Investigators

Author
Amira Elmadahm
MBBS

Supervisors
Professor P. Grantley Gill
MBBS MD (Adel) FRACS
Head, Breast Endocrine and Surgical Oncology Unit, Royal Adelaide Hospital
Department of Surgery, University Of Adelaide

Dr Melissa Bochner
MBBS, MS, FRACS
Staff Specialist, Breast Endocrine and Surgical Oncology Unit, RAH Clinical
Lecturer, Department of Surgery, University Of Adelaide
Table of Contents

Acknowledgment 1
Copyright Statement 2

Chapter 1 Abstract 3

Chapter 2 Aims and objectives 6

Chapter 3 Introduction and Literature Review 10
  3.1) Introduction 11
  3.2) Literature review 12
    3.2.1) The Concept of sentinel lymph nodes biopsy 12
    3.2.2) Complete axillary dissection versus sentinel lymph node biopsy 13
    3.2.3) Accuracy of the sentinel lymph node biopsy 13
    3.2.4) False Negative Rate (FNR) of sentinel lymph node biopsy 13
    3.2.5) Lymphatic drainage of the mammary gland 14
    3.2.6) Clinical factors influencing the sentinel lymph node identification 16
      3.2.6.a) Age 16
      3.2.6.b) Body weight 16
      3.2.6. c) Primary tumour size 17
      3.2.6.d) Tumour palpability 18
      3.2.6.e) Site of the primary tumour 18
      3.2.6. f) Multifocal / multicentric primary breast cancer 19
    3.2.7) The influence of the primary tumour’s histopathological features on the identification of sentinel lymph nodes 19
    3.2.8) Technical factors affecting the identification of the sentinel lymph node 20
      3.2.8.1) Surgeon skills 20
      3.2.8.2) The sentinel lymph nodes mapping substances 20
        3.2.8.2.1) Blue dye technique 20
        3.2.8.2.2) Radioactive tracers 21
      3.2.8.3) The route of injection and the identification of the sentinel lymph node 22
      3.2.8.4) The optimum number of retrieved sentinel nodes 23
      3.2.9) Histopathological assessments of sentinel lymph node 24
        3.2.9.1) Types of histopathological assessments used to examine the sentinel lymph nodes 24
      3.2.10) Factors predicting the axillary nodes status in breast cancer 25
        3.2.10.1) Clinical factors 25
        3.2.10.2) Impact of primary tumour features on the nodal status 25
      3.2.11) Factors that can predict the status of Non Sentinel Lymph Nodes 28
      3.2.12) Models predicting the status of non sentinel lymph nodes 29
      3.2.13) The clinical impact of micrometastases and Isolated Tumour Cells 30
      3.2.14) The differences between screen detected breast cancers and symptomatic breast cancers 31

Chapter 4 Methods 33
  4.1) Randomisation of patients in the SNAC trial 34
  4.2) Surgical procedures and histopathological assessments 35
  4.3) Statistical analysis 36

Chapter 5 Results 37
  5.1) Sentinel Node Biopsy Versus Axillary ClearanceTria 38
  5.2) Clinical management of patients in the SANC trial 39
5.2.1) Method of diagnosis and breast surgery 39
5.2.2) Time delay of the axillary surgery 40
5.2.3) Adjuvant therapy 40
5.2.3.a) Chemotherapy 40
5.2.3.b) Adjuvant endocrine therapy 40
5.2.3.c) Arm morbidity treatment 41
5.3) Clinical data of patients in the SNAC trial 42
5.3.1) patients' age 42
5.3.2) Body Mass Index (BMI) 43
5.3.3) Associated co-morbidity 44
5.3.4) Primary tumour features 45
5.3.5) Techniques used for detecting the sentinel lymph node 47
5.3.6) Histopathological features of the primary tumour 47
5.4) Overall outcomes of sentinel lymph node identification and the total number of removed sentinel nodes 48
5.5) Clinicopathological factors and the overall identification rate of the sentinel lymph node 50
5.5.1) Patients' data 50
5.5.1.a) The impact of age on the identification rate 50
5.5.1.b) The correlation between the BMI and sentinel lymph node detection 51
5.5.1.c) The impact of co morbidity on the identification of sentinel lymph node 51
5.5.1.d) Correlation between the method of detection of the primary tumour and sentinel lymph node identification 51
5.5.2) Primary tumour features influencing the sentinel lymph node identification 52
5.5.3) The influence of method of diagnosis and surgical management on the sentinel lymph node identification 55
5.5.4) The outcomes of the overall sentinel lymph node detection 56
5.5.4.1) Summary of univariate analysis outcomes 56
5.5.4.2) The multivariate analysis of overall outcomes of the sentinel lymph node detection 56
5.6) Technical factors affecting the sentinel lymph node identification 57
5.6.1) Blue dye injection 57
5.6.1.1) Outcomes of blue dye injection 57
5.6.1.2) The impact of clinicopathological factors on the identification of the blue sentinel lymph node 59
5.6.1.3) Summary of univariate and the outcomes of multivariate analysis 64
5.6.2) Outcomes of sentinel lymph node biopsy with the blue dye technique only 65
5.6.2.1) The impact of clinicopathological factors on the outcomes of blue dye techniques in patients who received blue dye only 65
5.6.2.1.1) The impact of clinical data of patients and the primary tumour features on the detection of sentinel lymph nodes using blue dye injection only 66
5.6.2.1.2) The influence of histopathological features of primary tumour on the detection of sentinel lymph nodes using the blue dye technique as the sole technique 69
5.6.2.1.3) The influence of surgical treatments and the method of detection on the detection of sentinel lymph nodes via sole blue dye 70
5.6.2.2) The multivariate analysis of the blue dye technique in patients who received blue dye only 71
5.6.3) The detection of sentinel lymph nodes with the preoperative lymphoscintigraphy 72
5.6.3.1) Outcomes of preoperative lymphoscintigraphy 72
5.6.3.2) Factors influencing the outcomes of preoperative lymphoscintigraphy 74
5.6.3.2.1) Clinical Factors and the outcomes of preoperative lymphoscintigraphy 74
5.6.3.2.1.a) The clinical factors which influence the visualisation of sentinel lymph node with preoperative lymphoscintigraphy 74
5.6.3.2.1. b) Clinical features of the primary tumour and the outcomes of preoperative lymphoscintigraphy 75
5.6.3.2.2) The influence of histopathological features of the primary tumour on the visualisation of the sentinel lymph nodes 76
5.6.3.2.3) The impact of the method of diagnosis and the surgical management on the visualisation of the sentinel lymph node 78
5.6.3.3) Multivariate analysis outcomes of preoperative lymphoscintigraphy mapping 79
5.6.4) Intraoperative gamma probe detection 79
5.6.4.1) The outcomes of sentinel nodes detected with intraoperative gamma probe 79
5.6.4.2) Factors which influence the detection of hot sentinel lymph nodes 81
5.6.4.2.1) The impact of clinical factors on the identification of sentinel lymph node with the gamma probe 81
5.6.4.2.2) The detection of hot sentinel lymph nodes and the clinical features of the primary tumour 83
5.6.4.2.3) The detection of hot sentinel lymph nodes and the pathological features of the primary tumour 84
5.6.4.2.4) The influence of the method of diagnosis and surgical treatments on the detection of sentinel lymph node by the use of gamma probe 85
5.6.4.3) The univariate analysis outcomes' summary and the multivariate analysis of sentinel lymph nodes detection by the use of the gamma probe 86
5.6.4.3.a) The summary of univariate analysis of factors influencing the detection of hot sentinel nodes 86
5.6.4.3. b) The outcomes of multivariate analysis of factors influencing the detection of the hot sentinel nodes 87
5.6.5) The Combined Technique 88
5.6.5.1) Factors influencing sentinel lymph node detection with the three-technique combination 88
5.6.5.1.1) Clinical factors influencing sentinel lymph node detection via the combined technique 89
5.6.5.1.2) Primary tumour features influencing the sentinel lymph node detection via the combined technique 91
5.6.5.1.3) Histopathological features of the primary tumour and the detection of sentinel lymph node via the combined technique 92
5.6.5.1.4) The surgical management and sentinel lymph node detection with the combined technique 93
5.6.5.2) The outcomes of univariate and multivariate analysis of sentinel lymph nodes detection by the use of the combined technique 94
5.6.6) Summary of factor influencing the sentinel lymph node identification with various techniques 95
5.6.7) The variability of identification rate in different centres 96
5.7) The False Negative Rate (FNR) 97
5.8) The locations of removed sentinel lymph nodes 100
5.9) The potential of different techniques to detect the sentinel lymph nodes in various lymphatic basins 101
5.10) Sentinel lymph nodes located in the internal mammary chain 102
5.11) Pathological outcomes of the sentinel lymph node biopsy in the SNAC trial 107
5.11.1) Details of the involved sentinel lymph nodes in the SNAC trial 109
5.12) The correlation between the clinical and pathological factors and the positivity of the sentinel lymph node 112
5.12.1) The impact of clinico-pathological factors on the sentinel lymph nodes involvement 112
5.12.2) The correlation between the total number of positive sentinel nodes and clinico-pathological factors 117
5.13) Techniques and Histopathology of sentinel lymph nodes located in the internal mammary chain 118
5.14) The optimal number of the removed sentinel lymph nodes 121
5.15) The techniques which identified the involved sentinel nodes 122
5.16) Non Sentinel Lymph Nodes (NSLNs) status in patients with positive sentinel lymph nodes 127
5.17) Comparison of three nomograms outcomes to predict the positivity of non sentinel lymph nodes 129
5.18) Symptomatic breast cancer versus screen detected breast cancer 133
5.18.1) Clinicopathological features of screen detected breast cancer versus symptomatic breast cancer 133
5.18.2) The lymph node status in screen detected breast cancer versus symptomatic breast cancer 138
Chapter 6 Discussion 140
6.1) Postoperative complications of complete axillary dissection versus sentinel lymph node biopsy 141
6.2) Detection of the sentinel lymph nodes 142
6.2.1) Factors which influenced the overall outcomes of sentinel lymph node identification in the SNAC trial 143
6.3) The impact of clinical and pathological factors on the identification of sentinel nodes with different techniques 144
6.3.1) Outcomes of the blue dye technique and factors influencing the identification of blue sentinel nodes 144
6.3.2) Outcomes of preoperative lymphoscintigraphy mapping and factors influencing the identification of blue sentinel nodes 146
6.3.3) Outcomes of the gamma probe detection and factors influencing the identification of hot sentinel nodes 148
6.3.4) Outcomes of the combined technique and factors influencing the identification of sentinel lymph nodes 149
6.4) False Negative Rate (FNR) in the SNAC trial 149
6.5) The location of retrieved sentinel lymph node and the internal mammary sentinel nodes 151
6.6) Histopathological outcomes of the sentinel lymph node biopsy in the SNAC trial 152
6.6.1) Outcomes of pathological assessments of sentinel lymph nodes and identifications of clinical and pathological factors predict the sentinel lymph node status 152
6.6.2) Factors which predict the total number of involved sentinel lymph nodes 155
6.7) Positive internal mammary sentinel lymph nodes 155
6.8) The optimum number of sentinel nodes should be removed by surgeons 156
6.9) Techniques which identified the involved sentinel lymph nodes 158
6.10) Factors which determine the non sentinel lymph node involvement in patients with positive sentinel lymph node 158
6.11) Nomograms predict the status of non sentinel lymph nodes 160
6.12) Outcomes of symptomatic primary tumours versus screen detected primary tumours 162
References 165
List of Tables 182
Table of Figures 187
Abbreviation list

Sentinel Lymph Node Biopsy (SLNB)

Complete Axillary Dissection (CAD)

Sentinel Lymph Node (SLN)

Sentinel Node biopsy versus Axillary Clearance trial (SNAC)

Non Sentinel Lymph Nodes (NSLN)

Internal Mammary Nodes (IMNs)

Preoperative lymphoscintigraphy (LSG)
Acknowledgment

This thesis owes its existence to the help and support of several people. I would like to thank Professor P. Grantley Gill for his enthusiasm, his encouragement and his support particularly during the most difficult period of my life in the last nine months. His guidance helped me during my research and the writing of this thesis. Thanks also go to those who provided me with statistical advice at times of need: Professor Val Gebski, Diana Zannino and Mark Donoghoe.

I would also like to thank my family for the support they provided me throughout my life and in particular, I must acknowledge my mother, without whose love and support, I would not have finished this thesis.

Lastly, I offer my regards and blessings to all those who supported me in any respect during the completion of the project.
Copyright Statement

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Amira A.S. Elmadahm and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I also give permission for the digital version of my thesis to be made available on the web via the University’s digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Amira Elmadahm