GENERIC EXPERT EVIDENCE

INTRODUCTION

Overview

The purpose of the generic days is to assist the Coroner in understanding the complex issues of adequacy of treatment and causation which have arisen and will arise during the course of these Inquests. It will provide an opportunity for the Coroner to consider the key literature. Time is limited so only key issues will be considered.

The purpose of this document is to provide an overview of the issues which will be considered. For the avoidance of doubt:

- CTI will ask other questions in addition to the ones listed.
- CTI will only ask questions which are relevant to the particular specialty – i.e. Oncology or Surgery.

This document is provided to all the Interested Persons and the experts.

Topics

CTI has identified the following topics for consideration during the generic days.

Topic 1 –	Delay
Topic 2 -	Incomplete Mastectomies
Topic 3 –	Involved Margins
Topic 4 –	Removal of the Axillary Lymph Nodes
Topic 5 –	Other Issues

Adequacy of Treatment

Inquests are not concerned with matters of civil liability such as negligence. However, consideration of the adequacy of treatment is necessary. A death from a natural occurring condition, such as breast cancer, may be 'natural' in the sense that medical treatment (good, bad or indifferent) may have no causative effect on a person's death. However, a death may be deemed 'unnatural' where it is caused or contributed to by some culpable human failing.

Adequate treatment is treatment in accordance with accepted practice at the time. The relevant period is 1990 to 2011.

The Causation Test[1]

Where the evidence in a particular case suggests that there is no causative link between the clinical treatment provided (or not provided), on the one hand, and death, on the other, it is essential that the conclusion reflects that evidence.

It is important to remember that a mere increase in the chance of death occurring is not sufficient to establish causation. In order for inadequate medical treatment to have *caused* the death it must have **contributed more than minimally, negligibly or trivially to the death**[2]. It is not necessary for it to have been the sole or predominant cause. But it must make an **actual and material contribution** to the death occurring when it did. This means a contribution that both really (not speculatively) occurred and was significant enough to contribute to the death in question.

General statistical evidence may well be relevant but it will normally not be sufficient evidence on its own to establish causation. There needs to be evidence that the Deceased would or would not have fallen into the group of survivors absent the inadequate treatment. In other words, there needs to be evidence relating the statistics to the Deceased's actual condition and presentation.

Inadequate medical treatment will meet the causation threshold test if:

(i) The death would not have occurred but for the inadequate treatment; OR

(ii) The patient would have lived for longer but for the inadequate treatment.

However,

(iii) Causation in an inquest is not limited to cases where the death would not have occurred when it did 'but for' the inadequate treatment. There may be cases where it is impossible to answer (i) or (ii) above (due to the limitations of the medical science),

[1] CTI is grateful to Nicholas Moss KC and Susan Jones (UHB) for their suggested wording, which we adopt in part.

[2] For the sake of convenience, this phrase is often shortened to "caused or contributed to".

but where the evidence establishes that the inadequate treatment nevertheless more than minimally, negligibly or trivially contributed to the death.

The Standard Of Proof

The standard of proof to which this threshold test for causation must be established in inquests is normally **the balance of probabilities**; i.e. more likely than not.

Since this is an Article 2 Inquest the Coroner may record circumstances which are **possible (i.e. more than speculative)** but not probable causes of the Deceased's death.

Phrases which do not amount to causation

For the avoidance of doubt, the following do not amount to "caused or more than minimally, negligibly or trivially contributed":

"a material contribution to an increase in risk of the Deceased dying of breast cancer"

"a reduction in the prospects of the Deceased living disease free from X% to Y%"

"an increase in risk of the Deceased developing a recurrence/new primary and metastatic disease"

"the inadequate treatment made it more probable that she would die of cancer than otherwise"

The reason these phrases do not meet the causation threshold is because they are not describing a contribution that both really (not speculatively) occurred and was significant enough to contribute to the death in question (one which was actual and material), rather they are describing whether the probability or potential for an outcome is increased or not and so are merely describing a hypothetical or statistical cause or contribution.

Causation Questions

Applying the tests above, the following questions will be asked at the individual Inquests if the experts are of the view that the Deceased received inadequate treatment.

- If the Deceased had received adequate treatment, would the death of the Deceased have been avoided or their life prolonged, on the balance of probabilities?

- If it is not probable that the Deceased's death would have been avoided or their life prolonged, is it possible (i.e. more than speculative) that the Deceased's death would have been avoided or their life prolonged, had they received adequate treatment?

- If it is impossible to say on the balance of probabilities whether the Deceased's death would or would not have been avoided or their life prolonged had they received adequate treatment (due to lack of evidence or medical science), did the inadequate treatment more than minimally contribute to her death;

Literature

CTI has identified the relevant literature for each topic and a bundle has been prepared. Literature which is generic to all the topics is:

1. BASO Guidelines 1995
2. BASO Guidelines 1998
3. BASO Guidelines 2005
4. BASO Guidelines 2009
5. NICE 2009 Guidelines "Early and locally advanced breast cancer: diagnosis and treatment."

The Interested Persons are requested to notify the Inquest Legal Team in advance of any additional literature they intend to rely on. This can then be added to the bundle.

General Approach

The experts will be asked about their approach to the issues which have arisen during the course of these Inquests and the methodology which has been used. In particular, whether the experts have adopted the same methodology adopted by Professor Dodwell. In particular:

In his evidence on Day 3 of Nikitas, Professor Dodwell stated[3]:

[3] Page 74 A to C

"I'd just like to make general points which is we've heard a lot about there's no evidence: there is evidence, there's no evidence. Well, there's no evidence for lots of things in the management of early breast cancer, so the response that there's no evidence for something isn't in itself enough. The supplementary question would be, well, is there evidence that you - is there no evidence because there's a lack of evidence or is there no evidence because there is contrary evidence that proves safety of margin orientation of preoperative open blind spots et cetera? And, of course, there isn't evidence of safety. So when we use the phrase, "There is no evidence of harm," there's also no evidence of no harm. I just think it's important to have that in mind because it will keep coming back, I think, throughout - throughout this case and probably many of the others."

In his Generic Report, when considering the oncological impact of residual breast tissue, Professor Dodwell stated[4]:

"To my knowledge there are no randomised trials (level 1 evidence) that have compared differing forms of mastectomy, with or without reconstruction, to address the issue of the effect of residual breast tissue on the risks of new primary breast cancer, locoregional recurrence, distant recurrence and death from breast cancer. Such an absence of direct randomised evidence is unsurprising, given the difficulties and ethical concerns in undertaking such a study, however, ***this does mean that reliance on other forms of evidence, that derive from observational studies, or are reliant on collective opinion, established practice, an accepted understanding of the pathophysiology of breast cancer and the effects of treatment, is needed to address the issue of the possible impact of residual breast tissue on oncological outcomes." [our emphasis]***

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Counsel to the Inquests

Dated May 2025

[4] [CB10/39]

TOPIC 1 - DELAY IN DIAGNOSIS

Adequacy of Treatment

CTI wishes to investigate whether there was any delay in the Deceased receiving treatment – whether surgery, radiotherapy, neo-adjuvant chemotherapy, adjuvant chemotherapy or endocrine therapy.

The following issues will be covered:

1. Between 1990 and 2011, the appropriate time periods for:
    a. GP referral to diagnosis
    b. Diagnosis to therapeutic surgery
    c. Therapeutic surgery to radiotherapy
    d. Therapeutic surgery to chemotherapy
    e. Therapeutic surgery to endocrine therapy

2. Relevance of the BASO guidelines to a breast surgeon. Was it mandatory for a breast surgeon to follow them?

3. Availability of provision of reconstruction surgeons when considering delays in treatment from 1990 to 2011.

Causation

Mechanisms

CTI wishes to investigate whether a delay in diagnosis and providing surgical and adjuvant treatment is capable of causing or more than minimally, negligibly or trivially contributed to the Deceased's death.

The generic reports agree that there is a correlation between delay in diagnosis/treatment and outcome/mortality in the general breast cancer population, but there is disagreement as to whether these statistics can be applied to an individual patient.

The following are postulated as plausible mechanisms which should be considered when considering whether the Deceased's death could have been caused or contributed to by a delay in providing surgical and/or adjuvant treatment.

The experts are invited to consider whether each is a possible[1] biological mechanism as to how the Deceased came to die of metastatic breast cancer. The possible mechanisms can then be applied to the specific facts of the Inquests. The experts are also invited to provide details of any other possible mechanisms.

It is recognised that whether any of the above mechanisms actually occurred is dependent on the precise factual circumstances of the Inquest including the individual and clinical factors. This will be considered when the Inquests are heard.

In considering the following possible mechanisms, please note the following:

Missed treatment date = the time when the primary cancer should have treated.

Actual treatment date = the time when the primary cancer was actually treated.

Culpable period = the time between the missed treatment date and the actual treatment date.

- **Mechanism 1** –
    - At the time of the missed treatment date, the primary cancer had already started to metastasise and produce micro metastasis ("micro mets")
    - These existing micro mets spread around the Deceased's body[2], seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the delay did not cause or contribute[3] to the Deceased's death.

- **Mechanism 2 -**
    - At the time of the missed treatment date, the primary cancer had not started to metastasise or had metastasized to the lymph nodes only.
    - The cancer started to metastasise during the culpable period of delay, creating micro mets which spread around the Deceased's body.

[1] Possible means more than speculative.
[2] Whether via the lymphatic system or the blood stream.
[3] In more than a "minimal, negligible or trial" way.

- These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
- This metastatic disease caused or contributed to the Deceased's subsequent death.
- Treatment at the time of the missed treatment date would not have been successful in preventing the invasive cancer metastasizing.
- In such circumstances, the delay did not cause or contribute to the Deceased's death.

- **Mechanism 3** –
  - At the time of the missed treatment date, the primary cancer had not started to metastasise or had metastasized to the lymph nodes only.
  - The cancer subsequently started to metastasise and created micro mets.
  - These micro mets spread around the Deceased's body during the culpable period of delay.
  - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
  - This metastatic disease caused or contributed to the Deceased's subsequent death.
  - Treatment at the time of the missed treatment date would have been successful in preventing the invasive cancer metastasizing.
  - In such circumstances, the delay did cause or contribute to the Deceased's death.

- **Mechanism 4 -**
  - At the time of the missed treatment date, the primary cancer had started to metastasise to the lymph nodes and micro mets had spread around the Deceased's body.
  - Chemotherapy at the time of the missed treatment date would have eradicated these micro mets and the patient would have been cured.
  - By the time of actual treatment, the micro mets had seeded in distant organs and turned into metastatic disease.
  - This metastatic disease caused or contributed to the Deceased's subsequent death.

- In such circumstances, the delay did cause or contribute to the Deceased's death.

- **Mechanism 5 -**
  - The Deceased already had metastatic disease at time of the actual diagnosis.
  - The Deceased would have been given endocrine treatment at the time of the missed treatment date, which would have slowed down the growth of the primary tumour, the metastases and the Deceased's metastatic load.
  - This "slowing down" of the process would have prolonged the Deceased's life.
  - In such circumstances, the delay did cause or contribute to the Deceased's death.

- **Mechanism 6 -**
  - The Deceased had micro mets which had spread around the Deceased's body at time of the missed treatment date.
  - Earlier treatment with chemotherapy would have reduced the number of micro mets in the Deceased's body, but not eliminated them.
  - With less micro mets initially, it would have taken longer for micro mets to seed and for the Deceased to develop the degree/burden of metastatic disease which subsequently caused or contributed to her death.
  - Treatment at the time of the missed treatment date would therefore have delayed the Deceased's death due to metastatic disease.
  - In such circumstances, the delay did cause or contribute to the Deceased's death.

- **Mechanism 7 -**
  - The Deceased had micro mets and metastatic disease at time of the missed treatment date.
  - Earlier treatment with chemotherapy would have reduced number of micro mets in the Deceased's body, but not eliminated them.
  - With less micro mets initially, it would have taken longer for micro mets to seed and for the Deceased to develop the degree/burden of metastatic disease which subsequently caused or contributed to her death.

- Treatment at the time of the missed treatment date would therefore have delayed the Deceased's death due to metastatic disease.

- **Mechanism 8 -**
  - Overview/Theory:
    - When a primary cancer produces micro mets which are spread around the body, these are at first eradicated by the body's immune system or by turbulence in the blood stream.
    - As time progresses, more micro mets are spread distantly and the micro metastatic load is increased.
    - At a critical point ("the critical point") the body's immune system can no longer destroy the micro mets and the micro mets seed in a distant organ (such as liver, lung or bone) and grows into a metastases.
    - The precise time or degree of the micro metastatic load at which this critical point occurs is not known and varies from patient to patient.
    - The Deceased subsequently dies of metastatic disease.
  - At the time of the missed treatment date, the Deceased's primary cancer had already started to metastasise to the lymph nodes and micro mets had spread distantly. It is not known whether the critical point had been reached at time of the missed treatment date but it had been reached by the time of the actual diagnosis.
  - During the culpable period, the primary cancer had continued to emit micro mets and made a more than minimal, trivial or negligible contribution to the critical point being reached (even though it is not possible to say on the balance of probabilities, but for the culpable period, the critical point would not have been reached).
  - In such circumstances, the delay did cause or contribute to the Deceased's death.

NB – the above analysis is dependent on the development of metastatic disease being a cumulative condition or dose dependent on the number of micro mets and expert evidence as to what period of time would make more than a minimal, trivial or negligible contribution to the micro metastatic load.

- **Mechanism 9 -**
    - Overview/Theory:
        - The primary cancer produces micro mets over time.
        - Many of these micro mets are destroyed by the body's immune system or by turbulence in the blood stream.
        - At some point, as a matter of random chance, one or more of these micro mets seeds in a distant organ and then grows to form a metastases.
    - At the time of the missed treatment date, the Deceased's primary cancer had already started to metastasise to the lymph nodes and micro mets had spread around the Deceased's body but had been destroyed by the patient's immune system.
    - During the culpable period, the primary cancer had continued to emit micro mets until the time of actual diagnosis and treatment.
    - The micro met (s) produced during the culpable period seeded in the Deceased's distant organs and she subsequently developed metastatic disease and died.
    - Treatment at the time of the missed treatment date would have been successful in preventing the invasive cancer metastasizing.
    - In such circumstances, the delay did cause or contribute to the Deceased's death.

- **Mechanism 10 -**
    - Overview/Theory:
        - The primary cancer produces micro mets over time.
        - Many of these micro mets are destroyed by the body's immune system or by turbulence in the blood stream.
        - Some of these micro mets seed in a distant organ and form metastases.
        - Some of these micro mets self-seed in the original primary cancer causing it to grow faster.
        - The new metastases produce micro mets which self-seed causing it to grow faster and also seed in other tissue to create further metastases.
        - The Deceased's metastatic load eventually causes or contributes to her death.
    - The primary cancer created micro mets which spread around the body prior to the date of the missed treatment date.

- The micro mets seeded in tissue and created a metastases.
- During the culpable period:
    - the primary tumour continued to produce micro mets which caused the primary cancer to grow more quickly, the metastases to grow more quickly and further metastases to seed and form.
    - The metastases produced micro mets which caused the primary cancer to grow more quickly, the metastases to grow more quickly and further metastases to seed and form.
- As a result of the above process, the metastatic load increased and the Deceased died earlier than she would have done without the culpable period.
- In such circumstances, the delay did cause or contribute to the Deceased's death.

Questions

The following issues will discussed:

1. The likelihood of these mechanisms occurring in a particular case.

2. Which factors should be taken into account when considering which of the above mechanisms occurred. In particular:
    a) Duration of time that the cancer was metastasizing prior to the missed treatment date/treatment.
    b) Duration of delay
    c) Doubling times
    d) Size of tumour
    e) Grade of tumour
    f) Stage of tumour
    g) Lymph node involvement
    h) Vascular involvement
    i) HER2 status
    j) Endocrine status

3. The minimal period of delay required for the mechanisms above to be possible or probable.

Relevant Literature

1. Cancer Research UK – "How cancer can spread"
2. Richards et al "Influence of delay on survival in patients with breast cancer: a systematic review"
3. Hanna et al "Mortality due to cancer treatment delay: systemic review and meta-analysis"
4. Lohrish et al – "Impact on Survival of Time from Definitive Surgery to Initiation of Adjuvant Chemotherapy for Early-Stage Breast Cancer"
5. Riggion et al – "The lingering mysteries of metastatic recurrence in breast cancer"
6. Comen et al – "Clinical Implications of cancer self-seeding." [2011]
7. Norton and Massague – "Is cancer a disease of self-seeding." [2006]

TOPIC 2 – INCOMPLETE MASTECTOMIES

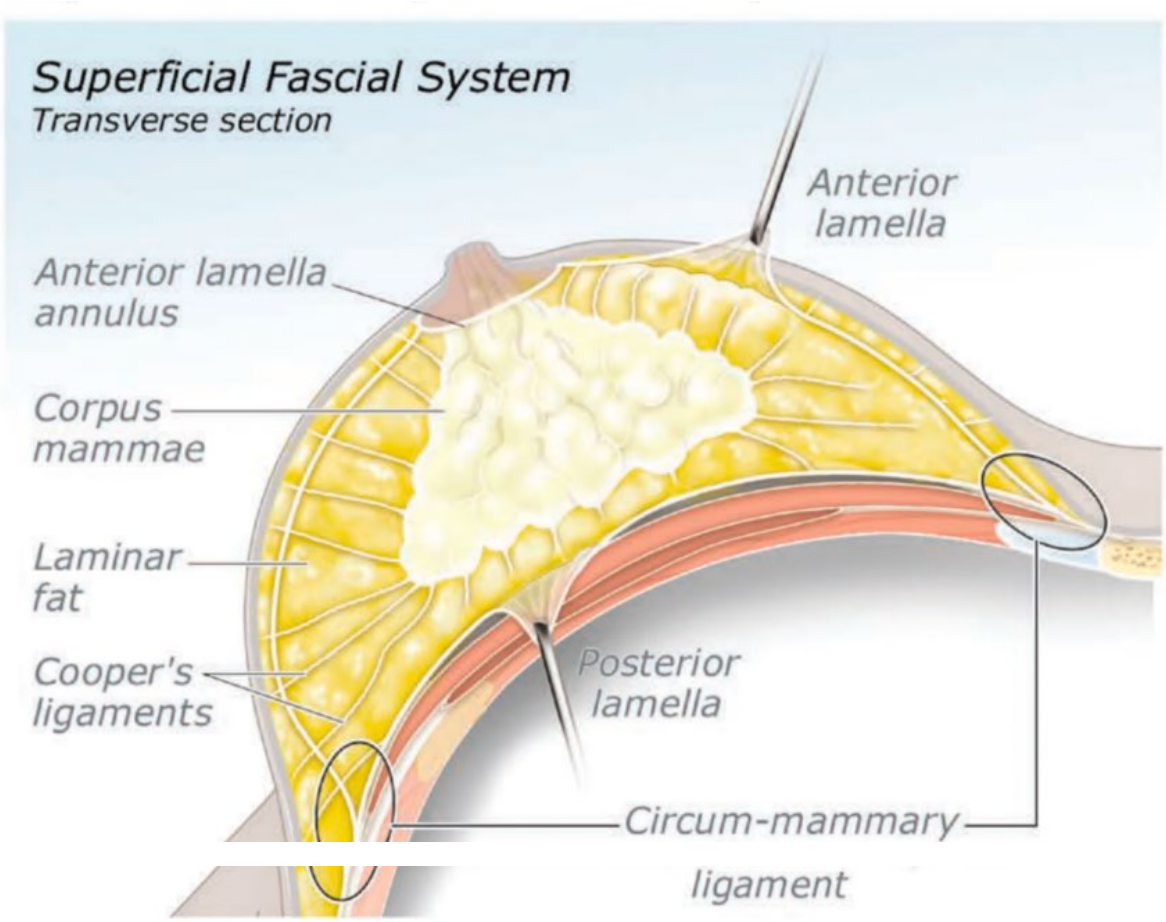
Introduction

The evidence indicates that a breast contains the following layers:

Skin
Subcutaneous fat
Fascia
Breast Tissue = ducts, lobes and lobules, breast fat & connective tissue
Deep fascia
Pectoralis Muscle

Anatomy

The diagram below is taken from Mr Macmillan's Generic Report dated December 2024 at page 12 [CB10/191].



Adequacy of Treatment

The following issues will be considered:

1. The surgical technique which should have been used when performing a mastectomy between 1990 and 2011.

2. Anatomical variations and the steps which should be taken by the surgeon when the fascia is not present.

3. The reason why some breast tissue is left behind during a properly performed standard mastectomy or skin sparing mastectomy.

4. Whether it is agreed that a surgeon should remove all macroscopic breast tissue during a mastectomy (of whatever type).

5. The difficulties for the surgeon in identifying macroscopic breast tissue from subcutaneous fat and the steps which a surgeon should take to address these difficulties.

6. The extent of breast tissue that can be left behind during a properly performed mastectomy.

7. The likely position of any breast tissue which is left behind following a mastectomy.

8. The appearance of the breast after a standard mastectomy.

9. Indicators as to whether an excessive amount of breast tissue has been left behind as a result of inadequate surgery. In particular the relevance of:
    a. The appearance of the breast after a standard mastectomy.
    b. The role of histology and the analysis of the amount of tissue removed during the mastectomy.
    c. The role of scanning.
    d. The finding of involved margins.
    e. The need to perform a shave when performing a mastectomy.

10. The description of a CSM by Mr Paterson in his statement dated 8 January 2013.

Causation

Mechanisms

The following are postulated as plausible mechanisms which the Coroner should consider when considering whether the Deceased's death has been caused or contributed to by an alleged incomplete mastectomy being performed followed by a local recurrence.

The experts are invited to consider whether each is a possible[1] biological mechanism as to how the Deceased came to die of metastatic breast cancer. The possible mechanisms can then be applied to the specific facts of the Inquests. The experts are also invited to provide details of any other possible mechanisms.

It is recognised that whether any of the above mechanisms actually occurred is dependent on the precise factual circumstances of the Inquest including the individual and clinical factors. This will be considered when the Inquests are heard.

- **Mechanism 1 –**
    - The invasive breast cancer which was present prior to the incomplete mastectomy had already metastasised and micro mets had spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - The Deceased developed a local recurrence but this did not metastasise.
    - In such circumstances, the incomplete mastectomy did not cause or contribute to the Deceased's death.

- **Mechanism 2 –**
    - The invasive cancer and all macroscopic breast tissue was removed properly from the breast cavity during the (complete) mastectomy.
    - In the microscopic breast tissue which was left behind, the cancer recurred and metastasised creating micro mets which spread distally.

[1] Possible means more than speculative.

- These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
- This metastatic disease caused or contributed to the Deceased's subsequent death.
- In such circumstances, the mastectomy did not cause or contribute to the Deceased's death.

- **Mechanism 3 –**
  - The invasive cancer and all macroscopic breast tissue was removed properly from the breast cavity during the (complete) mastectomy.
  - In the microscopic breast tissue which was left behind, a new primary cancer formed and metastasised creating micro mets which spread distally.
  - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
  - This metastatic disease caused or contributed to the Deceased's subsequent death.
  - In such circumstances, the mastectomy did not cause or contribute to the Deceased's death.

- **Mechanism 4 –**
  - Macroscopic breast tissue was left behind in the breast cavity during the incomplete mastectomy; for example behind the nipple, on the chest wall or on the skin flaps.
  - A recurrence of invasive cancer developed in microscopic breast tissue which would have been present with a complete mastectomy.
  - This recurrence metastasised creating micro mets which spread around the Deceased's body.
  - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
  - This metastatic disease caused or contributed to the Deceased's subsequent death.
  - In such circumstances, the incomplete mastectomy did not cause or contribute to the Deceased's death.

- **Mechanism 5 –**
    - Macroscopic breast tissue was left behind in the breast cavity during the incomplete mastectomy; for example behind the nipple, on the chest wall or on the skin flaps.
    - A new primary cancer developed in microscopic breast tissue which would have been present with a complete mastectomy.
    - This new primary cancer metastasised creating micro mets which spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the incomplete mastectomy did not cause or contribute to the Deceased's death.

- **Mechanism 6 –**
    - Macroscopic breast tissue was left behind in the breast cavity during the incomplete mastectomy; for example behind the nipple, on the chest wall or on the skin flaps.
    - In this macroscopic tissue, a recurrence of invasive cancer developed which metastasised creating micro mets which spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the incomplete mastectomy caused or contributed to the Deceased's death.

- **Mechanism 7 –**
    - Macroscopic breast tissue was left behind in the breast cavity during the incomplete mastectomy; for example behind the nipple, on the chest wall or on the skin flaps.
    - In this macroscopic tissue, a new primary invasive cancer developed which metastasised creating micro mets which spread distally.

- These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
- This metastatic disease caused or contributed to the Deceased's subsequent death.
- In such circumstances, the incomplete mastectomy caused or contributed to the Deceased's death.

- **Mechanism 8 –**
  - Overview/Theory:
    - The primary cancer produces micro mets over time.
    - Many of these micro mets are destroyed by the body's immune system or by turbulence in the blood stream.
    - Some of these micro mets seed in tissue in a distant organ and form a metastases.
    - Some of these micro mets self-seed in the original primary cancer causing it to grow.
    - The new metastases produce micro mets which self-seed causing it to grow and also seed in distant organs to create further metastases.
    - The Deceased's metastatic load eventually causes or contributes to her death.
  - The Deceased's primary cancer created micro mets which spread around the body prior to the date of the mastectomy.
  - The micro mets seeded in tissue and creased a metastases.
  - A local recurrence occurred in macroscopic residual breast tissue due to an incomplete mastectomy being performed.
  - As a result of the recurrence forming:
    - The recurrence produced micro mets which 1) joined the metastases and caused them grow (i.e. by self-seeding) and 2) seeded in the Deceased's distant organs and formed new metastases.
    - The enlarged metastases and the new metastases produced micro mets which 1) joined the metastases and caused them to grow (i.e. by self-seeding) and 2) seeded in the Deceased's distant organs and formed new metastases.
  - As a result of the above process, the Deceased's metastatic load increased and:

        - On the balance of probabilities, the Deceased died earlier than she would have done without the local recurrence; or
        - It is not possible to say on the balance of probabilities whether the Deceased did or did not die earlier than she would have done without the local recurrence. However, the increased metastatic load contributed to her death.
    - In such circumstances, the incomplete mastectomy caused or contributed to the Deceased's death.

Questions

The following issues will be considered:

1. The difference between the linear approach and the parallel approach to metastatic spread.

2. Whether leaving residual breast tissue during a mastectomy increases the risk of:
    a. A local recurrence occurring in the residual breast tissue.
    b. A new primary occurring in the residual breast tissue

3. From a pathological perspective, how and why does a recurrence in breast tissue occur?

4. Is the risk of a new primary developing in residual breast tissue dependent on the amount of residual breast tissue?

5. Is the risk of a recurrence developing in residual breast tissue (assuming clear margins) dependent on the amount of residual breast tissue?

6. Whether a local recurrence which forms in residual breast tissue can metastasise?

7. Whether a new primary which forms in residual breast tissue can metastasise?

8. Whether, in the absence of a diagnosed local recurrence, macroscopic breast tissue left behind during the mastectomy can still cause or contribute more than minimally, trivially or negligibly to the Deceased's death. Is it possible that this can occur? If so, how?

9. Whether it is agreed that causation between the incomplete mastectomy and the Deceased's death is established if the Coroner finds the following occurred as a matter of fact:

    - *The recurrence occurs in breast tissue which would have been removed in a properly performed mastectomy.*
    - *The recurrence metastasises and causes metastatic disease.*
    - *The Deceased dies of metastatic disease.*

10. Whether the above scenarios are scientifically possible.

11. The factors which will assist in determine:
    a. Whether a recurrence occurred in macroscopic breast tissue left behind during the surgery or would have occurred with a properly performed mastectomy.
    b. Whether metastatic disease has been caused by the original cancer or by the recurrence.

    Please consider:
    a. The extent of the residual breast tissue
    b. The position of the recurrence
    c. The timing of the recurrence
    d. The biological characteristics of the recurrence
    e. The time to diagnosis of metastatic disease
    f. The biological characteristics of the metastatic disease

12. In any given case, whether it is possible to conclude that on the balance of probabilities, the local recurrence caused the person's death.

Literature

1. Kaidar-Person et al – "Superficial Fascial System of the Trunk and Extremities Residual Glandular Breast Tissue after Mastectomy: A systematic review."
2. Christine – "Risk factors for residual fibroglandular breast tissue following a mastectomy – an overview and retrospective cohort study"
3. Mastectomy – by Mr Macmillan

4. Kaidar-Person et al – “A BRILLIANT-BRCA study : residual breast tissue after mastectomy and reconstruction” [2024]
5. Kaidar-Person et al – “Spatial location of local recurrences after mastectomy: a systematic review” [2020]
6. Deutschmann et al – “Residual fibroglandular breast tissue after mastectomy is associated with an increased risk of a local recurrence or a new primary breast cancer”
7. EVCTCG [2005] – “Effects of radiotherapy and of differences in the extent of surgery for early breast tissue on local recurrence and 15 year survival: an overview of the randomised trials.”
8. EVCTCG [2011] – “Effect of radiotherapy after breast-conserving surgery on 10 year recurrence and 15 year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomised trials.”
9. NSABP-06 study by Fisher et al “Twenty year follow up of randomised trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer”
10. Christiansen, Peer, Marco Mele, Anne Bodilsen, Nicola Rocco, and Robert Zachariae. 2022. ‘Breast-Conserving Surgery or Mastectomy?: Impact on Survival.’ *Annals of Surgery Open* 3 (4): e205.
11. Bundred et al “Do surgical margins matter after mastectomy? A systematic review.”
12. Bundred et al “Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis.” (2022)
13. Michael, Bundred et al “Surgical margin involvement increases distant recurrence, not just local recurrence”
14. Riggio, AI, Varley et al “The lingering mysteries of metastatic recurrence in breast cancer.” Br. J. Cancer 124, 13-26 (2021)
15. Gofrit – “Patterns of metastases progression – The linear parallel ratio” (2022)
16. Dent et al – “Factors associated with breast cancer mortality after local recurrence.” [2014]
17. EBCTCG – “Long term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials.” (2018)

TOPIC 3 – INVOLVED MARGINS

Adequacy of Treatment

The following issues will be considered:

1. Between 1990 and 2011, whether it was mandatory for the surgeon to orientate any specimens after performing:
    a. A WLE
    b. A mastectomy (of whatever type).

2. Between 1990 and 2011, what should a histology report contain in respect of:
    a. A WLE?
    b. A Mastectomy?

3. Between 1990 and 2011, whether there was any agreed definition or practice amongst breast surgeons and oncologists as to:
    a. A clear margin.
    b. A close margin.
    c. An involved margin.

4. In pathological terms, what would a) a close margin or b) an involved margin indicate?

5. Whether it was usual practice in the period from 1990 to 2011 for a surgeon to x-ray the excised tissue during a WLE whilst the patient was still under anaesthetic to check that there were clear margins?

6. Whether patients who have undergone a Mx or a WLE should have been informed of the presence of an involved margin.

7. Between 1990 and 2011, whether treatment would be offered to a patient who, following a WLE for an invasive tumour or DCIS, histology revealed:
    a. A close margin.
    b. An involved margin.

8. Between 1990 and 2011, whether treatment would be offered or recommended to a patient who, following a mastectomy[1] for an invasive tumour or DCIS, histology revealed:
    a. A close margin?
    b. An involved margin?

Causation

Mechanisms

The following are postulated as plausible mechanisms which the Coroner should consider when considering whether the Deceased's death has been caused or contributed to by an involved or close margin followed by a recurrence.

The experts are invited to consider whether each is a possible[2] biological mechanism as to how the Deceased came to die of metastatic breast cancer. The possible mechanisms can then be applied to the specific facts of the Inquests. The experts are also invited to provide details of any other possible mechanisms.

It is recognised that whether any of the above mechanisms actually occurred is dependent on the precise factual circumstances of the Inquest including the individual and clinical factors. This will be considered when the Inquests are heard.

- **Mechanism 1 –**
    - The invasive breast cancer which was present prior to the WLE/mastectomy had already metastasised and micro mets had spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - The Deceased developed a local recurrence due to the involved/close margin but this did not metastasise.
    - In such circumstances, the involved or close margin did not cause or contribute to the Deceased's death.

[1] Any type of mastectomy.
[2] Possible means more than speculative.

- **Mechanism 2 –**
    - The invasive cancer was not all removed properly during the WLE/mastectomy (i.e. there was an involved or close margin).
    - In the remaining breast tissue, the cancer recurred due to the involved/close margin.
    - This recurrence metastasised and created micro mets which spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the involved or close margin caused or contributed to the Deceased's death.

- **Mechanism 3 –**
    - The invasive cancer was not all removed properly during the WLE/mastectomy (i.e. there was an involved or close margin).
    - In the remaining breast tissue, the cancer recurred but this was not due to the fact that it had not all been removed; rather it recurred for reasons unconnected with the involved or close margin.
    - This recurrence metastasised and created micro mets which spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the involved or close margin did not cause or contribute to the Deceased's death.

- **Mechanism 4 –**
    - The invasive cancer was not all removed properly during the WLE/mastectomy (i.e. there was an involved or close margin).
    - In the remaining breast tissue, a new primary invasive cancer formed.

- This new primary invasive cancer metastasised and created micro mets which spread around the Deceased's body.
- These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
- This metastatic disease caused or contributed to the Deceased's subsequent death.
- In such circumstances, the involved or close margin did not cause or contribute to the Deceased's death.

- **Mechanism 5 –**
  - Overview/Theory:
    - The primary cancer produces micro mets over time.
    - Many of these micro mets are destroyed by the body's immune system or by turbulence in the blood stream.
    - Some of these micro mets seed in tissue in a distant organ and form metastases.
    - Some of these micro mets seed in the original primary cancer causing it to grow further.
    - The new metastases produce micro mets which self-seed causing them to grow and also seed in distant organs to create further metastases.
    - The Deceased's metastatic load eventually causes or contributes to her death.
  - The Deceased's primary cancer created micro mets which spread around the body prior to the date of the WLE/mastectomy.
  - The micro mets seeded in tissue and creased metastases.
  - A local recurrence occurred in residual breast tissue due to the cancer not all being removed properly during the WLE/mastectomy (i.e. there was an involved or close margin).
  - As a result of the local recurrence forming:
    - The recurrence produced micro mets which 1) joined the metastases and caused them grow (i.e. by self-seeding) and 2) seeded in the Deceased's distant organs and formed new metastases.
    - The enlarged metastases and the new metastases produced micro mets which 1) joined the metastases and caused them to grow (i.e. by self-

seeding) and 2) seeded in the Deceased's distant organs and formed new metastases.

- As a result of the above process, the Deceased's metastatic load increased and:
  - On the balance of probabilities, the Deceased died earlier than she would have done without the local recurrence; or
  - It is not possible to say on the balance of probabilities whether the Deceased did or did not die earlier than she would have done without the local recurrence. However, the increased metastatic load contributed to her death.
- In such circumstances, the involved or close margin caused or contributed to the Deceased's death.

- **Mechanism 6 -**
  - Overview:
    - When a primary cancer produces micro mets which are spread around the body, these are at first eradicated by the body's immune system or by turbulence in the blood stream.
    - As time progresses, more micro mets are spread distally and the micro metastatic load is increased.
    - At a critical point ("the critical point") the body's immune system can no longer destroy the micro mets and the micro mets seed in a distant organ (Such as liver, lung or bone) and grows into a metastases.
    - The precise time or degree of metastatic load at which this critical point occurs is not known and varies from patient to patient.
  - At the time of the Mastectomy/WLE, the Deceased's primary cancer had already started to metastasise to the lymph nodes and micro mets had spread around the Deceased's body. It is not known whether the critical point had been reached at time of the Mastectomy/WLE.
  - The invasive cancer was not all removed properly during the WLE/mastectomy (i.e. there was an involved or close margin).
  - After the Mastectomy/WLE, a local recurrence occurred due to the involved/close margin. This local recurrence emitted micro mets which spread around the Deceased's body.

- These micro mets made a more than minimal, trivial or negligible contribution to the critical point being reached (even though it is not possible to say on the balance of probabilities, but for the recurrence, the critical point would not have been reached).
- The Deceased developed metastatic disease and this metastatic disease caused or contributed to the Deceased's subsequent death.
- In such circumstances, the involved or close margin caused or contributed to the Deceased's death.

NB – the above analysis is dependent on the development of metastatic disease being a cumulative condition or dose dependent on the number of micro mets circulating in the Deceased's body.

Questions

The following issues will be considered:

1. The main risk factors for local recurrence after:
    a. A WLE
    b. A WLE plus radiotherapy
    c. A mastectomy

2. Whether an involved margin can cause a recurrence?

3. Whether radiotherapy removes the risk of recurrence when there is an involved margin?

4. If a WLE is performed with involved or close margins, whether it is possible to distinguish between a recurrence or a new primary cancer? If so, what factors are taken into account.

5. If a mastectomy is performed with involved or close margins, is it possible to distinguish between a recurrence or a new primary cancer? If so, what factors should be taken into account.

Literature

1. National Institute of Health and Clinical Excellence. Guidance on Cancer Services Improving Outcomes in Breast Cancer Manual Update. *National Institute for Clinical Excellence* (August 2002)
2. Bundred et al "Do surgical margins matter after mastectomy? A systematic review."
3. Bundred et al "Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis.
4. Michael, Bundred et al "Surgical margin involvement increases distant recurrence, not just local recurrence"
5. Freedman G, Fowble B, Hanlon A, et al. Patients with early-stage invasive cancer with clos or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. International Journal Radiation Oncology Biology Phys (1999); 44(5); p.1005–1015. PII: S0360-3016(99)00112-1
6. Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. The Breast (2010); 19(1); p.14- 22. ISSN 0960-9776.
7. Klein "Parallel progression of primary tumours and metastases." Nat. Rev. Cancer 9.302-12
8. Pilewski et al "Margins in breast cancer: How much is enough" Cancer 1335-1341 (2018)

TOPIC 4 – REMOVAL OF AXILLARY LYMPH NODES

Adequacy of Treatment

The following issues will be discussed.

1. The practice amongst breast surgeons from 1990 to 2011 in determining:
    a. Whether axillary node sampling should be performed.
    b. Whether an axillary clearance should be performed and the extent of the operation.
    c. Whether sentinel node biopsies should be performed and the date when such an approach became mandatory (if at all).
    d. If so, the level of clearance which should be performed.
    e. Whether a sentinel lymph node biopsy should be performed (from 2005 onwards)

2. The factors which should determine the type of axillary surgery performed.

3. Whether axillary surgery should be performed for DCIS or micro-invasive DCIS. If so, in what circumstances.

4. The advantages and disadvantages of performing axillary surgery.

5. The number of nodes which should be removed during an axillary clearance.

6. The likely treatment given to the patient following a finding of positive nodal involvement and the role of radiotherapy and further axillary surgery.

Causation

The following are postulated as plausible mechanisms which the Coroner should consider when considering whether the Deceased's death has been caused or contributed[1] to by the failure to perform an ANC or by performing an inadequate ANC (i.e. insufficient lymph nodes removed).

The experts are invited to consider whether each is a possible[2] biological mechanism as to how the Deceased came to die of metastatic breast cancer. The possible mechanisms can then be

[1] i.e. more than minimally, negligibly or trivially.
[2] Possible means more than speculative.

applied to the specific facts of the Inquests. The experts are also invited to provide details of any other possible mechanisms.

It is recognised that whether any of the above mechanisms actually occurred is dependent on the precise factual circumstances of the Inquest including the individual and clinical factors. This will be considered when the Inquests are heard.

The following mechanisms are based on the assumption that an axillary clearance should have been performed at the same as the WLE/Mastectomy but due to inadequate treatment, an axillary clearance was not performed.

- **Mechanism 1 –**
    - The lymph nodes contained metastatic disease from an invasive breast cancer.
    - The disease in the lymph nodes created micro mets prior to the Mastectomy/WLE which had spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the failure to perform an axillary clearance did not cause or contribute to the Deceased's death.

- **Mechanism 2 –**
    - The lymph nodes contained metastatic disease from an invasive breast cancer.
    - The disease in the lymph nodes had not yet created micro mets prior to the Mastectomy/WLE.
    - Following the Mastectomy/WLE, the disease in the lymph nodes did create micro mets which then spread around the Deceased's body.
    - These micro mets seeded in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the failure to perform an axillary clearance caused or contributed to the Deceased's death.

- **Mechanism 3 –**
    - The lymph nodes contained metastatic disease from an invasive breast cancer.
    - The disease in the lymph nodes created micro mets prior to the Mastectomy/WLE and the micro mets already had spread around the Deceased's body.
    - These micro mets did not seed and cause metastatic disease since they were destroyed by the patient's own immune system.
    - After the Mastectomy/WLE the lymph nodes continued to produce micro mets which spread around the Deceased's body.
    - These micro mets did seed in a distant organ (s) and caused metastases to form (i.e. metastatic disease).
    - This metastatic disease caused or contributed to the Deceased's subsequent death.
    - In such circumstances, the failure to perform an axillary clearance caused or contributed to the Deceased's death.

- **Mechanism 4 -**
    - Overview:
        - The primary cancer produces micro mets over time which spread initially to the axillary lymph nodes. Micro mets can also spread from the primary cancer via the blood stream.
        - The disease in the axillary lymph nodes then grows and creates mini mets which are spread around the body via the lymphatic system.
        - These micro mets are at first eradicated by the body's immune system or by turbulence in the blood stream.
        - As time progresses, more micro mets are spread distally and the micro metastatic load is increased.
        - At a critical point ("the critical point") the body's immune system can no longer destroy the micro mets and the micro mets seed in a distant organ (Such as liver, lung or bone) and grows into a metastases.
        - The precise time or degree of metastatic load at which this critical point occurs is not known and varies from patient to patient.
    - At the time of the Mastectomy/WLE, the Deceased's primary cancer had already started to metastasise to the axillary lymph nodes and micro mets had spread

around the Deceased's body. It is not known whether the critical point had been reached at time of the Mastectomy/WLE.

- After the Mastectomy/WLE, the axillary lymph nodes continued to emit micro mets which made a more than minimal, trivial or negligible contribution to the critical point being reached (even though it is not possible to say on the balance of probabilities, but for the failure to remove the lymph nodes, the critical point would not have been reached).
- In such circumstances, the failure to perform an axillary clearance caused or contributed to the Deceased's death.

NB – the above analysis is dependent on the development of metastatic disease being a cumulative condition or dose dependent on the number of micro mets circulating in the Deceased's body.

- **Mechanism 5 –**
  - Overview/Theory:
    - The primary cancer produces micro mets over time which spread initially to the axillary lymph nodes. Micro mets can also spread from the primary cancer via the blood stream.
    - The disease in the axillary lymph nodes then grows and creates mini mets which are spread around the body via the lymphatic system.
    - Many of these micro mets are destroyed by the body's immune system or by turbulence in the blood stream.
    - Some of these micro mets seed in tissue in a distant organ and form a metastases.
    - Some of these micro mets self-seed in the original primary cancer causing it to grow.
    - The new metastases produce micro mets which self-seed causing it to grow and also seed in distant organs to create further metastases.
    - The Deceased's metastatic load eventually causes or contributes to her death.
  - The axillary lymph nodes in the Deceased contained metastatic disease from an invasive breast cancer.

- The disease in the axillary lymph nodes created micro mets prior to the Mastectomy/WLE and the micro mets already had spread around the Deceased's body.
- These micro mets seeded in distant organs and created metastases.
- After the Mastectomy/WLE the Deceased's axillary lymph nodes continued to produce micro mets which spread around the Deceased's body.
- These micro mets 1) joined the existing metastases and caused them grow and 2) seeded in the Deceased's distant organs and formed new metastases.
- The enlarged metastases and the new metastases produced micro mets which 1) joined the existing metastases and caused them to grow (i.e. by self-seeding) and 2) seeded in the Deceased's distant organs and formed new metastases.
- As a result of the above process, the Deceased's metastatic load increased and:
  - On the balance of probabilities, the Deceased died earlier than she would have done had an axillary clearance been performed; or
  - It is not possible to say on the balance of probabilities whether the Deceased did or did not die earlier than she would have done with an axillary clearance. However, the increased metastatic load contributed to her death.
- In such circumstances, the failure to perform an axillary clearance caused or contributed to the Deceased's death.

Questions

The following issues will discussed.

1. Which factors should be taken into account when considering which of the above mechanisms occurred. In particular:
   a) Duration of time that the cancer was metastasizing prior to the presumed WLE/Mastectomy.
   b) Duration of time during which the primary invasive cancer was present prior to removal.
   c) Size of tumour.
   d) Grade of tumour.
   e) Stage of tumour.
   f) Where an inadequate axillary clearance was performed, the number of lymph nodes found to have metastatic disease.

g) HER2 status.

h) Endocrine status.

Literature

1. ALMANAC trial – "Randomised multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer"
2. EBCTCG trial – Mannu et al 'Overview of Axillary Treatment in Early Breast Cancer: patient-level meta-analysis of long-term outcomes among 20,273 women in 29 randomised trials."
3. Fisher et al – "The Landmark Series: Axillary Management in Breast Cancer"
4. Ullal et al – "Evolutionary history of metastatic breast cancer reveals minimal seeding from axillary lymph nodes"

TOPIC 5 – OTHER ISSUES

The following general issues have application to some of the Inquests.

1. In the period from 1990 to 2011, was it mandatory for a breast surgeon to have been a member of a professional specialist breast cancer organization (i.e. BASO).

2. In the period from 1990 to 2011, was a triple assessment always necessary to reach a diagnosis?

3. Treatment of DCIS in the period from 1990 to 2011.

4. In the period from 1990 to 2011, was it appropriate for patients with metastatic disease to undergo a mastectomy. If so, in what clinical circumstances.

5. In considering the growth of cancers over time:
    a. What doubling time should be used for invasive cancer?
    b. What growth rate should be used for DCIS?

6. Whether it is possible to extrapolate back in order to calculate when 1) the cancer became invasive 2) the cancer started to metastasise.

7. In the period from 1990 to 2011, when it was appropriate for a patient to have:
    a. A core biopsy.
    b. An open biopsy.

Literature

1. Gnerlich et al – "Surgical Removal of the Primary Tumour increases overall survival in patients with metastatic breast cancer" (2007)
2. Carmichael et al – "Does local surgery have a role in the management of stage IV breast cancer?" (2003)
3. Dominici et al – "Surgery of the primary tumour does not improve survival in stage IV breast cancer" (2011)
4. Lane et al – "Surgical Resection of the Primary Tumour in Women with De Novo Stage IV Breast cancer" (2019)

The literature is extensive in relation to doubling times. The experts are referred to the Generic reports for a summary of the relevant doubling times.