5 to 3.6% and cancer related 5-years survival increased from 82.1 to 89.1%.

CME is challenging due to vascular anatomical variety of right colon. Post-operative morbidity can be high, survival advantage is unclear.

Characteristics of the procedure to qualify as CME are central vascular ligation, exposure of superior mesenteric vein and intact mesocolic excision. Theoretically CME should improve overall survival and Disease-free survival (DFS) for selected patients with right sided colon cancer. Concerns about perioperative morbidity has been raised.

ANATOMY

Carl Toldt showed that there is an extra fascial plane between the mesocolon and retroperitoneum and called it as "Toldt's Fascia". Culligan *et al*. describe the mesocolic anatomy in detail. They defined three points: (I) Mesocolon starts at ileocecal level and continues up to rectosigmoid level; (II) Mesocolon of the transvers colon and the mobile part of sigmoid mesocolon does not include "Toldt's Fascia". Rest of the mesocolon (ascending, descending, non-mobile part sigmoid colon's) are apposed to the retroperitoneum and "Toldt's Fascia" is defined in these places; (III) confluence of sigmoid mesocolon and mesorectum is the inception of proximal rectum. Three surgical interfaces between two contiguous structures were described by Heald: (I) "Colo-fascial interface" (confluence of colonic surface and "Toldt's Fascia"); (II) "Meso-fascial interface" (confluence of mesocolon and "Toldt's Fascia"); (III) "Retro-fascial interface" (confluence of retroperitoneum and "Toldt's Fascia"

Vascular anatomy of the right colon

Vascular anatomy should be learned in detail to perform CME for right colon cancers within the proper anatomical planes. SMA has 2 or 3 major branches that provide the arterial blood supply of right colon. The most important one of these branches is “ileocolic artery” (ICA). Presence of “right colic artery” (RCA)—which originates from SMA—differs from 0% to 63% at cadaveric reports, it can be originated from ICA or “middle colic artery” (MCA). MCA divides into right and left branches but it has many anatomical variations; can be absent (up to 25%), doubled or accessory MCA.

Major colonic arteries of the right-side colon.

Two main arteries—ICA and RCA—are ligated during CME so topography of these two arteries towards SMA should be known. Both these arteries have important neighborliness with “superior mesenteric vein” (SMV). In 63–100% of the cases RCA runs anterior to the SMV, and ICA crosses anteriorly in 17–83% of cases.

Also venous anatomy of the right colon and variations of the venous anatomy should be known to avoid vascular complications during CME. Venous blood flow of cecum, ascending colon, and the right side of transverse colon drain into SMV. Topographical anatomy of right colic vein (RCV), superior RCV, gastrocolic trunk and middle colic vein (MCV) has too many variations. The confluence of right gastroepiploic vein, superior RCV and anterior superior pancreaticoduodenal vein which is known as “gastrocolic trunk of Henle” present in 46–70% cases.

The configuration of gastrocolic trunk of Henle.

Surgical technique of open CME

A “lateral-to-medial” approach is usually preferred in open CME technique. The dissection starts with the lateral peritoneal fold, and then continues in the mesofascial plane towards medially. Mesocolon of the right colon is mobilized towards the root of superior mesenteric vessels. Ascending colon, caecum and mesocolon are separated from retroperitoneum with sharp dissection towards the upper border of the duodenum and pancreatic uncinate process. Duodenal Kocherization in the original description of Hohenberger *et al*. is not routinely performed. The autonomic nervous plexus which is situated close to SMA should be preserved during mobilization. When mesocolon and right colon is fully mobilized, vascular ligations begin from ICA. Both structures (ileocolic and right colic vessels) are ligated from their origin at SMA and SMV. The dissection is performed through superior mesenteric vessels and all associated fatty tissue and lymph nodes are harvested.

Cecum, ascending colon and mesocolon are separated from the retroperitoneum, and the vessels are revealed after the sharp dissection. ICV, ileocecal vein; SMV, superior mesenteric vein; RGOV, right gastro-omental vein; RCV, right colic vein; MCV, middle colic vein (by courtesy of M. Ayhan Kuzu).

The vessels of the right colon are ligated at their origin from the superior mesenteric vessels. ICV, ileocecal vein; ICA, ileocecal artery; RCV, right colic vein; RCA, right colic artery; SMV, superior mesenteric vein; RGOV, right gastro-omental vein; RGOA, right gastro-omental artery; RCV, right colic vein; MCV, middle colic vein; MCA, middle colic artery; GDA, gastroduodenal artery; ASPDA, anterior superior pancreaticoduodenal artery; ASPDV, anterior superior pancreaticoduodenal vein; AİPDV, anterior inferior pancreaticoduodenal vein (by courtesy of M. Ayhan Kuzu).

MCA’s right branch is ligated for cecum and ascendant colon cancers, and transvers colon is prepared for transection at the level of middle colic vessels. Also surgical approach is slightly different for hepatic flexure and proximal transverse colon cancers.

Primarily right gastroepiploic artery—that runs with a vertical plan to transverse colon—is transected to enter the lesser sac. The MCA and MCV both are ligated at closest point of their origin (SMA and Henle's trunk respectively). If there are suspected lymph nodes around the head of the pancreas, these lymph nodes are removed by ligating from the root of the right gastroepiploic artery, also—if possible—superior pancreaticoduodenal artery should be preserved during dissection. After the transection of distal ileum and transvers colon, the resection is completed and the anastomosis is performed by hand-sewn sutures or linear staplers.

Pathology

Number of harvested nodes is much higher with CME; 5 Year disease free survival is slightly better with CME as well as 5-year overall survival.

Postoperative results of CME and conventional (nCME) surgery in 2019 and 2020 (Published online: 15 June 2023)

Systematic review and meta-analysis by De Lange et al looking at 586 publications found that CME increased lymph node harvest, 5 year overall survival was increased, 5 year DFS increased, decreased recurrence rate when compared to standard right hemicolectomy. Peri operative morbidity including Blood loss, incidence of reoperation, Length of hospital stay, Post-operative complications, 30-day mortality were found to be similar between the 2 procedures.

Long term outcome: 3-year overall survival, 5-year survival, Distant recurrence, were similar in the 2 groups.

COMPARISONS OF TWO PROCEDURES BY STAGE OF CANCER

No difference in long term outcome when comparing stage 1-3 of colon cancer between the two procedures.

Short-term outcomes and complications (Prospective multi-centre study (Stefan Benz et al, BJS 2022)

	All patients	No CME	CME	*P**
No. of deaths				
Within 30 days	1 (0.1)	1 (0.2)	0 (0)	1.000
Within 90 days	13 (1.3)	9 (1.8)	4 (0.8)	0.26
No. of intraoperative complications	12 (1.2)	6 (1.2)	6 (1.2)	1.000

Tumour laceration	1 (0.1)	1 (0.2)	0 (0)	1.000
Blood loss > 500 ml	2 (0.2)	0 (0)	2 (0.4)	0.499
Pancreatic injury	0 (0)	0 (0)	0 (0)	1.000
Intestinal injury	6 (0.6)	5 (1.0)	1 (0.2)	0.217
Ureteral injury	1 (0.1)	0 (0)	1 (0.2)	1.000
Anastomotic complications	1 (0.1)	0 (0)	1 (0.2)	1.000
Injury to SMV	1 (0.1)	0 (0)	1 (0.2)	1.000
No. of general postoperative complications	181 (18.0)	92 (18.1)	89 (17.9)	0.780
Pulmonary embolism	3 (0.3)	2 (0.4)	1 (0.2)	1.000
Pneumonia	35 (3.5)	21 (4.1)	14 (2.8)	0.305
Other pulmonary	14 (1.4)	6 (1.2)	8 (1.6)	0.601
Urinary tract infection	25 (2.5)	13 (2.6)	12 (2.4)	1.000
Fever	13 (1.3)	4 (0.8)	9 (1.8)	0.174
Cardiac	29 (2.9)	15 (3.0)	14 (2.8)	1.000
Multiple organ failure	1 (0.1)	0 (0)	1 (0.2)	0.449

Deep vein thrombosis	1 (0.1)	1 (0.2)	0 (0)	1.000
Renal	15 (1.5)	10 (2.0)	5 (1.0)	0.299
Other	45 (4.5)	20 (3.9)	25 (5.0)	0.449
No. of surgical postoperative complications	249 (24.8)	120 (23.6)	129 (26.0)	0.290
Bleeding	7 (0.7)	3 (0.6)	4 (0.8)	0.723
Wound abscess	6 (0.6)	3 (0.6)	3 (0.6)	1.000
Sepsis	7 (0.7)	5 (1.0)	2 (0.4)	0.452
Anastomotic leakage	25 (2.5)	8 (1.6)	17 (3.4)	0.071
Aseptic wound complication	12 (1.2)	5 (1.0)	7 (1.4)	0.575
Wound infection	42 (4.2)	23 (4.5)	19 (3.8)	0.690
Intra-abdominal abscess	8 (0.8)	4 (0.8)	4 (0.8)	1.000
Mechanical ileus	5 (0.5)	2 (0.4)	3 (0.6)	0.634
Peritonitis	12 (1.2)	5 (1.0)	7 (1.4)	0.575
Postoperative functional	72 (7.2)	38 (7.5)	34 (6.9)	0.807
Abdominal wall dehiscence	19 (1.9)	8 (1.6)	11 (2.2)	0.496

Other	34 (3.4)	16 (3.1)	18 (3.6)	0.730
No. of patients who had relaparotomies				0.490
1	61 (6.1)	30 (5.9)	31 (6.1)	
2	7 (0.7)	3 (0.6)	4 (0.8)	
> 2	15 (1.5)	5 (1.0)	10 (2.0)	
Not available	20 (2.0)	16 (3.1)	4 (0.8)	
No. of patients with complications	289 (28.8)	141 (27.8)	148 (29.8)	0.466
Clavien–Dindo grade I–IIIa	202 (20.1)	101 (19.9)	101 (20.4)	0.878
Clavien–Dindo grade IIIb–IV	87 (8.7)	40 (7.9)	47 (9.5)	0.435
Duration of hospital stay (days), mean(s.d.)	14.6 (9.6)	13.9 (11.4)	13.1 (8.3)	0.206 †

CONCLUSION:

CME is challenging, takes longer to perform compared to traditional right hemicolectomy. Intra-operative complications are higher. Lymph node harvest is significantly higher but does not confer statistically significant outcome in terms of 5-year overall survival and DFS. Laparoscopic CME seems safe also and comparable to traditional right hemicolectomy. Results of large randomised trials are awaited (RELARC, COLD TRIALS, Italian CME Trial) and may provide crucial evidence in evaluating the efficacy of this procedure.

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Perforated T4 colon cancer management
Dr T. SUmbana

The management of perforated T4 colon cancer is challenging with a very high perioperative mortality and morbidity followed by very poor oncological outcomes. We know that sepsis is associated with poor oncological outcomes even in those non perforated colon cancer where the surgical management is complicated by postoperative sepsis.

The goals of the management will be to:

1. Control the sepsis
2. Achieve good Oncological outcome

- Sepsis control determine the first 30 days' mortality.
- Those who survive 30 days, peritoneal metastasis is the main driver of mortality and poor oncological outcome.

The sepsis control management would depend on whether it is a:

1. localised perforation- abscess/inflammatory mass/fistula
2. free perforation-generalised peritonitis with purulent or faecal peritonitis

But the Initial management should be directed at the management of sepsis where the surviving sepsis guideline can be of great assistance in guiding the resuscitation and timing of source control.
Perforated tumour resection may be part of sepsis control and oncological principles should be observed at all time as majority of these tumours can be resected without violating any oncological principles.

Peritoneal metastasis not local recurrence is the main driver of mortality after surviving the sepsis, that's why post-operative radiation of the tumour bed has fallen out of favour only recommended in a case by case basis.
To try to reduce the peritoneal metastases relapse in these patients, prophylactic HIPEC was studied in the COLOPEC trial and it did not show any statistical significant benefit and with HIPEC associated complications still another point of concern.
Pressurised intraperitoneal aerosolised chemotherapy is another technique which is being tried and studies but so far there nothing much to say about it other than, some limited success in reducing the burden of disease in patients with already documented peritoneal metastases.

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ULCERATIVE COLITIS; CONTROVERSIES 2024.

Ulcerative colitis (UC) is a chronic, relapsing, and remitting incurable inflammatory disease of the colon. The inflammation involves the mucosa of the rectum and/or the colon.

The most common symptoms are diarrhea, rectal bleeding, and constipation if there is isolated rectal involvement. The patients may also have fever, weight loss, and extraintestinal manifestations.

UC is generally a disease of young people in the second and third decades.

It is defined as active (relapse) when the patient experiences clinical symptoms with measurable inflammatory markers such as elevated fecal calprotectin and endoscopic and microscopic signs of inflammation.

Remission is when there are no signs and symptoms of the disease, defined as less than three bowel movements a day without lower GI bleeding, a PRO 2 score of 0, and Endoscopic remission, defined by a MAYO score of 0.

Clinical response is an improvement in the patient's general condition, as measured by a reduction of the patient's PRO-2 score by at least 50%.

The endoscopic response is a reduction of the MAYO score of disease activity by at least 1 point.

Relapse is the reappearance of active disease in a patient in remission. An early exacerbation occurs when the disease appears within three months of remission.

Extensive UC refers to inflammation involving the colon proximal to the splenic flexure (rectum, sigmoid, descending, and left part of the transverse colon) as per the Montreal classification.

Goals of treatment:

- Induction of remission phase.
- Maintenance of remission phase.
- Reduction of the risk of relapse phase.

Steroid Refractory disease:

Failure to achieve remission despite the use of full dose for four weeks or three days in acute severe UC (ASUC).

Steroid dependent disease:

Inability to reduce steroid dose to an equivalent of 10mg of prednisone or 3mg of budesonide per day within three months or exacerbation within the same time after therapy termination.

Primary non-response:

Lack of clinical improvement after induction treatment, usually with biologics.

Loss of response:

The relapse in the course of maintenance in a patient who previously achieved remission.

Management:

- In the severe clinical form of the disease, the examination of choice is recto sigmoidoscopy. In all other cases, an ileo-colonoscopy with macroscopic evaluation and collection of at least two biopsy specimens for each segment for histological examination is preferred.

- Microscopic signs suggestive of UC include intestinal crypt architectural distortion (irregular branching or atrophy), infiltration of the epithelial basement membrane by lymphoplasmacytic and granulocytes within the epithelium of the intestinal crypts (cryptitis), and crypt abscesses.

- The following should be excluded:

Toxigenic C-Diff, CMV, Salmonella/Shigella or E. histolytica and E-Coli. In those with unusual presentations, HIV should be tested.

- Complementary tests include the following:

Fecal calprotectin level, which correlates with severity. Severe disease is indicated by fecal calprotectin of >250ug/g, with <150ug/g indicating mucosal healing.

FBC

IRON studies. (Chronicity and route of iron therapy)

C-reactive protein.

Essential radiological examinations include abdominal U/S, which assesses the intestinal wall, and abdominal and chest X-rays to rule out toxic megacolon perforation and infections.

MAYO SCORE parameters include stool frequency, endoscopic mucosal appearance, and physical assessment.

TREATMENT:

In low and middle-income countries, the approach is based on a step-up strategy, except for acute severe ulcerative colitis (ASUC).

Disease activity should be determined before treatment initiation by:

- MAYO Score

- PRO-2

- TRUE-LOVE AND WITTS

- ENDOSCOPIC SCALE.

The extent of the disease/inflammation.

Disease history as:

- Number of remissions/recurrences.
- Medication that worked.
- Maintenance treatment.

Mild to moderate disease:

- Mesalazine/SSA oral and or topical forms. (Combination is more effective than either alone)

    1. In isolated proctitis, suppository at 1g/day(nocte) is preferred.
    2. In the involvement of the rectum and sigmoid, rectal enema is at dose >1g/day.
    3. In left colon involvement, a combination of oral at a dose of at least >3g/day and topical formulation are preferred.
    4. In extensive disease, the same as above is preferred. Rectal use is sometimes questioned, but the argument is that rectal involvement is responsible for the symptoms affecting quality of life (QOL).

Because of the risk of nephropathy, renal function should be monitored before and during therapy.

The same agent should be used for maintenance if remission is achieved.

If remission is not achieved with mesalazine, topical budesonide in the MMX (9mg/day) form for eight weeks or systemic prednisone (0.5-1mg/kg/methylprednisolone is recommended for 2-4 weeks and then taper off.

The entire induction treatment should last at most 8-12 weeks.

Thiopurines should be added for maintenance if:

- Disease activity was high at baseline.
- Exacerbations occur frequently.
- Failure of mesalazine to maintain remission.

Monitoring of FBC, U/E, and liver function is required when using these drugs. (Every two weeks for the initial two months and then every three months).

Monitor for non-melanoma skin cancer, cervical cancer, and B-cell lymphoma (EBV).

Escalation:

Most researchers recommend immunosuppressants, biological agents, or tofacitinib in patients with steroids-dependent or refractory UC.

Targeted therapies (AGENTS):

1. Anti-TNF antibodies both need drug monitoring.

Revellex;

It is potent but has side effects, such as hypersensitivity, high immunogenicity (to be used with thiopurines to reduce this), infection risk, and skin melanoma.

Adalimumab

It is less immunogenic but has the same properties as revellex. It is also to be used with thiopurines to reduce immunogenicity.

2. Anti-integrin.

Vedolizumab (lower immunogenicity, low infection rate, and higher oncological safety),

3. IL 12 and 23 antibodies.

Ustekinumab: It has a good safety profile and low immunogenicity.

4. Janus-kinase inhibitor.

Tofacitinib has a good safety profile.

These are the drugs of first choice if:

· Conventional therapy is ineffective or not tolerated.

· In primary non-responders or loss of efficacy.

· Patient profile or preference.

MODERATE TO SEVERE UICERATIVE COLITIS.

Systemic steroids with mesalazine are recommended as treatment of first choice for induction, with steroids for 2-4 weeks before tapering off, with the entire course lasting not more than 12 weeks. Budesonide can also be used.

Maintenance should include thiopurine and mesalazine in steroid-responsive UC.

Targeted therapies should be introduced early should this first line fail or steroid-dependent/refractory UC.

Drug choice is still not determined.

AGA: Risk factors for complicated UC are:

· Age<40 years at diagnosis

· High endoscopic activity.

· The need for hospitalization for UC exacerbations.

· Extensiveness of lesions.

· Elevated inflammatory markers.

ACUTE SEVERE ULCERATIVE COLITIS (ASUC).

It is characterized by high-activity inflammatory lesions in the colon (rectosigmoidoscopy without preparation is indicated).

Severe intestinal symptoms:>6 bloody stools/day.

Accompanied by systemic response: HB <10.5, ESR >30 mm/h or CRP>30 mg/l, temperature of 37.8 degrees C, and tachycardia of >90 bpm.

Truelove and Witts criteria is used to characterize and assess the severity of ASUC. This condition is still associated with high colectomy and mortality rates

The Initial assessment should include the plain abdomen and chest X-rays to exclude toxic megacolon and perforation, stool MCS to exclude infections that may cause ppt UC and electrolytes.Ultrasound and Cat scans depend on the patient's clinical situation.

Treatment of ASUC.

- A multidisciplinary team is needed.
- Hospital admission.
- IV hydrocortisone at 300-400mg/day or methylprednisolone at 40-60 mg/day.
- Clexane for thromboembolic complications.
- If there is no response in 3 days, a biologic like infliximab or, alternatively, ciclosporin should be added.
- The following are indications for escalation: eight stools/day or 3-8 stools with CRP of >45mg/l.

Ciclosporin should not be used as a maintenance therapy; the duration should be limited to 3-6 months and not in patients who developed ASUC on thiopurines.IV steroids should be switched to the oral route.

PCJ prophylaxis should be started in those on steroids taper, azathioprine, and ciclosporin combination.

Indications for surgery in ASUC.

- Toxic megacolon
- Shock.
- Non-response to infliximab/ciclosporin after five consecutive days of therapy.
- Massive bleeding.
- Perforation.

Novel medicines:

- Ozanimod (sphigosine-1-phosphate receptor modulator) is indicated for adult with moderate to severe UC with no response to the above medications.
- The novel selective Janus kinase inhibitors such as upadacitinib and filgotinib; indications are like tofacitinib.

Surgical treatment:

This can be elective, urgent, or emergency. It can be taken into consideration at any stage of the disease.

The common surgical treatment is restorative proctocolectomy with ileal pouch-anal anastomosis (Which can be done laparoscopically in centers with experience).

Indications for elective surgery include:

- Lack of full medical efficacy.
- Adverse effects.
- Precancerous lesions/cancer.
- Strictures of unclear origin.

Other types of surgery that may be considered are:

- Colectomy with rectal preservation and ileorectal anastomosis in women intending to have children and those with minimal rectal involvement it is better than IPAA in terms of functional results (Number of stools or nocturnal bowel movements)
- Hartmann colostomy in debilitated patients.
- Proctocolectomy with end-ileostomy (Has lower complications)

Regardless of the type of surgery, the patient needs to be well prepared, especially nutritionally and educated about the procedure.

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Surgery in ulcerative colitis the full spectrum.

DR RL Fourie

The indications for surgery in ulcerative colitis:

- Acute severe colitis
- Toxic megacolon
- Medically refractory Ulcerative Colitis
- HGD and Malignancy in the setting of ulcerative colitis
- Medical Refractory UC
- Severe extraintestinal manifestations.
- Growth retardation in children

Acute Severe Colitis

Acute severe colitis will usually present as an acute flare up in the setting of chronic disease but in 1/3rd of patients it will be the presenting condition. Acute severe colitis is an acute life-threatening condition. The diagnosis can be made my using the True Love and Witts criteria.(Holvoet et al., 2021; Spinelli et al., 2022)

Table 1

Truelove and Witt's Criteria for Acute Severe Ulcerative Colitis

Activity	Mild	Moderate	Severe
Number of bloody stools a day	< 4	4–6	≥ 6
Pulse rate (bpm)	Normal	Intermediate	≥ 90
Temperature (°C)	Afebrile	Subfebrile	> 37.8
Haemoglobin (g/dl)	>11	10.5–11	< 10.5
Erythrocyte sedimentation rate (ESR) (mm/h)	Not elevated	Not elevated	>30

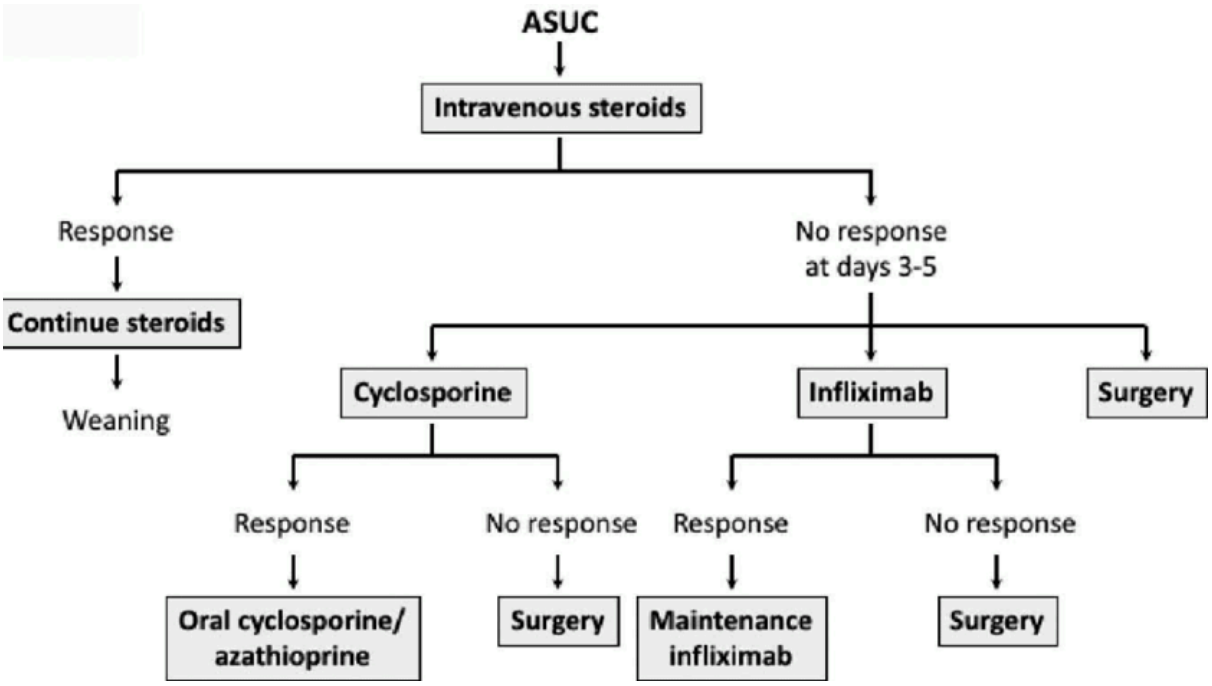
Notes: Adapted with permission form Truelove SC, Witts LJ. Cortisone in ulcerative colitis final report on a therapeutic trial. *Br Med J*. 1955;2(4947):1041–1048. Copyright © 1955, BMJ Publishing Group Ltd.5
(Holvoet et al., 2021)

Patients with acute severe colitis are acutely ill and will require urgent hospitalisation. During hospitalisation 20% will require surgery during the admission. Treatment will commence with intravenous fluid resuscitation. Intravenous corticosteroids should be administered. Treatment with intravenous steroids should continue for up to 3-4 days. If no significant improvement has been achieved, then rescue therapy should be commenced. Rescue therapy usually consists of Infliximab and a calcineurin inhibitor such as cyclosporin. If the patient does not show significant improvement, then treatment in the next 3 days then the patient should be referred for surgery.(Spinelli et al., 2022)

Predictive Indices for Corticosteroid Failure in Acute Severe Ulcerative Colitis

Score	Criteria	Probability of IV Corticosteroids Failure
Travis or Oxford criteria	>8 stools or CRP > 45 mg/L	If any present on day 3 = 85% probability of colectomy
Ho or Scottish index	Colonic dilatation > 5.5 cm = 4 points Albumin < 3 g/dl on admission = 1 point Average daily number of stools over first 3 days: < 4 = 0 points; 4–6 = 1 points, 6–9 = 2 points; ≥ 9 = 4 points	≥ 4 points on day 3 = 85% probability of non-response
Lindgren score	Stool frequency per day + 0.14 x CRP (mg/L)	>8 points on day 3 = 72% probability of non-response

Note: Data from Gisbert et al. [8]
(Holvoet et al., 2021)



(Yamamoto et al., 2020)

In the perioperative period it is important to be vigilant the following conditions may occur that will impact the mortality rate of patients with Ulcerative colitis:
Contributors to mortality:

- DVT
- CMV
- C Diff
- Toxic mega colon
- Time to colectomy

(Spinelli et al., 2022)

Endoscopy plays an important role in the assessment of disease severity. It is also important in diagnosis of CMV and d Diff both of which are important conditions to diagnose and treat in the setting of ulcerative colitis.
It is crucial to not delay surgery when indicated. Time to colectomy is a significant indicator of mortality. Further recue therapy with calcineurins does not reduce the rate of colectomy it only delays colectomy and may result in more adverse events. If the patient does not show significant improvement on day 7 an urgent surgical referral should be made.(Spinelli et al., 2022)
In the perioperative period specific attention should be paid to nutrition and DVT prevention.

Toxic megacolon

This is a potentially fatal complication of UC. Other pathologies like C Diff, CMV, shigella and Salmonella may also cause this condition. It is characterised by systemic toxicity and open lumen obstruction of the colon. A markedly dilated colon can be viewed on abdominal x ray.
Patients will present with fever, tachycardia, neutrophilia and anaemia. Abdominal x-ray will reveal a dilated segment of colon. Usually, the transverse or ascending colon. A dilatation of >6m is diagnostic.
The management consists of fluid resuscitation, electrolyte correction, NGT, TPN and directed therapy. Urgent surgical referral is indicated. Colonic perforation in this setting will significantly increase mortality. (Skomorochow et al)

Subtotal Colectomy/Total abdominal colectomy

This is the procedure of choice for acute sever colitis and toxic megacolon. It includes resection of the entire colon leaving a rectal stump. The procedure is completed with end ileostomy.
There are variations in the management of the rectal stump. A Hartmann procedure with closure of the stump at the pelvic brim is appropriate. A longer stump may be brought out as a mucous fistula, or it may be placed subcutaneously. A systematic review found that intraperitoneal rectal stump (Hartmann stump) complicated with a higher rate of pelvic sepsis than the other two options, but subcutaneous placement had more wound infections. Overall, they found that the mucous fistula had the lowest rate of complications overall.

Systematic review of rectal stump management during and after emergency total colectomy for acute severe ulcerative colitis
Sergei Bedrikovetski, Nagendra Dudi-Venkata, Hidde M. Kroon, Jianliang Liu, Jane M. Andrews, Mark Lewis, Matthew Lawrence, Tarik Sammour
First published: 28 March 2019
https://doi.org/10.1111/ans.15075
Citations: 10

Management	Total no. of patients	Pelvic sepsis rate (range)	Wound infection rate (range)	Overall complications (range)	Mortality (range)
Intraperitoneal	266	5.3% (3–12%)	7.9% (0–26%)	25% (20–72%)	1.5% (0–3%)
Subcutaneous	144	2% (0–4%)	14.5% (6–35%)	27% (10–35%)	0% (NR)
Mucous fistula	64	3.1% (SS)	9.4% (SS)	12.5% (7–17%)	0% (SS)
Systemic/topical medication	Insufficient data				

	Hartmann stump (n = 99)	Subcutaneous placement of rectosigmoid stump (n = 105)	p
Overall stump-related morbidity, n (%)	8 (8)	12 (11)	0.42
Rectal stump leak, n (%)	5 (5)	10 (10)	0.23
Bleeding from stump, n (%)	3 (3)	2 (2)	0.68
Pelvic sepsis, n (%)	6 (6)	4 (4)	0.46
Wound infection,[a] n (%)	5 (5)	14 (13)[a]	0.04

[a]Includes 10 patients secondary to subcutaneous stump leak. The wound infection rates after exclusion of stump leaks was 5 (5%) for the Hartmann stump group vs 4 (4%) for subcutaneously placed group ($p = 0.74$).

Intraperitoneal or Subcutaneous: Does Location of the (Colo)rectal Stump Influence Outcomes After Laparoscopic Total Abdominal Colectomy for Ulcerative Colitis?

Gu, Jinyu; Stocchi, Luca; Remzi, Feza; Kiran, Ravi P.
Diseases of the Colon & Rectum56(5):615 - 621, May 2013.

Retained rectal stump

It is prudent to have a plan regarding the remaining rectal stump in patients with ulcerative colitis. Most UC patients will continue to have symptoms form the rectal stump like pain, bleeding, tenesmus and mucous discharge. The rectal stump is also at risk of dysplasia and malignancy.
Patients with minimal rectal symptoms and inflammation may choose to remain with their ileostomy. These patients will require surveillance of the rectal stump.
Symptomatic patients and patients at risk for malignancy will be considered for completion proctectomy. This can be done with or without reconstruction.(Bedrikovetski et al., 2019)

Completion proctectomy

The completion proctectomy can be done open or laparoscopically. A combined approach has also been described, laparoscopic mobilisation of the rectum anterior up to the seminal vesicles and posterior to the levator muscles. The procedure is then completed trans perineal by dissecting in the intersphincteric plane. A newer approach is the laparoscopic total trans perineal proctectomy.

Dysplasia and malignancy

The risk for malignancy increases with disease duration and disease severity. Patients diagnosed with UC should have their first colonoscopy 8 years from the onset of symptoms. However, patients with high-risk features should have a colonoscopy as soon as possible. High risk features include PSC, First degree relative with malignancy under age 50 years, pancolitis and strictures. Surveillance colonoscopies are best done during periods of remission. Patients may have no dysplasia, visible dysplasia or invisible dysplasia.
Visible dysplasia will be in the form of a raised lesion this lesion may be polypoid or flat. It is important to characterise these lesions in terms size, site, shape, surface(kudo) and surroundings (mucosal activity). Treatment for visible dysplasia includes EMR or ESD.
Invisible dysplasia. In the case of low-grade dysplasia, the diagnosis should be confirmed by two pathologist that are experienced in diagnosing dysplasia in inflammatory bowel disease. If it has been confirmed close surveillance is recommended with repeat colonoscopy in 3 months. The

patient should be counselled on the risk of colectomy. If low grade dysplasia persists Total proctocolectomy should be considered. Patients with high grade dysplasia should be referred for total proctocolectomy.(Gordon et al., 2023; Ullman et al., 2009)

Total proctocolectomy

IPAA

This procedure was described by Ravich and Sabiston in 1947 after a serial of animal experiments. In 1978 Sir Alan Parks and J Nicholls designed the three limbed ileal pouch.
The timing of surgery is crucial. Consideration like age, fertility and nutritional status should be made. Anti TNF drugs should be stopped a few weeks prior to surgery.
This procedure is complex and should ideally be performed by surgeons with sufficient experience. There is debate about a one step or two stage (proximal diversion) IPAA. There are no randomised controlled trials to provide high level evidence. Most surgeons will still perform a two-stage procedure to mitigate pelvic sepsis in the event of a leak. (Ng et al., 2019)
Various pouch configurations exist. Most surgeons prefer the J pouch. It is easier to construct and fits comfortably in the pelvis. This is supported by a meta-analysis by Lovegrove et al.(Lovegrove et al., 2007)There are also variations in the technique used for anastomosis of the pouch stapled or hand sewn. The hand sewn technique offers the benefit of concurrent mucosectomy. With the stapled technique a 1 cm rectal cuff is left. The rectal cuff may complicate with cuffitis or dysplasia. This risk is relatively low and is offset by the benefit of superior pouch function with less episodes of incontinence and seepage. (Lovegrove et al., 2006)

Pouch complications:
Pouchitis
Cuffitis
Bacterial overgrowth in the pouch
Evacuation problems
Pouch ischaemia
Pouch stenosis
Fistulas, strictures and abscesses
CMV infection
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Eosinophilic pouchitis
Chron's disease of the pouch
Irritable pouch syndrome

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What Constitute Negligence In Surgical Practice? (N Pearce)

Definition of negligence in medical practice.

Negligence in medical practice occurs when a healthcare professional fails to provide the standard of care expected in their field, resulting in harm or injury to the patient.

- It involves a deviation from the accepted norms and practices that a reasonably competent professional would follow.
- Is the breach of a duty of care owed to the patient, which leads to adverse outcomes that could have been avoided with proper attention and skill?
- It encompasses errors in diagnosis, treatment, and patient management that fall below the acceptable standards of medical practice.

Malpractice vs negligence in surgical practice

- Negligence refers to the failure to meet the standard of care that a reasonably competent professional would provide, which can occur in any context.
- Malpractice, however, specifically involves negligence by a professional (such as a surgeon) and includes a breach of duty that results in harm to the patient. While all malpractice is a form of negligence, not all negligence constitutes malpractice. Malpractice is often used in legal contexts to describe professional errors that lead to significant patient harm or injury.

Legal Framework

In South Africa, negligence law is rooted in the principles of civil liability and is governed primarily by the common law.

1. **Key Elements of Negligence**

To establish negligence, the plaintiff must prove the following elements:

- Duty of Care: The defendant owed a duty of care to the plaintiff. In medical cases, this duty arises from the professional relationship between the healthcare provider and the patient.
- Breach of Duty: The defendant failed to meet the standard of care required. This involves demonstrating that the defendant's actions or omissions deviated from what a reasonable professional in the field would have done.
- Causation: There must be a direct link between the breach of duty and the harm suffered. The plaintiff must show that the breach was a proximate cause of their injury.
- Damage: The plaintiff must have suffered actual harm or damage as a result of the breach. This can include physical injury, emotional distress, or financial loss.

2. **Standard of Care**

In South Africa, the standard of care is generally defined by the conduct of a reasonable person in similar circumstances. For medical professionals, the standard is determined by what a reasonably competent practitioner in the same field would do.

3. **Legal Procedures**

- Civil Action: Negligence claims are usually pursued through civil litigation. The plaintiff files a lawsuit seeking damages for the harm suffered due to the defendant's negligence.
- Proof of Negligence: The burden of proof lies with the plaintiff, who must demonstrate that negligence occurred and that it directly caused their injuries. Evidence often includes medical records, expert opinions, and witness testimony.

4. **Defences to Negligence**

In South African law, several defenses can be raised against claims of negligence, including:

- Contributory Negligence: The plaintiff's own negligence contributed to their harm, potentially reducing the amount of damages awarded.
- Volenti Non Fit Injuria: The plaintiff consented to the risk involved, which may negate liability if they willingly accepted the risk of harm.
- Necessity: The defendant's actions were necessary to prevent a greater harm, which can sometimes justify otherwise negligent behavior.

5. **Recent Developments**

South African courts continue to refine the principles of negligence through case law. Recent decisions can impact how negligence is interpreted and applied in various contexts, including medical malpractice.

Definition and determination of the standard of care in surgery.

The standard of care in surgery refers to the level of care and skill that a reasonably competent surgeon, with similar training and experience, would provide under comparable circumstances.

Definition of Standard of Care

- Reasonable Skill and Knowledge: The standard requires that surgeons act with the level of skill, knowledge, and care that is expected from professionals in their field.
- Customary Practices: It is defined by the customary practices and procedures accepted by the majority of competent surgeons. This includes adherence to established protocols, guidelines, and best practices.

Determination of the Standard of Care

1. Professional Guidelines: Standards are influenced by professional medical guidelines and protocols from surgical societies and organizations. These guidelines often reflect current best practices and innovations in the field.

2. Expert Testimony: In legal cases, expert witnesses, usually other surgeons or medical professionals, provide testimony on what the accepted standard of care is.

3. Clinical Evidence: The determination involves examining clinical evidence, including peer-reviewed research, case studies, and historical practices within the specific surgical specialty.

4. Circumstances of the Case: The specific facts of the case are considered, such as the complexity of the surgery, the patient's condition, and available resources at the time of the procedure.

5. Legal Precedents: Courts may rely on previous rulings and case law to interpret what constitutes acceptable practice and to judge whether a breach of the standard of care occurred.

Role of Expert Witnesses in Establishing Negligence

In cases of surgical negligence, expert witnesses play a critical role in determining whether the standard of care was breached and whether this breach caused harm to the patient. Here's an in-depth look at their role:

1. **Definition and Function**

- Expert Witness: An expert witness is a qualified individual with specialized knowledge, skills, or experience in a particular field. In medical negligence cases, this often means a medical professional with expertise in the relevant area of surgery or healthcare.

- Function: Expert witnesses provide independent, objective opinions about the standard of care and whether the actions of the medical professional in question met or deviated from this standard.

2. **Establishing the Standard of Care**

- Benchmarking: Expert witnesses help establish what constitutes the acceptable standard of care within the specific surgical specialty. They describe the norms, protocols, and practices that a reasonably competent surgeon should follow.

- Professional Guidelines: Experts may refer to established guidelines, protocols, and best practices issued by medical boards, surgical societies, or other authoritative bodies to define the standard of care.

3. **Analyzing Actions and Decisions**

- Review of Case Details: Experts analyze the details of the surgical procedure, including preoperative, intraoperative, and postoperative actions. They evaluate whether the surgical team's conduct deviated from what is expected of a competent practitioner in the same circumstances.

- Identifying Breaches: Experts identify specific actions or omissions that constitute a breach of the standard of care. For example, they may determine if there were errors in technique, failure to follow procedural guidelines, or inadequate communication with the patient.

4. **Determining Causation**

- Linking Breach to Harm: Experts assess whether the identified breach of the standard of care directly caused the patient's injuries or complications. They establish a causal link between the negligence and the adverse outcomes experienced by the patient.
- Assessing Impact: They provide opinions on how the breach affected the patient's condition, including the extent of the harm and whether it was a foreseeable consequence of the negligence.

5. Testifying in Court

- Providing Testimony: Expert witnesses present their findings and opinions in court. Their testimony is crucial for explaining complex medical concepts and practices to judges and juries who may not have specialized medical knowledge.
- Clarifying Evidence: They help clarify medical records, surgical procedures, and other evidence related to the case. Their expert opinion assists in interpreting whether the actions taken were consistent with the standard of care.

Strategies for Reducing the Risk of Surgical Negligence

Reducing the risk of surgical negligence involves a multi-faceted approach that emphasizes best practices, effective communication, and adherence to established standards. Here are key strategies to mitigate the risk of surgical negligence:

1. **Adherence to Standard Operating Procedures**
   - Protocols and Guidelines: Follow established surgical protocols and clinical guidelines that outline best practices for various procedures. These guidelines are designed to ensure consistency and safety in surgical practices.
   - Checklists: Use surgical checklists (e.g., WHO Surgical Safety Checklist) to ensure all necessary steps are completed before, during, and after the procedure. Checklists help in minimizing errors and omissions.

2. **Effective Preoperative Planning**
   - Thorough Assessment: Conduct comprehensive preoperative assessments to evaluate the patient's health status, medical history, and potential risks. This includes reviewing imaging studies, lab results, and other diagnostic information.
   - Informed Consent: Ensure that patients are fully informed about the risks, benefits, and alternatives of the procedure. Obtain written informed consent and document the discussion thoroughly.

3. **Enhanced Communication**
   - Team Communication: Foster effective communication among surgical team members. Clear and concise communication can prevent misunderstandings and errors during the procedure.
   - Patient Communication: Maintain open lines of communication with patients and their families. Keep them informed about the surgical process, potential risks, and any changes in the treatment plan.

4. **Continuing Medical Education**
   - Training and Development: Engage in ongoing medical education to stay updated with the latest advancements, techniques, and best practices in surgery. Regular training helps in maintaining competency and adapting to new technologies.
   - Skills Assessment: Participate in regular skills assessments and simulations to practice and refine surgical techniques. This can help in identifying and addressing areas for improvement.

5. **Quality Assurance and Improvement**
   - Audits and Reviews: Conduct regular audits and reviews of surgical cases and outcomes. Analyze any adverse events or near misses to identify areas for improvement.
   - Feedback Mechanisms: Implement feedback systems where staff can report issues or suggest improvements. Analyzing feedback helps in refining processes and preventing future errors.

6. **Risk Management**
   - Identify Risks: Regularly assess potential risks associated with surgical procedures and implement strategies to mitigate these risks. This includes addressing factors such as patient comorbidities, surgical environment, and equipment.
   - Incident Reporting: Encourage reporting of incidents and near misses to learn from mistakes and prevent recurrence. Foster a culture of transparency and continuous improvement.

7**. Technological Integration**
   - Use of Advanced Technology: Incorporate advanced surgical technologies and tools that enhance precision and safety. Ensure that the surgical team is well-trained in using these technologies.
   - Monitoring Systems: Implement monitoring systems to track patient vitals and other critical parameters during surgery. Real-time data can help in promptly identifying and addressing issues.

Conclusion

Implementing strategies to reduce surgical negligence involves a combination of adherence to established protocols, effective communication, ongoing education, and the integration of advanced technologies. Continuous education ensures that medical professionals remain current with best practices and innovations, while adherence to protocols helps standardize care and reduce the risk of errors. Together, these efforts contribute to improving patient safety and achieving better surgical outcomes.

Balancing Risk and Benefit in Surgical Procedures

Balancing risk and benefit is a crucial aspect of surgical decision-making, ensuring that the advantages of a procedure outweigh the potential hazards. Here's how this balance is managed:

1. **Risk Assessment**
   - Preoperative Evaluation Assess patient-specific factors such as medical history, current health status, and comorbidities to identify potential risks associated with surgery.
   - Procedure Risks Evaluate the inherent risks of the surgical procedure itself, including potential complications and the likelihood of adverse outcomes.

2. **Benefit Analysis**
   - Expected Outcomes: Determine the anticipated benefits of the surgery, such as improved health, symptom relief, or enhanced quality of life.
   - Long-Term Gains: Consider the long-term benefits, such as recovery time, functional improvement, and potential for a better prognosis.

3**. Informed Consent**
   - Risk Disclosure: Provide patients with clear and comprehensive information about the risks and benefits of the procedure, including potential complications and the likelihood of success.
   - Patient Decision-Making: Ensure that patients understand the information and can make an informed choice based on their values and preferences.

4. **Alternatives Consideration**
   - Non-Surgical Options: Explore and present alternative treatments or management options that may offer similar benefits with fewer risks.
   - Comparative Analysis: Compare the risks and benefits of surgical versus non-surgical options to help patients make informed decisions.

5. **Monitoring and Adjustment**
   - Ongoing Assessment: Continuously monitor patients throughout the surgical process and adjust the approach as needed based on their response and evolving condition.
   - Postoperative Care: Implement a thorough postoperative care plan to manage complications and enhance recovery, further balancing risks and benefits.

Ethical Implications of Negligence and Patient Autonomy

1. Ethical Considerations of Negligence
   - Accountability: Medical professionals have a duty to uphold high standards of care. Negligence breaches this duty, leading to ethical questions about responsibility and accountability.
   - Patient Harm: Negligence often results in patient harm, raising ethical concerns about the responsibility to prevent harm and provide safe and effective care.
   - Professional Integrity: Maintaining professional integrity involves adhering to established standards and protocols, and addressing negligence issues transparently and responsibly.

2. **Patient Autonomy**
   - Informed Consent: Respecting patient autonomy means ensuring that patients are fully informed about their treatment options and the associated risks and benefits, allowing them to make autonomous decisions about their care.
   - Choice and Consent: Patients have the right to make decisions about their treatment based on their values and preferences, which includes the right to refuse or discontinue treatment.
   - Respect for Decisions: Even if a patient's decision may lead to a less favorable outcome, their autonomy must be respected, provided they are fully informed and capable of making sound decisions.

3. **Balancing Autonomy and Medical Responsibility**
   - Guidance and Support: While respecting autonomy, medical professionals should guide patients by providing clear, unbiased information and helping them understand the implications of their choices.
   - Ethical Dilemmas: Situations may arise where respecting patient autonomy conflicts with professional judgment about what is in the patient's best interest. Navigating these dilemmas requires careful consideration and ethical sensitivity.

4**. Transparency and Rectification**
   - Disclosure: If negligence occurs, it is ethically important to disclose it to the patient transparently, explain the impact, and take steps to rectify the situation.
   - Remediation: Addressing and correcting errors is not only an ethical obligation but also a critical aspect of maintaining trust and improving future care.

Conclusion

Balancing risk and benefit in surgical procedures requires a careful evaluation of the potential advantages and hazards of a surgery, thorough informed consent, and consideration of alternative treatments. Ethical implications of negligence involve accountability, responsibility, and maintaining patient autonomy. Respecting patient autonomy while ensuring high standards of care requires clear communication, ethical decision-making, and a commitment to

patient-centered practice. Addressing these issues thoughtfully ensures that patients receive safe, effective, and ethically sound care.

Physical, Emotional, and Financial Consequences of Surgical Negligence

Surgical negligence can have profound effects on patients, affecting various aspects of their lives. These consequences can be categorized into physical, emotional, and financial impacts.

1. **Physical Consequences**
    - Injuries and Complications. Surgical negligence can lead to significant physical injuries or complications, such as infections, organ damage, or incorrect procedures. These complications may require additional surgeries, extended hospital stays, or long-term medical treatments.
    - Permanent Disability: Some cases of negligence result in permanent disabilities, such as loss of limb function, impaired mobility, or chronic pain. This can affect a patient's ability to perform daily activities or return to work.
    - Reduced Quality of Life: Persistent physical issues may diminish a patient's overall quality of life, affecting their ability to engage in normal activities, hobbies, or even basic self-care.

2. **Emotional Consequences**
    - Mental Health Issues: The stress and trauma of experiencing surgical negligence can lead to mental health problems such as anxiety, depression, or post-traumatic stress disorder (PTSD). The emotional burden of dealing with unforeseen complications and prolonged recovery can be significant.
    - Loss of Confidence: Patients may experience a loss of confidence in the healthcare system or in their own body's ability to recover. This can lead to ongoing psychological distress and fear of future medical procedures.
    - Relationship Strain: The emotional toll of dealing with negligence can strain personal relationships. Family members and caregivers may experience stress and frustration, which can affect interpersonal dynamics and support systems.

3. **Financial Consequences**
    - Medical Expenses: The costs associated with additional treatments, surgeries, or long-term care resulting from surgical negligence can be substantial. This includes costs for follow-up visits, medication, rehabilitation, and possibly even home modifications.
    - Lost Income: Prolonged recovery or permanent disability may lead to loss of income if the patient is unable to return to work. This financial strain can exacerbate the impact of medical costs and affect the patient's economic stability.
    - Legal Costs: Pursuing legal action against a negligent party involves legal fees, which can be significant. Even in successful cases, the financial burden of litigation can be substantial and may not always be fully recovered.

Conclusion

The consequences of surgical negligence are far-reaching and affect various aspects of a patient's life. Physical consequences can include lasting injuries, disabilities, and diminished quality of life. Emotionally, patients may face mental health challenges, loss of confidence, and strained relationships. Financially, the impacts include substantial medical costs, lost income, and legal expenses. The case examples provided illustrate the profound effects that surgical negligence can have on individuals, highlighting the importance of maintaining high standards of care and addressing negligence issues comprehensively.

MEDICAL NEGLIGENCE IN SURGERY

PRESENTED BY : ADVOCATE MUSHAISANO MUGODO-MAKAMU

This presentation will follow the following format:

- Introduction
- Definition of the concept of 'medical negligence'
- The test for negligence
- What are examples of acts of medical negligence?
    - Incorrect diagnosis
    - Lack of informed consent
    - Lack of skill
    - Failure to follow up and provide post-operative care
    - Lack of experience
    - Lack of skill in an emergency situation
    - Diagnosis disclosure

INTRODUCTION

Medical negligence claims in South Africa have been steadily rising in both quantity and damages recovered.[1] In reality, the volume of complaints against medical professionals has increased exponentially and is still rising. The likelihood of a medical practitioner being sued by a patient was negligible more than thirty years ago. Right now, this possibility is quite real. Changes are evident everywhere in South Africa.

There are numerous factors contributing to the significant rise in medical malpractice lawsuits. Inter alia, it is said that the dramatic shift in law that was brought in by the Constitution and patient centred legislation has a huge part in the increase.[2] According to the South African Law Reform Commission, our constitutional democracy has resulted in

[1] Saner J *Medical Malpractice in South Africa.*
[2] NV Dokkum'the evolution of medical malpractice law in South Africa

increased awareness of rights and thus an upsurge in litigation as patients attempts to give effects to their rights[3]

Government resources are being stretched ever thinner, and as a result human as well as material resources are being rationed. Medical professionals have to "the best for the most," which can mean "cutting corners," less oversight, and less support systems." In the private sector, medical insurance companies' pressure in many cases has meant compromising the quality of treatment; what might have been accessible in the past no more exists.[4]

To illustrate the crisis in medical negligence litigation in the public sector, it was recently reported that Gauteng has 2,450 medico-legal claims, 611 of which are under investigation, totalling R4.175 billion. Fifty-eight cases have been finalised, saving the province's health department R66 million.[5] The Government's contingency liability for medical negligence claims in 2021 tops R100 billion.[6] The financial crisis this liability represents, becomes clear if the 2020/21 Public Health budget of R249 billion is considered.[7]

As a result, it goes without saying that the medical fraternity needs to be better educated about the prevalence of medical negligence claims and the importance of taking the best preventative measures. Although it is understandable that doctors cannot be expected to cure the incurable or succeed in every operation, it is still their responsibility to act with reasonable skill and care, among others.[8]

DEFINITION OF THE CONCEPT OF 'MEDICAL NEGLIGENCE'

Negligence begins if a legal duty to act or not to act is breached. Medical negligence, in a medico-legal context, is the failure of a medical practitioner to adhere to medical standards that have been established and are practiced by any ordinary and reasonable

[3] South African Law Reform Commission Discussion Paper 154 'Medicolegal Claims (October 2021)
[4] Saner J *Medical Malpractice in South Africa.*
[5] https://www.timeslive.co.za/news/south-africa/2024-08-24-its-game-over-motsoaledi-and-siu-go-after-law-firms-submitting-fraudulent-medical-negligence-claims/
[6] Spotlight "In-depth: This is how health departments (mis)spend public funds" at https://www.spotlightnsp.co.za/2021/04/19/in-depth-this-is-how-health-departments-misspend-public-funds/.
[7] Klopper H "*The public health medical negligence claims conundrum"* 1.
[8] As it will be explained below, the test for medical negligence was enunciated in the case of *Mitchell v Dixon* 1914 AD 519 where Acting Chief Justice Innes observed, "A medical practitioner is not expected to bring to bear upon the case entrusted to him the highest possible degree of professional skill and care, he is bound to employ reasonable skill and care; and he is liable for the consequences if he does not." At para 525.

medical practitioner in the same field. The aforementioned definition of medical negligence can be traced back to two very old case laws that are still relevant in South African jurisprudence: *Mitchell v Dixon* 1914 AD 519 and Van *Wyk v Lewis* 1924 AD 438. The courts established the standard of "what medical negligence" in the aforementioned cases, as will be demonstrated below.

According to other esteemed authors, medical negligence is the result of a medical practitioner's failure to demonstrate the level of skill and care that is expected of a reasonably competent practitioner in that particular branch of the profession. This implies that the level of skill and care required increases as the complexity of the procedure increases, although the courts will take into account the health care practitioner's resources at the time.[9]

An error in diagnosis, for example, is not always negligent; the issue is whether a reasonable practitioner in the same field of medicine would have made a similar mistake as will be discussed in more detail below. If the medical negligence directly resulted in damage or injury to the patient, then a malpractice lawsuit may develop. Should a doctor misdiagnose flu, for instance, this could be a medical negligence. On the other hand, should the patient heal in a week free of any long-lasting damage, this would not lead to a medical malpractice lawsuit since the patient could be reimbursed for no resulting harm resulting from the medical negligence.

THE TEST FOR NEGLIGENCE

In general, when a doctor is sued, he or she is almost always sued for "delict". If, at the end of the case, the doctor's conduct is found to have fallen short of the standard the law expects of a reasonable doctor (in a specific field of medicine) in the given circumstances, the doctor will be found negligent. If the other elements of delictual liability are present, the doctor is liable for any damage caused by negligence.[10]

The test for negligence was formulated by Holmes JA in the 1966 matter of Kruger v Coetzee 1966 (2) SA 428 (A) at 430 E-F as follows:

"For the purpose of liability culpa arises if-

a) a diligens paterfamilias in the position of the defendant-
    i. would foresee the reasonable possibility of his conduct injuring another in his person or property and causing him patrimonial loss; and

[9] McQuoid-Mason DJ "What constitutes medical negligence? A current perspective on negligence versus malpractice" *SA Heart* 248.
[10] Saner J *Medical Malpractice in South Africa*.

ii. would take reasonable steps to guard against such occurrence; and

b) the defendant failed to take such steps"

In the case of medical negligence, the test is adapted to the standard of a reasonable medical practitioner or reasonable medical specialist in that field, with a similar degree of professional skill in the same circumstances as the defendant.[11]

The test for medical negligence was enunciated in the case of *Mitchell v Dixon* 1914 AD 519, where Acting Chief Justice Innes observed, "a medical practitioner is not expected to bring to bear upon the case entrusted to him the highest possible degree of professional skill and care, he is bound to employ reasonable skill and care; and he is liable for the consequences if he does not."[12]

In the case of *Van Wyk v Lewis* 1924 AD 438 at 438, reference is made to "the general level of skill and diligence possessed and exercised at the time by the members of the branch of the profession to which the practitioner belongs." What is required, however, is not the highest possible degree of professional care and skill, but reasonable knowledge, ability, experience, care, skill, and diligence.'

As has already been noted, when applied to the medical profession the standard has always been, and continues to be, that of the reasonable medical professional or practitioner in the particular circumstances of the case.

In the case of *Oppelt v Department of Health*[13], Cameron J provided a clear explanation of the elements involved in the test for negligence as follows:

> *"In our law Kruger embodies the classic test. There are two steps. The first is foreseeability-would a reasonable person in the position of the defendant forsee the reasonable possibility of injuring another and causing loss? The second is preventability-would that person take reasonable steps to guard against the injury happening?*
>
> *The key point is that negligence must be evaluated considering all the circumstances. And, because the test is defendant -specific ("in the position of the defendant"), this standard is upgraded for medical professionals. The question, for them, is whether a reasonable medical professional would have foreseen the damage and taken steps to avoid it. In Mitchell v Dixon the then Appellate Division noted that this standard does not expect the impossible of medical personnel:*

[11] Carsten &Pearmain 619

[12] At para 525.

[13] Oppelt v Department of Health, Western Cape [2015] ZACC 33: 2016 (1) SA 325 (CC) Paras 106-108

“a medical practitioner is not expected to bring to bear upon the case entrusted to him the highest possible degree of professional skill, but he is bound to employ reasonable skill and care and he is liable for the consequences if he does not.”

This means that we must not ask: what would exceptionally competent and exceptionally knowledgeable doctors have done? We must ask: “what can be expected of the ordinary for average doctor in view of the general level of knowledge, ability, experience, skill and the diligence possessed and exercised by the profession, bearing in mind that a doctor it's a human being and not a machine and that's no human being is infallible.” Practically, we must also ask was the medical professional approach consonant with a reasonable and responsible body of medical opinion. This test always depends on the facts. With a medical specialist, the standard is that of the reasonable specialist.”

WHAT ARE THE EXAMPLES OF ACTS OF MEDICAL NEGLIGENCE?

Error of judgment

A medical professional's error of judgment may or may not constitute negligence. The extent to which an error of professional or clinical judgment constitutes negligence is consistently assessed in comparison to the standard of a reasonable, competent medical practitioner in the same situation. In other words, a doctor's error of judgment during the treatment or execution of a procedure on a patient will not be considered negligent by the law if a reasonable, competent doctor in the same circumstances would, despite exercising reasonable skill and care, make the same error.

In summary, the law of medical negligence in South Africa acknowledges that doctors are human beings, not machines, and that it is human nature to make mistakes. However, it also acknowledges that certain errors exceed the standard that is expected of a reasonable medical practitioner.

In summary then, the law does not require a doctor to be infallible in his or her conduct. An error of clinical judgement will not constitute negligence if the doctor has adhered to the requisite standard of reasonable care. But if the error is one that would not have been made by the reasonable medical practitioner in the circumstances, then the practitioner is negligent.

Lack of informed consent

In cases of medical malpractice, there is often a failure to obtain informed consent.[14] Medical malpractice resulting from a lack of informed consent can be attributed to the evolution of medical law from a paternalistic approach to one that prioritises individual autonomy. In the past, patients were required to make decisions based on the information provided by their healthcare provider, if any was given. The current position requires that the patient be fully informed.[15] Giesen advocated for a shift from paternalism to self-determination to shared decision making,[16] Informed consent requires that a doctor has to warn a patient of all material risks. In Esterhuizen v Administrator Transvaal 1957 (3) SA 710 (T), the court held that mere consent to undergo an X-ray treatment, under the belief that it is innoxious or undergoing it without being aware of the attended risks cannot amount to effective consent to undergo the risk.

Lack of skill

Although, as previously stated, the notional reasonable person possesses no special skills, a lack of skill or knowledge does not constitute negligence. It may be negligent to perform a task or treat a patient when such an undertaking necessitates a certain level of expertise and the person or doctor performing it lacks the required level of competence.

In the medical field, this means that a doctor will be held liable (for negligence) when he or she begins to treat a patient despite knowing that he or she lacks the necessary skill, knowledge, or experience, and the patient suffers harm.

Lack of experience

The effect of a lack of experience on an otherwise fully qualified health professional's expertise is closely related to the issue of lack of skill, but differs slightly. It follows, almost logically, that the general level of ability of a newly qualified health professional will be lower in almost all cases than that of a practitioner with the same qualifications but who has been in practice for many years. However, if a novice's lack of expertise causes harm to a patient, his or her lack of experience will not excuse the practitioner's error.

Incorrect diagnosis

When making a diagnosis, a medical professional must use the same level of skill and care that a reasonable practitioner would use in his or her situation. If the healthcare provider falls short of that standard, negligence will be established. If he or she follows the standard but makes an incorrect diagnosis, there will be no fault (negligence). The lack of culpability for a wrong diagnosis when the doctor has adhered to the required standard, was emphasised by the SCA in *Louwrens v Oldwage* where Mthiyane JA said:

[14] SA Strauss 'Doctor, patient and the law: a delicate triangle (2008) SA Orthoaedic Journal 10.
[15] NV Dokkum 'the evolution of medical malpractice in South Africa' (1997) 41 Journal of African Law 175
[16] D Giesen 'From Paternalism to self-determination to shared decision making' (1998) Acta Juridica 107

Accordingly, on all the evidence, the defendant's surgical intervention was justified and there is no basis for a finding of misdiagnosis. In *Mitchell v Dixon* Innes ACJ said:
'A practitioner can only be held liable in this respect, if his diagnosis is so palpably wrong as to prove negligence, that is to say, if his mistake is of such a nature as to imply absence of reasonable skill and care on his part, regard being had to the ordinary level of skill in the profession.'

That is to say, a doctor is not liable for making an incorrect diagnosis, provided the diagnosis was not made negligently, with reference to the yardstick of the reasonable competent doctor in the same circumstances. It is, of course, not the incorrect diagnosis itself which is indicative of medical negligence; the wrong diagnosis, without any treatment consequent thereupon, is merely a wrong diagnosis 'in the air', so to speak. It is the application of the wrong or inappropriate treatment, dictated by the wrong diagnosis, which actually constitutes negligence.

Failure to refer

In practical terms, if a medical professional is unable to make a diagnosis or provide additional effective treatment, he or she should refer the patient to a specialist or alternative facility to avoid falling short of the standard expected of a reasonable medical professional in the circumstances. The obligation to refer in appropriate circumstances follows logically from the practitioner's obligation not to continue to treat when he or she knows, or ought to know, that continuing to treat is beyond his or her skill, knowledge, or expertise, or when he or she should recognize that onward referral is in the patient's best interests over continued treatment.

CONCLUSION

In a nutshell it is imperative that medical professionals implement the requisite measures to prevent patient dissatisfaction from escalating into full-scale court cases, which could jeopardize the reputations of practitioners and subject them to the costly and unpleasant consequences of civil and criminal claims. This is especially true when South Africa is experiencing an increase in unnecessary litigation with the intention of obtaining financial compensation, as previously mentioned. Medical negligence claims are avoidable, particularly in cases where the damage is predictable and preventable. Failure to act in a manner that would have been reasonable for a reasonable oncologist in the same position would result in liability for the medical practitioner. In this case, the oncologist.[17]

[17] Maimela CA "Medical negligence and the res ipsa loquitur doctrine in the administration of cancer treatment in South Africa" *Obiter* 23.