Effects of delays in Neoadjuvant or Adjuvant therapy for Breast Cancer

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5 October 2018
The optimal time interval between surgery and initiation of adjuvant therapy for early-stage breast cancer is not well established. Although most physicians aim to initiate adjuvant chemotherapy within a few weeks of surgery, clinical factors may cause delay. The influence of delay on relapse and mortality is uncertain, and whether its impact varies by breast cancer subtype is not well defined.

ASCO Post 2014
Current Approach

Early Breast Cancer

- No wish for breast conservation or breast conservation not possible (e.g. multicentricity)
  - Mastectomy ± reconstruction
    - Postoperative ChT ± trastuzumab, if applicable
      - Postoperative RT, if applicable (mandatory after BCS)

- Tumour ≤2 cm and/or optimal surgery feasible
  - Unsatisfactory response

- Tumour >2 cm or optimal surgery not feasible and wish for breast conservation and breast conservation potentially feasible after down staging
  - Systemic induction therapy (if ChT planned, should all be given as neoadjuvant)
    - Satisfactory response
      - Breast conserving surgery
    - Concomitant
      - Postoperative ET, if applicable

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
### Patient Information and Assessment of the Disease

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>Imaging</th>
<th>Core Biopsy</th>
<th>Definite Indication for Adjuvant Systemic Therapy</th>
<th>Additional Considerations that Should Be in Place at Each MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mammogram (size, M score)</td>
<td>Type, grade, receptor status of the tumor (e.g., HR, HER2)</td>
<td>Definition of assessment criteria (e.g., pCR definition)</td>
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</tr>
<tr>
<td>Clinical History (e.g., comorbidities)</td>
<td>Ultrasound (size, U score)</td>
<td>Axilla biopsy or fine needle aspiration</td>
<td>Protocols for testing and receiving timely results (e.g., receptor status)</td>
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<tr>
<td>Drug History (e.g., concomitant medications)</td>
<td>Axilla ultrasound (N score)</td>
<td>Other (e.g., logistical/planning reasons, BRCA testing)</td>
<td>Downstage breast tumour</td>
<td>Downstage axilla</td>
</tr>
</tbody>
</table>

### Purpose

- What is the aim of NAC for this patient?

### Management and Treatment

#### Surgical and Axillary Management
- Current Breast Surgical Plan
- Will the surgical plan change following NAC? (If so, provide alternative surgical plan, and which parameters trigger alternative plans)
- Current Axillary Plan
- Post-NAC Sentinel Lymph Node Biopsy or Axillary Node Clearance
- Current Adjuvant Radiotherapy Plan

#### Checklist
- Staging CT (if indicated)
- USS clip placement
- Surgical review planned
- Plan for imaging assessment of response

#### Outstanding Issues
- Any outstanding issues should also be discussed
Clinical benefits and potential concerns associated with neoadjuvant treatment for early breast cancer

Downstage tumours to enable breast-conserving surgery rather than mastectomy, improving cosmetic outcomes.
De-escalate surgical treatment of the axilla
Provide time for germline mutation test results (i.e. BRCA1/2) that may influence surgical plan.
Cancer may progress and become inoperable (a rare event with appropriate monitoring of response).
Reduced window of opportunity for fertility preservation
Increasing tumour response may not achieve a reduction in mastectomy rates, regardless of downstaging and effectiveness of therapy regimen
Increased locoregional recurrence rates in patients who do not undergo surgery after neoadjuvant treatment. Disease information and monitoring
Provide individualised post-treatment prognostic information (e.g. pathological complete response, residual cancer burden) for management decisions.
Permits clinicians to monitor response to therapy at an early stage; potentially allowing time and flexibility to switch therapies if patients do not respond.
Potential loss of staging information.
Potential for over-treatment, if decision is based on incomplete information (e.g. size of lesion is overestimated because of associated ductal carcinoma in situ seen radiologically).
Potential for under-treatment if therapy is stopped or changed mid-course.
Limited evidence base to guide adjuvant radiotherapy decisions or management of patients with residual disease.
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- Delay in time to adjuvant chemotherapy (TTC) is associated with adverse outcomes in both overall survival and disease specific survival ( > 90 days after definitive surgery)

- Of particular relevance is the impact of delays in more advanced disease and highly proliferative tumours like triple negative breast cancer (TNBC)
## Factors associated with Delays

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>Clinical</th>
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</thead>
<tbody>
<tr>
<td>Socioeconomic</td>
<td>Mastectomy vs BCS</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Reconstruction</td>
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<tr>
<td>Type of medical care – private insurance or other</td>
<td>Readmission</td>
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<td></td>
<td>Margins and re-excisions</td>
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<td>Facility type and volume</td>
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<tr>
<td></td>
<td>Co-morbidities – not a major factor.</td>
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</table>
Evidence on the effect of delays

Assessment of Breast Cancer Treatment Delay Impact on Prognosis and Survival: a Look at the Evidence from Systematic Analysis of the Literature

Faustine Williams* Department of Surgery, Washington University, USA

Journal of Cancer Biology and Research

Abstract

Introduction:
Breast cancer has remained the most commonly diagnosed disease among women globally. Despite the advancement in biomedical sciences leading to improve survival outcomes, some patients endure longer wait periods prior to initiation of treatment.

Objective:
To elucidate the impact of treatment delay on breast cancer patient’s quality of life and survivorship. Second was to determine the optimal length of time (delay) between breast cancer diagnosis and start of first treatment in order to improve prognosis and general health and well-being of survivors.

Methods: Systematic search of the literature was conducted across five electronic databases: Pub Med, EMBASE, CINAHL, Scopus and Science Direct as well as the reference list of all articles retrieved.
Results:

A total of 33 articles were included in the evidence based systematic review, which comprised of 255,366 observations. The results of the studies were categorized under five main themes as: study characteristics, cancer staging and classification, treatment delay time definition and interval, treatment regimen classification and delay impact on quality of life and survival. Analysed wait times from diagnosis to the initiation of first therapy ranged from 7 days to a period of over 180 days. Combinations of standardized treatment including loco-regional radiotherapy, systemic chemotherapy surgery as well as hormonal therapy were examined. Even though some of the studies showed mixed results, overall, findings indicated that early detection, diagnosis and initiation of treatment within 90 days increase survival.

Conclusions:
Evidence revealed that delaying the initiation of treatment for breast cancer more than 90 days after diagnosis has a detrimental effect on disease free and overall well-being of survivors.
Adjuvant treatment delay in breast cancer patients

**Background:** to evaluate if time between surgery and the first adjuvant treatment (chemotherapy, radiotherapy or hormone therapy) in patients with breast cancer is a risk factor for lower overall survival (OS). **Method:** data from a five-year retrospective cohort study of all women diagnosed with invasive breast cancer at an academic oncology service were collected and analyzed. **Results:** three hundred forty-eight consecutive women were included. Time between surgery and the first adjuvant treatment was a risk factor for shorter overall survival (HR=1.3, 95CI 1.06-1.71, p=0.015), along with negative estrogen receptor, the presence of lymphovascular invasion and greater tumor size. A delay longer than 4 months between surgery and the first adjuvant treatment was also associated with shorter overall survival (cumulative survival of 80.9% for delays ≤ 4 months vs. 72.6% for delays > 4 months; p=0.041, log rank test). **Conclusion:** each month of delay between surgery and the first adjuvant treatment in women with invasive breast cancer increases the risk of death in 1.3-fold, and this effect is independent of all other well-established risk factors. Based on these results, we recommend further public strategies to decrease this interval.
Abstract
Objective
Our objective was to determine whether a delay in adjuvant radiotherapy is related to a decrease in relapse-free survival and disease-specific survival of women with operable breast cancer.

Methods
Data on 1000 patients diagnosed with breast cancer were recorded. The cohort was divided into five groups according to the timing of radiotherapy: ≤30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, and >120 days. The relapse-free survival and disease-specific survival were also calculated in relation to the number of patients.

Results
This study found no statistical difference for delays in adjuvant radiotherapy in patients with early breast cancer, but we noted a statistical decrease in disease-specific survival in patients with locally advanced breast cancer receiving radiotherapy after a delay of at least 60 days.

Conclusion
Waiting times for radiotherapy should be as short as reasonably achievable, given the
Summary/Update

Timing and Delays in Breast Cancer Evaluation and Treatment. Bleicher RJ¹. Department of Surgical Oncology, Room C-308, Fox Chase Cancer Center, Philadelphia, PA, USA

Abstract

BACKGROUND:
Even small delays in the treatment of breast cancer are a frequently expressed concern of patients. Knowledge about this subject is important for clinicians to counsel patients appropriately and realistically, while also optimizing care. Although data and quality measures regarding time to chemotherapy and radiotherapy have been present for some time, data regarding surgical care are more recent and no standard exists. This review was written to discuss our current knowledge about the relationship of treatment times to outcomes.

METHODS:
The published medical literature addressing delays and optimal times to treatment was reviewed in the context of our current time-dependent standards for chemotherapy and radiotherapy. The surgical literature and the lack of a time-dependent surgical standard also were discussed, suggesting a possible standard.

RESULTS:
Risk factors for delay are numerous, and tumour doubling times are both difficult to determine and unhelpful to assess the impact of longer treatment times on outcomes. Evaluation components also have a time cost and are inextricable from the patient's workup. Although the published literature has lack of uniformity, optimal times to each modality are strongly suggested by emerging data, supporting the current quality measures. Times to surgery, chemotherapy, and radiotherapy all have a measurable impact on outcomes, including disease-free survival, disease-specific survival, and overall survival.
CONCLUSIONS:

Delays have less of an impact than often thought but have a measurable impact on outcomes.

Optimal times from diagnosis are

< 90 days for surgery,

< 120 days for chemotherapy,

and, where chemotherapy is administered, < 365 days for radiotherapy