A randomised clinical trial of surgery versus surgery plus adjuvant radiotherapy for regional control in patients with completely resected macroscopic nodal metastatic melanoma.

Trans-Tasman Radiation Oncology Group Inc.
Australian and New Zealand Melanoma Trials Group

An Intergroup Australian and New Zealand Multicentre Study

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FOREWORD

This document is intended to describe an Intergroup Trans-Tasman Radiation Oncology Group (TROG) and ANZ Melanoma Trials Group study and to provide information about procedures for entering patients. It is not intended that the protocol be used as a guide for the treatment of other patients. TROG will not be accept any data for analysis unless the local ethics committee has approved this study for patient entry.

Amendments to the document may be necessary; these will be circulated to known participants in the study, but centres entering patients for the first time are advised to contact the TROG Secretariat, Newcastle, to confirm the details of the protocol in their possession.

ABBREVIATIONS

AJCC American Joint Committee on Cancer
ANZ MTG Australian and New Zealand Melanoma Trials Group
BMI Body mass index
CI Confidence interval
CRF Case record form
CT Computed tomography
ECE Extracapsular extension
ECOG Eastern Cooperative Oncology Group
ELND Elective lymph node dissection
ENS Extranodal spread
FACT G Functional Assessment of Cancer Therapy- general
FBE Full blood examination
FNA Fine needle aspirate
ICH International Conference on Harmonisation
LDH Lactate dehydrogenase
LVSI Lympho-vascular space invasion
MRI Magnetic resonance imaging
MV Mega-volts
MVT Mega-voltage therapy
NATA National Association of Testing Authority Australia
NCI National Cancer Institute
NHMRC National Health and Medical Research Council
PMCI Peter MacCallum Cancer Institute
PTV Planning target volume
QA Quality assurance
QoL Quality of life
RT Radiotherapy
RTOG Radiation Therapy Oncology Group
SAE Serious adverse event
TLND Therapeutic lymph node dissection
TROG Trans-Tasman Radiation Oncology Group
WHO World Health Organisation
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1 SUMMARY OF TRIAL

Design: This is a two-armed randomised trial in patients with nodal metastatic melanoma with no other evidence of active melanoma but who are at significant risk of regional relapse following surgical resection.

Main objective: To test the hypothesis that there is a difference in regional relapse rates for patients undergoing complete surgical resection of macroscopic nodal metastatic melanoma alone compared with patients receiving complete surgical resection followed by adjuvant radiotherapy.

Patient selection: The main eligibility criterion is that patients are at significant risk of regional relapse, this being defined as:

- Palpable (macroscopic) metastatic nodal involvement of
  - $\geq 1$ parotid node, or
  - $\geq 2$ neck or axillary nodes, or
  - $\geq 3$ groin nodes
- OR Extranodal spread (of tumour)
- OR Maximum metastatic node diameter: $\geq 3$ cm in neck, or
  - $\geq 4$ cm in axilla or groin

Randomisation and stratification: Patients will be randomised between the two arms, radiotherapy and no radiotherapy. Allocation to treatment will be balanced according to:

- Institution
- nodal basin site (parotid or neck; axilla; groin)
- number of nodes involved depending on site ($\leq 3$; $\geq 4$)
- maximum node diameter ($\leq 4$ cm; $> 4$ cm).
- extent of extranodal tissue spread (none; limited; extensive).

Treatment given: Patients who are randomised to receive post-operative adjuvant radiotherapy will receive 48 Gy reference dose in 20 fractions over 30 days.

Follow-up schedule: Patients will be followed up 3 monthly during the first 2 years, 6 monthly until 5 years and annually thereafter.

Endpoints: The main endpoint is the rate of regional relapse. Secondary endpoints are treatment morbidity, quality of life, patterns of relapse, failure-free survival, and overall survival.

Sample Size: The target sample size for the trial is 270 patients, which will enable a difference in 3-year regional relapse rates of 30% versus 15% to be detected with a power of 80% (using a two sided test at the 5% level of significance). It is anticipated that the 270 patients will be accrued by 4 years and it is planned to have a further 3 years of follow-up.
2 SCHEMA

Surgery for nodal metastatic melanoma

Main Eligibility Criteria

- Completely resected nodal metastatic melanoma
- No previous or concurrent local, in transit or distant metastatic relapse
- At significant risk for regional relapse

Treatment allocation will be balanced according to:

- Institution
- Nodal basin region
- Number of positive nodes
- Metastatic node diameter
- Extent of extra nodal spread

RANDOMISATION

1:1

Immediate post-operative RADIOTHERAPY

OBSERVATION with delayed radiotherapy for relapse
3 BACKGROUND

3.1 Introduction

Melanoma is a serious and common malignancy in Australia. It is the third commonest cancer in Australia and approximately 1000 Australians will die of the disease each year. At least a quarter of these will be patients under the age of 40 years and the majority will develop nodal metastases during the course of their disease. Surgical excision is the standard treatment for relapsed regional disease and many of these patients will achieve long term control. Patients with a significant disease burden in the regional lymph glands have a high rate of local recurrence, which may approach 50%. Uncontrolled regional disease after failed surgery is a debilitating condition which is frequently impossible to manage satisfactorily. It has long been held that adjuvant radiotherapy after surgical excision will reduce the risk of regional recurrence. Radiotherapy following radical node surgery may be associated with significant morbidity. Research is needed for the appropriate selection of patients who may benefit from adjuvant radiotherapy in whom the risk of morbidity is justified.

This study will investigate patients with palpable (macroscopic) lymphadenopathy staged as N1b, N2b and N3 disease. The reported disease specific survival of these patients is 27 to 59% at 5 years and 18 to 48% at 10 years. This wide range of survival characterises patients with regional metastatic disease as a clinically heterogeneous group.

3.2 Outcomes for stage III nodal melanoma treated with surgery alone

3.2.1 Survival and disease related prognostic factors

The most powerful prognostic factor (and the most reproducible) for survival for patients with regional lymph node metastases is the number of nodes containing tumour. Other surrogates for tumour burden, being the percentage involvement of nodes (positive nodes versus nodes harvested) and involvement of the highest node (e.g. iliac and level III axillary node involvement) have also shown a trend influencing survival. Extracapsular extension (ECE) and the maximum diameter of the largest metastatic lymph node have been unreliable prognostic factors for survival.

Among primary tumour factors survival is secondarily and more weakly influenced by the absence or presence of ulceration of the primary, the Breslow thickness, anatomic site of the primary and patient age.

3.2.2 Survival and treatment-related prognostic factors

The timing of surgery, i.e. elective lymph node dissection (ELND) or delayed therapeutic lymph node dissection (TLND), has not been shown to influence survival. The results of a randomised multicentre trial evaluating early selective lymphadenectomy following lymphatic mapping and sentinel node biopsy should be available in the next few years. The extent of dissection, e.g. supragingual dissection added to standard superficial inguinal and femoral lymphadenectomy or radical versus conservative neck dissection has not been shown reliably to influence survival. The addition of adjuvant radiotherapy post-lymphadenectomy similarly has not shown an improved survival.

At the present time the only agent demonstrated to significantly improve survival in patients with node metastases is interferon, utilizing a regimen of one-year high dose adjuvant interferon α-2b. The difficulty in evaluating the three trials (ECOG 1684, ECOG 1690 and Intergroup trial E1694), the modest improvements in survival and the high treatment toxicity have limited the popularity of this approach in Australia and New Zealand.

3.2.3 Regional relapse following lymphadenectomy

Compared to prognostic criteria for survival, prognostic factors predictive of regional recurrence following lymphadenectomy are less well defined. The significance of putative prognostic factors is...
summarised in Appendix 1. The most important prognostic factor appears to be the number of positive nodes. Other prognostic factors less reliably associated with subsequent failure are extranodal spread (exemplified by matted nodes clinically), metastatic node size and probably the anatomic site of nodal basin metastases. Recurrence is more likely to follow lymphadenectomy for regional disease in the head and neck, compared to the axilla and least likely in the groin. In the lower limb satellite or in transit disease are far more common and frequently occur with further relapse in the groin.

Reported rates of relapse following lymphadenectomy for metastatic nodal involvement varies from 10% to 80%. Based on the data tabulated in Appendix 1, an estimated three tier categorisation of risk for regional relapse and survival in node positive melanoma post-lymphadenectomy can be expressed as follows:

Table 1. Categories of risk of regional relapse and mortality in node-positive, post-lymphadenectomy melanoma.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>5-year regional relapse rate</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Low risk”</td>
<td>5 – 10%</td>
<td>50%</td>
</tr>
<tr>
<td>1-2 nodes and microscopic nodal involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Intermediate risk”</td>
<td>25-30%</td>
<td>30%</td>
</tr>
<tr>
<td>“High risk” any of</td>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;5 nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>matted nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>size &gt; 6 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>close resection margins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.3.4 Morbidity from lymphadenectomy

Standard operative complications including wound infection, haematoma, etc, are well documented and occur infrequently. Seroma formation may complicate the post-operative phase in up to one-third of patients. It is uncommon after cervical node dissection and most common following inguinal dissection. Skin edge necrosis post-operatively occurs occasionally after cervical or axillary dissection but may be a significant problem following inguinal dissection. Less well documented complications, which tend to be medium to long term and are non-life threatening but likely to impact upon patients’ quality of life, include alteration in local skin sensation, reduced regional function and lymphoedema. The addition of adjuvant radiotherapy is likely to increase the frequency and severity of these last two regional complications particularly. Adjuvant interferon may be associated with a higher risk of complications, as are co-morbidities such as age, diabetes and obesity.6

3.3 Evidence for the efficacy of radiotherapy in controlling nodal melanoma.

3.3.1 Results of palliative radiotherapy for gross nodal melanoma

Palliative radiotherapy for gross nodal metastatic melanoma is beneficial in most patients. The mean complete response rate is 24 % (range 23%-74%)37-39 and the partial response rate is in the range 35 to 45%38,39 giving an overall response rate of approximately 60%.39 Response outcomes are diminished by an increase in tumour size or burden,39 and conversely improved control rates can be anticipated when radiotherapy is given earlier and for subclinical disease.
3.3.2 Results of adjuvant radiotherapy for resected nodal melanoma

Published evidence for the efficacy of adjuvant radiotherapy for nodal melanoma metastases is mostly from single institution series, with improved regional control claimed by comparison with historical results for surgery alone.

MD Anderson⁴⁰ have reported the largest prospective series on head and neck adjuvant radiotherapy using a hypofractionated schedule (30 Gy in 5 fractions over 2.5 weeks) in high risk cases for regional relapse, and cite a five-year actuarial regional control rate of 88%, compared with 50% in their surgery alone historical cohort.

Three Australian series³⁷,³⁸,⁴¹ support this finding across the three nodal basin metastatic sites, viz parotid/neck, axilla, and groin regions. These retrospective series contain therapeutic and adjuvant cohorts. The Queensland series³⁷ on 26 adjuvant radiotherapy cases reported an observed 88% overall crude regional control rate. The Victorian series³⁸ on 42 adjuvant radiotherapy cases reported a cumulative incidence of regional relapse of 20% at 5 years (however, only 44% of these were infield relapses). The Sydney Melanoma Unit reported results from 45 patients receiving adjuvant radiotherapy following neck dissection and parotidectomy showing a crude regional recurrence rate of 6.5%.⁴² The Sydney Melanoma Unit also reported on 139 patients receiving post-operative radiotherapy to all nodal basin sites post-lymphadenectomy, for which there was a 11% crude infield relapse rate.⁴¹ The radiotherapy schedules were variable.

A multicentre Phase II Study conducted by the Trans-Tasman Radiation Oncology Group (TROG) utilizing a radiotherapy regimen approaching a conventional schedule (48 GY in 20 fractions over 4 weeks) completed accrual in early 2001. Preliminary results verify a high control rate and well tolerated treatment.⁴³ In an interim report given at the 5th World Conference on Melanoma in Venice 2001, 150 patients receiving adjuvant radiotherapy post-lymphadenectomy had a recurrence rate within the treated area of 9.3%.⁴³,⁴⁴

Finally, an MD Anderson series of 21 patients receiving adjuvant radiotherapy following axillary dissection had a 5% crude regional relapse rate.⁴⁵

In summary, the evidence to date suggests an infield relapse rate for adjuvant radiotherapy following complete resection of nodal metastatic melanoma of between 5 to 13%. None of the reports indicate that this confers any survival advantage, including one randomised trial²³ aimed specifically to detect a difference in survival. This trial, however, used a radiotherapy schedule unlikely to be considered efficacious in modern times (a split course of treatment with a 1 month break mid-course) and 26 of the 82 enrolled patients were rendered ineligible for analysis. Three of 27 irradiated patients had an infield relapse.

Table 2 below summarises the results of adjuvant radiotherapy for resected nodal metastatic melanoma.

<table>
<thead>
<tr>
<th>Series</th>
<th>Node basin site</th>
<th># of patients</th>
<th>Regional relapse rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson</td>
<td>Parotid/neck</td>
<td>174</td>
<td>12</td>
</tr>
<tr>
<td>Ang/Peters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strom</td>
<td>Axilla</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Queensland</td>
<td>All</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Burmeister</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis (TROG Phase II)</td>
<td>All</td>
<td>150</td>
<td>9.3</td>
</tr>
<tr>
<td>PMCI</td>
<td>All</td>
<td>42</td>
<td>20*</td>
</tr>
<tr>
<td>Sydney Melanoma Unit</td>
<td>Parotid/Neck</td>
<td>45</td>
<td>6.5</td>
</tr>
<tr>
<td>O'Brien</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens</td>
<td>All</td>
<td>139</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* includes in transit relapses

The regional relapse rate, as a weighted average over all series, is 11%.
3.3.3 Morbidity from combined lymphadenectomy and post-operative adjuvant radiotherapy

Adjuvant radiotherapy will potentially increase the risk of regional treatment complications by both enhancing the rate and severity of surgical complications and by adding radiotherapy-specific toxicities. The evidence so far indicates that adjuvant radiotherapy is well tolerated. The early results from the TROG phase II study (in press) using the radiotherapy schedule to be employed in this trial, with a median follow-up of 24 months, appears very acceptable. The differences in morbidity between surgery alone and surgery plus adjuvant radiotherapy have not been measured in magnitude and significance by direct comparison in a randomised trial before. Interestingly there are limited reports that interferon may enhance radiotherapy toxicity. While patients for this trial remain eligible if they are receiving adjuvant systemic treatment, they are likely to be very few in number and an awareness of potential interaction is important.

3.4 Aspects of the trial design

Surgery is the long established treatment of nodal metastases from melanoma. In the past 20 years important questions regarding survival have been addressed in surgical trials with intense clinical research into optimal surgical management of regional melanoma. It is clear that regional control is very high when metastases are detected early (microscopic in elective and selective lymphadenectomy). When more advanced nodal metastases present, surgery continues to be the mainstay of treatment but an ill-defined regional failure rate emerges that is untested in a prospective randomised trial setting with stratification for prognostic variables and measurement of surgical toxicity. Finally the surgical salvage rate for regional relapse following initial lymphadenectomy is unknown. Thus a treatment arm of surgery alone followed by observation will provide the base data for this more advanced disease category.

The role of adjuvant radiotherapy in improving regional control in melanoma at high risk of relapse after lymphadenectomy remains largely unanswered. There is concern for increased regional toxicity with the addition of radiotherapy. Furthermore the prognostic factors predictive for an increase in risk of regional relapse are similar to those for diminished survival, narrowing the perceived benefits of securing regional control with the competing risk of systemic disease. The effect on patients’ quality of life of the different types of relapse has not been researched. However it is an important therapeutic goal to improve regional control, if treatment morbidity is acceptable, in all categories of patients. This trial therefore aims to measure the difference in treatment toxicity between the two treatment arms and the effect of regional relapse, with their respective impact on patients’ quality of life.

There has been renewed debate and interest in the field as seen in recent publications from expert melanoma centres in the literature. Two randomised trials addressing this question have been undertaken in the US. The RTOG head and neck trial was conducted in the era of discovery of a survival benefit for adjuvant interferon and did not reach planned accrual. In an ongoing ECOG (E3697) trial all patients receive interferon and are randomised to observation or hypofractionated radiotherapy: the trial is slowly accruing. The adjuvant sub-radical hypofractionated radiotherapy regimen (30 Gy in 5 fractions over 2.5 weeks) being utilized in this trial was reported as having a less than 2% late complication rate in the head and neck, however it may still be potentially associated with enhanced late radiotherapy toxicity when used in the axilla and groin. Completion of ECOG (E3697) will contribute significantly to knowledge in this area. Results of the TROG phase II study (on which the radiotherapy regimen of this trial is based) are comparable to hypofractionated regimens in disease control rates but carry a considerably lower risk of late radiotherapy side effects and therefore offer an improved therapeutic ratio. The likelihood that a minority of patients in an Australian and NZ trial will be receiving adjuvant interferon also differentiates this trial from US. attempts to address this important question.

3.4.1 Patient selection (eligibility criteria using prognostic factors)

Refer to table 1.

Treating “low risk” node positive disease with adjuvant radiotherapy seems unwarranted as the risk of nodal basin relapse is too small, and the risk of increasing regional morbidity is not justified.
Patients at higher risk of regional relapse have increasingly poorer survival prospects, so the competing risk of suffering from distant relapse may clinically overshadow the importance of regional relapse for some patients at the high end of the risk spectrum. However gaining regional control for all patients is an important therapeutic goal. No upper limit of disease burden has been incorporated into the eligibility criteria except the mandatory requirement of complete surgical resection of all regional nodal metastases.

Patients with nodal disease that could be categorised as “intermediate risk” would be expected to benefit most from radiotherapy if this modality significantly reduces the rate of nodal basin relapse with acceptable tolerability, and includes a reasonable prospect of long-term survival.

Prognostic factors determining the eligibility of patients for the study have been based on these premises. A further modification has been an adjustment for anatomic site for both the perceived increase in relapse rates in the head and neck and the highly visible nature of regional relapse at this site, plus the greater tolerability of radiotherapy in the head and neck. Thus a lower threshold of prognostic criterion applies to this site compared to the axilla and groin respectively, where the therapeutic ratio increasingly narrows.

3.4.2 Measurement of major endpoint

There is no universally accepted convention for measuring the main endpoint in this trial, being regional (nodal basin) relapse. Regional relapse is defined, identically for both arms of the trial and regardless of the treatment received, by use of a set of anatomical boundaries for each node basin region. Refer to section 8.2 for full details. Careful documentation is specified for recording the anatomic location and confirmation of regional relapse(s). Any equivocal cases will undergo adjudication of data collected at relapse by an independent panel.

4 OBJECTIVES

The primary objective of the trial is:

To determine, in patients who have completely resected nodal metastatic melanoma, whether there is a difference in the rate of regional relapse between patients treated with surgery alone and patients treated with surgery plus adjuvant post-operative radiotherapy.

Secondary objectives are:

1. To determine, in these patients, whether there is a difference in morbidity and quality of life between patients treated with surgery alone and those treated with surgery plus adjuvant radiotherapy, both overall and within each of the node basins (parotid/neck, axilla and groin).

2. To determine, in these patients, whether there is a difference in failure-free survival, patterns of relapse and overall survival between patients treated with surgery alone and those treated by surgery plus adjuvant radiotherapy.

3. To identify prognostic factors for risk of regional relapse from data obtained from the lymphadenectomy specimen. The main factors of interest are (a) number of nodes containing metastatic melanoma, (b) presence of extranodal spread, and (c) maximum diameter of metastatic node.

4. To describe the outcomes in patients in the observation arm who develop an isolated regional relapse that is treated with salvage surgery and adjuvant radiotherapy.

5 PATIENT SELECTION

The lymphadenectomy findings (refer to Appendix 5) are crucial in determining if a patient is eligible for this trial. Important minimum information derived from the full pathology report is to be recorded.
in a Synoptic Pathology Report (refer to Appendix 5, section 3 or Case Record Form A2). The Synoptic Pathology Report contains information on the number of harvested nodes (eligibility criterion 2) and the relevant prognostic factors (eligibility criterion 3) pertinent to the region under study.

5.1 Eligibility criteria

All of the following criteria must apply for the patient to be eligible for the trial:

1. Regional macroscopic (palpable) nodal metastatic melanoma in one nodal basin region only (either parotid/neck, axilla or groin) which has been completely resected.

Patients presenting according to any of the three following ways are eligible: node metastases (i) occurring concurrently with the initial diagnosis of primary melanoma, (ii) appearing subsequently after the successful treatment of the primary, or (iii) as a first presentation of melanoma with an unknown primary.

Patients who undergo two or more operations to achieve total standards specified for lymphadenectomy must complete them within 8 weeks. A previous biopsy (open or closed) where the operative intent was not a definitive curative procedure does not need to be included within this 8 week period. Patients who undergo a procedure that is not curative in intent (e.g. revision of wound edges) after a definitive procedure that is curative in intent (e.g. inguinal lymphadenectomy) will need to have this procedure completed within 12 weeks following the final definitive procedure.

2. A completed Synoptic Pathology Report which states that:

   (a) resection is complete

   And

   (b) the lymphadenectomy specimen contains the required minimum numbers of harvested nodes in the involved sites, as follows:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minimum Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial parotidectomy</td>
<td>2</td>
</tr>
<tr>
<td>Neck dissection</td>
<td>25</td>
</tr>
<tr>
<td>Comprehensive (levels I-V)</td>
<td>20</td>
</tr>
<tr>
<td>Selective</td>
<td>15</td>
</tr>
<tr>
<td>4 levels (e.g. SND (I-IV) or SND (II-V, ±postauricular/occipital)</td>
<td></td>
</tr>
<tr>
<td>3 levels (e.g. SND (I-III) or SND (III-V)</td>
<td></td>
</tr>
<tr>
<td>Axillary dissection</td>
<td>10</td>
</tr>
<tr>
<td>Superficialinguinaldissection (4 for deep inguinal/pelvic node dissection if performed in conjunction with superficial inguinal dissection)</td>
<td>6</td>
</tr>
</tbody>
</table>

3. At significant risk of regional relapse, defined as at least one of the following being present (as per Synoptic Pathology Report):

   a) the number of nodes involved is:
      - ≥ 1 node for parotid, or
      - ≥ 2 nodes for neck or axilla, or
      - ≥ 3 nodes for groin.

   or

   b) Extranodal tissue spread;

   or

   c) Any one metastatic node of maximum diameter ≥ 3 cm neck, or ≥ 4 cm in axilla or groin.

4. All staging investigations have been completed: CT of nodal basin, CT of chest/abdomen/pelvis and CT of brain. (Brain MRI may be substituted for brain CT for initial staging only.)
5. Serum LDH ≤ 1.5 times the upper limit of normal.
6. WHO performance status of 0 or 1.
7. Age 18 years or older.
8. Expected life span of two or more years in the absence of melanoma.
9. A photograph has been taken of the involved nodal basin region; the photograph is to include the recent lymphadenectomy scar(s) and the defined anatomic boundaries drawn on the skin for the node basin region concerned (refer to section 8.2 for details).
10. Radiotherapy must be able to be commenced within 12 weeks of lymphadenectomy.
11. Patient must not be pregnant and if fertile must use a medically acceptable contraceptive throughout the treatment period.
12. Written informed consent has been given.

5.2 Exclusion criteria
None of the following criteria must apply for the patient to be eligible for the trial.
13. Evidence of active or previous local recurrence or in transit disease; or evidence of nodal metastases or regional disease beyond the lymphadenectomy bed.
14. Evidence of distant metastases on clinical or radiological investigation.
15. Patients with prior cancers, except: those diagnosed more than five years ago with no evidence of disease recurrence within this time and with clinical expectation of recurrence of less than 10 %; and successfully treated basal cell or squamous cell skin carcinoma; and carcinoma in situ of cervix; and multiple primary melanoma. However, any patient with previous invasive breast cancer or prostate cancer is excluded.

Note: Treatment with adjuvant systemic therapy does not exclude participation in the trial. However cytotoxic drugs, other than interferon, should not be delivered during, or in close association with, radiation treatment. Documentation of adjuvant systemic therapy will be required.

6 REGISTRATION AND RANDOMISATION

6.1 Registration
To randomise a patient, first check that all eligibility criteria have been satisfied and that all information required for stratification is available (refer section 6.2).

Complete the registration form and Synoptic Pathology Report prior to telephoning to register the patient. Telephone the Trial Centre on +61 3 9656 3786 and ask for the trial centre data manager. Eligible patients will be randomised to either the radiotherapy arm or the observation arm.

A copy of the checklist of eligibility criteria completed at the Trial Centre at the time of registration will be sent to the relevant investigator, with written confirmation of the assigned treatment arm.

If the patient has been assigned to receive adjuvant radiotherapy, this treatment should be started no later than 12 weeks after lymphadenectomy.

6.2 Randomisation and stratification
Patients will be randomised to a treatment arm while maintaining balance with respect to each of the following prognostic variables:
1. Institution
2. Nodal basin region (parotid/neck; axilla; groin)
3. Number of involved nodes in region (≤ 3 nodes; ≥ 4 nodes)
4. Maximum node diameter (≤ 4 cm; > 4 cm)
5. Extent of extranodal spread (none; limited; extensive)

7 TREATMENT DETAILS

7.1 Initial radiation treatment

Patients randomised to the adjuvant radiotherapy arm will receive 48 Gy reference dose in 20 fractions at 5 fractions per week, with a maximum overall treatment time of 30 days.

Radiotherapy should ideally commence as soon as possible after the patient has healed from surgery. Specifically, radiotherapy is required to be commenced no later than 12 weeks following lymphadenectomy, as delays in commencement of radiotherapy may be due to delayed healing, unavoidable radiotherapy department waiting times, or the intervention of high dose adjuvant interferon (intravenous phase).

Details of the radiotherapy treatment prescription for each node basin site and sample radiotherapy treatment techniques and dose planning and are outlined under Appendices 6, 7 and 8.

7.2 Treatment of isolated regional relapse for observation arm patients

The diagnosis should be confirmed with fine needle biopsy or aspiration for cytology. CT scanning of the node basin region, whole body and brain should be undertaken to exclude any distant spread and then a surgical opinion sought as to whether repeat node basin surgical resection is recommended.

If salvage surgery is undertaken and complete resection is again achieved, radiotherapy should be given according to the trial protocol as it applies to the adjuvant radiotherapy of patients randomised to the radiotherapy arm, as long as this is feasible and with practical clinical modifications as might be appropriate.

7.2.1 Eligibility criteria for crossover

Observation arm patients are eligible to crossover to the radiotherapy arm of the trial if all of the following criteria apply:

1. The patient presents with a first diagnosis of isolated regional relapse amenable to surgical resection (salvage surgery).
2. A pathology report is available documenting details of the surgical operation.
3. There is no evidence of local recurrence, in transit disease, or distant metastasis beyond the nodal region under study.
4. Investigational work up, including CT scan of nodal basin, CT scan of chest abdomen/pelvis and brain has been performed within 12 weeks of start of radiotherapy and demonstrates no other evidence of melanoma.
5. A photograph has been taken of the nodal basin following salvage surgery showing surgical scars and defined anatomic boundaries drawn on the skin (refer to section 8.2 for details).
6. Radiotherapy must be able to be commenced within 12 weeks of salvage surgery.
7. The patient is not pregnant and, if fertile, will be using a medically acceptable contraceptive throughout the treatment period.

7.2.2 Registration of crossover patients

To register a crossover patient, check that all eligibility criteria have been satisfied. Complete the registration form [A-R] and telephone the Trial Centre on (03) 9656 3786.
7.2.3 Monitoring procedures and tests

7.2.3.1 Prior to crossover registration

Investigations must be performed prior to the start of radiotherapy: These investigations are:
- Full blood count and differential (FBE)
- Urea, creatinine and electrolytes
- LFTs, serum LDH
- Clinical examination
- Chest X-ray (antero-posterior and lateral)
- CT nodal basin, either pre-operative or post-operative
- CT brain, chest, abdomen/pelvis (MRI brain may be done as an alternative to CT brain)

7.2.4 At crossover registration

- QoL assessment
- Early surgical morbidity assessment
- Lymphoedema measurements (for axilla and groin patients)

7.2.5 Early surgical morbidity and lymphoedema assessments

For all patients, early surgical morbidities and lymphoedema measurements (for axilla and groin patients only) must be assessed at 3 months following salvage surgery.

7.2.6 Early radiotherapy toxicities for crossover patients

For all patients, early radiotherapy toxicities are to be assessed at 2 and 6 weeks following the completion of radiotherapy.

7.2.7 Scheduled follow-up visits for crossover patients

Follow-up visits are to be scheduled every 3 months from registration to the radiotherapy arm of the trial for the first 2 years, then every 6 months until 5 years, and then annually. Investigations at these visits are to include:
- History & clinical examination
- Disease status
- QoL assessments
- Lymphoedema
- Late surgical morbidities (more than 90 days after salvage surgery)
- Late radiotherapy toxicities - assessments to commence 6 months from randomisation

In addition, the following should also be performed annually from the date of registration to the radiotherapy arm:
- Full blood count and differential (FBE)
- Urea, creatinine and electrolytes
- LFTs, serum LDH
- Chest X-ray (antero-posterior and lateral)
- CT nodal basin

7.3 Treatment of relapse other than described in 7.2.

There is no prescribed treatment for relapse. This will be at the discretion of the treating physician. However documentation of relapse details will be required (refer section 9.3).

Note: all regional relapse cases are to be reported to the Trial Centre as soon as possible for review by the Trial Management Committee. Additional data collection in salvage cases (as defined in 7.2) will be required according to the monitoring schedule as if restarting from time of randomisation.
8 DEFINITIONS OF OUTCOME MEASURES

8.1 Types of relapse

The following three types of relapse will be recognised:

- regional (nodal basin) relapse
- local or in transit relapse
- distant relapse

A relapse at a particular site will be classified as being of only one of these types. A diagnosis of regional relapse will take precedence in cases where overlap occurs; e.g., relapses which nominally may be both regional and local or in transit will be classified as regional. Similarly, a diagnosis of local or in transit relapse will take precedence over that of distant relapse.

Simultaneous relapse of two or three types (from those above) may occur. Relapses are considered to be simultaneous if diagnosed within one month of one another (within two months for three relapse types).

The date of relapse will be taken to be the date of the occurrence of palpable disease or biopsy or radiographic diagnosis, whichever occurs first.

8.1.1 Measures to ensure lack of bias

It is of the utmost importance that the relapse rate, particularly the regional relapse rate, is measured without bias in the two arms of this trial. Bias will be eliminated or at least minimized by:

(a) carefully defining, a priority, the anatomical limits of the regional nodal basin under study regardless of what arm the patient will be randomised to,

(b) independent review of all reported relapses, and

(c) ensuring that, as far as possible, follow-up is conducted with equal frequency and rigor for patients in both arms of the trial.

8.2 Regional relapse

A relapse will be defined as a regional (nodal basin) relapse if the relapse occurs within the defined anatomic borders defined as follows;

8.2.1 Parotid and neck region

Patient position – lying supine; head rotated fully to the contralateral side (nose in the plane of the contralateral anterior shoulder) exposing the ipsilateral face and neck to full view.

Boundary outline – The superior edge of the boundary is the upper border of the zygoma; it stops, at the anterior end, 2 cm from the palpable lateral bony orbital rim; it extends inferiorly to join and run along the anterior border of the masseter (palpable on clenching the jaw); it follows the mandible anteriorly to the midline, then extends inferiorly in the midline over the thyroid notch and continues inferiorly in the midline to the sternal notch; it continues medially around the perimeter of the clavicular head and along the inferior border of the clavicle to the medial palpable coracoid process; it then passes superiorly to the anterior border of the trapezius; it runs along the anterior border of the trapezius muscle to the superior nuchal line on the occiput; it runs anteriorly overlying the attachment of the base of the mastoid process to the base of the skull to join the junction of the lower 2/3 with the upper 1/3 of the pinna to cross the pinna, below the scaphoid fossa of the pinna, to the superior attachment of the pinna to the scalp; it then joins with the upper border of the zygoma.

This incorporates all nodes of the preauricular/parotid, postauricular and occipital/suboccipital regions, and the anterior and posterior triangles of the ipsilateral neck. Refer to the diagram below.
8.2.2 Axilla and supraclavicular region

Patient position – lying supine, looking directly ahead (nose in midplane), hands resting on lower abdomen; angle of humerus approximately 35° to the vertical.

Superior boundary – a horizontal line through junction of the medial trapezius muscle silhouette with vertical neck muscles;

Inferior boundary – a horizontal line extended through the lower level of the 8th rib in the mid axillary line (being congruent with radiological landmark of lateral rib cage outline of 8th rib on end)

Medial boundary – a vertical line 2 cm off midline to ipsilateral side from superior junction with superior border to 2 cm below palpable sternal notch. This joins a curved line that follows the inferior border of the 4th rib posteriorly running laterally until it stops 1.5 cm inside the profile of the projected radiological internal edge of the ribcage. Maintaining the 1.5 cm margin on the internal edge of the lateral ribcage follow down to join inferior border.

Note: the thoracic medial border can only be accurately placed on an x-ray, being a simulator x-ray or a diagnostic radiograph with a magnification marker. High axillary relapse may require localization on such a hemi-thorax / lower neck x-ray with transferred CT scan information of location and size of relapse drawn onto this film.

Lateral boundary – junction of proximal 1/3 with distal 2/3 of upper arm defined by measuring from olecranon tip to acromion tip (divide by 3 and measure down deltoid profile from acromion tip); draw line across arm perpendicular to long axis of humerus; exclude deltoid muscle and glenohumeral joint from lateral border. Refer to diagram below.
8.2.3 Inguinal and iliac region

Patient position – lying supine with knees separated in frog like position (hips slightly flexed, abducted and externally rotated with heels of externally rotated feet approximating each other) so profile of patellae in vertical plane of skin profile overlying greater trochanter. This exposes and opens the medial groin crease.

Superior border – A transverse line through inferior end of sacro-iliac joint (which is a little inferior to the anterior palpable landmark of anterior superior iliac spine); pelvis shape varies between the sexes.

Note; superior border can only be confirmed accurately on a radiograph in defined patient position as above, with placement of any regional nodal pelvic relapse(s) transposed from CT scan.

Inferior border – transverse line through the junction of proximal 1/3 and distal 2/3 of thigh (defined by measuring along a line drawn between the palpable femoral pulse to palpable superior border of patella, dividing by 3 and measuring down from femoral pulse) OR 3 cm beyond distal end of femoro-inguinal lymphadenectomy scar, whichever is the most caudal measurement.

Medial border – vertical line drawn parallel and ipsilaterally 2 cm from midline.

Lateral border – a vertical line drawn through anterior superior iliac spine that connects approximately with medial border of patella (with leg positioned as described above under patient position). Refer to diagram below.
8.2.3 Additional notes

A diagnosis of regional relapse in the study region for any one of the three sites will be accepted if:

(a) disease occurred within the anteriorly placed defined anatomic boundaries as above (from the skin surface down to the maximum posterior depth of node subgroup placement); and

(b) histologic (biopsy) or cytologic (fine needle aspiration) confirmation of disease was obtained, and

Note: regional relapse does not include disease occurring on the posterior surface of the body (opposite the anteriorly defined areas) beyond the recognized depth of the specific node groups that comprise the regions under study. For example: posteriorly placed in transit disease or bone metastases that might coincidentally lie within these anteriorly defined boundaries.

If biopsy or cytological diagnosis is not feasible, diagnosis may be made on the basis of progressive radiographic (CT scan) changes. In this case, confirmation is required from independent review.

The procedure to be followed when regional relapse is diagnosed is as per 9.3.1.

8.3 Local or in transit relapse and distant relapse

A local or in transit relapse will be defined as dermal or subcutaneous relapse at the primary site or between it and the adjoining nodal basin region but outside the boundary defining regional relapse.

Distant relapse will be defined as haematogenous spread, visceral metastasis or distant soft tissue metastasis which does not conform to the definitions of local, in transit or regional relapse.
Local, in transit or distant relapse must be documented by:

(a) histological (biopsy) or cytological (fine needle aspiration); or
(b) radiographic diagnosis using ultrasound, CT, MRI, or bone scan; or
(c) clinical examination only (in the case of progressive disease).

8.4 Time-to-event outcomes

8.4.1 Failure-free survival
This will be measured from the date of randomisation to the date of a relapse in any site or death, which-ever comes first.

8.4.2 Overall survival
This will be measured from the date of randomisation to the date of death from any cause.

8.4.3 Cumulative incidences of competing events (patterns of relapse)
The competing events will be (i) regional relapse, (ii) distant relapse, (iii) local and in transit relapse and (iv) death without prior relapse. At each point of time from randomisation, the incidence of each type of event, as a first event, will be calculated. That is, once one of these four competing events occurs in a patient, subsequent events are ignored, for the purposes of the primary analysis. The recording of regional relapse more than 2 months following local, in transit or distant relapse will continue, however, as an ongoing measure for documenting regional control, as a means of validating regional QoL scoring and as a means to capture data on secondary patterns of relapse; these data will be analysed as part of carrying out secondary objectives.

8.4.4 Summary table of time-to-event definitions
The following definitions apply to all patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Start date</th>
<th>End date</th>
<th>Censored by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure-free survival</td>
<td>Randomisation</td>
<td>Regional relapse</td>
<td>Close-out date or loss to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant metastasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local or in transit relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death without prior relapse</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>Randomisation</td>
<td>Death from any cause</td>
<td>Close-out date or loss to follow-up</td>
</tr>
<tr>
<td>Cumulative incidences</td>
<td>Randomisation</td>
<td>The first of:</td>
<td>Close-out date or loss to follow-up</td>
</tr>
<tr>
<td>(competing risks analysis)</td>
<td></td>
<td>• Regional relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Distant metastasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Local or in transit relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Death without prior relapse</td>
<td></td>
</tr>
</tbody>
</table>

8.5 Surgical morbidity
Surgical morbidity will be measured using the morbidity scoring systems and lymphoedema measurements of limb circumference given in Appendices 9 and 10. Surgical side-effects will be recorded for all patients in the trial. Early surgical morbidity is measured pre-randomisation and then 3 months from the date of lymphadenectomy. Late surgical morbidity is assessed at scheduled follow-up visits.

8.6 Radiotherapy morbidity
Complications unique to radiotherapy include acute and late radiation toxicities, some of which are site-specific. A radiation oncologist will be required to monitor and review each patient on the radiotherapy arm and to record these toxicities. Using the morbidity scoring systems given in Appendix 9, early radiotherapy toxicities will be assessed at 2 and 6 weeks following completion of...
radiotherapy. Late radiotherapy toxicities are defined as those occurring more than 90 days from the commencement of radiotherapy and will be assessed at scheduled follow-up visits.

The toxicity scoring systems used will be the Common Toxicity Criteria (Version 2.0, Cancer Therapy Evaluation Program, NCI criteria) for scoring acute radiation toxicities, and the RTOG/EORTC Late Radiation Morbidity Scoring System for scoring late radiation toxicities.

8.7 Quality of life

The global quality of life\textsuperscript{54-59} (QoL) instrument to be used will be the FACT-G (refer to Appendix 4). The FACT-G is a copyrighted QoL instrument and is used under the agreement with Dr David Cella for the purposes of this study. QoL assessment is to be performed at baseline (pre-randomisation), then at 3, 6, 12, 15, 18, 21 and 24 months from the date of randomisation, then every 6 months until 5 years and thereafter annually. QoL will also be recorded at the time of any type of relapse, however QoL assessments will cease following the diagnosis of the first distant relapse.

QoL assessment will include, in addition to the FACT-G, a regional symptomatology questionnaire which will be used to measure the impact of the health of regional tissues under study on patients’ QoL (refer Appendix 4). This tool is designed to measure differences in morbidity between surgery alone versus surgery plus adjuvant radiotherapy, in addition to physician documentation of toxicity scoring and objective lymphoedema measurement, and to document the effect on the QoL of living with uncontrolled regional disease relapse. Measuring the subjective and relative importance of these impacts on patients’ QoL is an important part of assessing the efficacy of adjuvant radiotherapy, which forms the basis of this trial. A literature search has suggested that there are no established regional symptomatology questionnaires in use and so a simple regional symptomatology questionnaire has been devised for use in this trial, although it is acknowledged that this is not being validated. Variables from this questionnaire will be correlated with toxicity and lymphoedema scores and relapse data.

9 MONITORING PROCEDURES AND TESTS

9.1 Schedule

9.1.1 Pre-randomisation

Eligibility investigations must be performed within 6 weeks prior to randomisation with the exception of CT scans which must be performed no later than 12 weeks prior to randomisation. These investigations are:

- History and clinical examination
- Disease status
- Full blood count and differential (FBE)
- Urea, creatinine and electrolytes
- LFTs, serum LDH
- Chest X-ray (antero-posterior and lateral)
- CT nodal basin
- CT brain, chest, abdomen/pelvis (MRI brain may be done as an alternative to CT brain)

9.1.2 At randomisation

- QoL assessment
- Early surgical morbidity assessment
- Lymphoedema measurements (for axilla and groin patients)
9.1.3 Early surgical morbidity and radiotherapy assessments

For all patients, in addition to the pre-randomisation assessment, early surgical morbidity is to be assessed at 3 months from the date of lymphadenectomy.

For patients randomised to the radiotherapy arm, early radiotherapy toxicities are to be assessed at 2 and 6 weeks following completion of radiotherapy.

9.1.4 Scheduled follow-up visits

Follow-up visits are to be scheduled every 3 months from randomisation for the first 2 years, then every 6 months until 5 years, and then annually. Investigations at these visits are to include:

- History and clinical examination
- Disease status
- QoL assessment
- Lymphoedema measurements (for axilla and groin patients only)
- Late surgical morbidity scoring (more than 90 days after lymphadenectomy)
- Late radiotherapy toxicities – assessments to commence 6 months from randomisation

In addition, the following should also be performed annually from the date of randomisation:

- Full blood count and differential (FBE)
- Urea, creatinine and electrolytes
- LFTs, serum LDH
- Chest X-ray (antero-posterior and lateral)
- CT nodal basin, brain, chest, abdomen/pelvis

9.2 Summary of monitoring schedule

<table>
<thead>
<tr>
<th>Investigation and observation recording</th>
<th>Pre-randomisation</th>
<th>3 mo. post-surgery</th>
<th>2 and 6 weeks post-radiotherapy</th>
<th>Scheduled follow-up visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and clinical examination</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Disease status</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>FBE</td>
<td>X</td>
<td></td>
<td>Xa</td>
<td></td>
</tr>
<tr>
<td>Urea, creatinine, electrolytes</td>
<td>X</td>
<td></td>
<td></td>
<td>Xa</td>
</tr>
<tr>
<td>LFTs, serum LDH</td>
<td>X</td>
<td></td>
<td></td>
<td>Xa</td>
</tr>
<tr>
<td>Chest x-ray (antero-posterior and lateral)</td>
<td>X</td>
<td></td>
<td>Xa</td>
<td></td>
</tr>
<tr>
<td>CT nodal basin, brain, chest, abdomen/pelvis</td>
<td>Xb</td>
<td></td>
<td></td>
<td>Xa</td>
</tr>
<tr>
<td>QoL assessment</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Early surgical morbidity</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Late surgical morbidity</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Early radiotherapy toxicities</td>
<td></td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>Late radiotherapy toxicities</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

a annually only

b MRI brain may be performed as an alternative to CT brain. In addition, CT nodal basin pre- or post-surgery must be performed within 14 weeks of start of radiotherapy.
9.3  Documentation required upon relapse

9.3.1 On first relapse
Careful documentation upon identification of first relapse is required.

(i)  Local or in transit or regional disease is suspected at clinical examination:

   a. Must confirm melanoma recurrence with FNA cytology or biopsy.
   b. Ideally record with a second observer.
   c. Photograph the involved nodal basin as follows:
      ▪ place the patient in the position as defined for regional documentation and
draw the defined nodal anatomic boundaries on the skin (see section 8.2);
      ▪ mark relapse site(s) on skin;
      ▪ photograph the area, making sure all the boundary lines and disease
markings are included (refer to initial photographic documentation to
compare accuracy of remarking);
      ▪ in order to show all the requested features in one photograph and maintain
patient position, the patient may need to be placed on a mattress on the
floor. Otherwise, multiple photographs can be taken.
   d. CT scan of regional node basin under study;
   e. For relapses (palpable or impalpable) not amenable to accurate correlation with all
aspects of boundary delineation:
      ▪ take a plain radiograph (or “simulation film”) of the node basin region in
the specified patient position;
      ▪ include all relevant anatomy required to display the full extent of the
anatomic boundaries as defined for purpose of defining regional relapse
(refer to section 8.2 for details);
      ▪ for axilla or groin, indicate with wire the distal anatomic boundary of the
regional node basin defined by measurement of surface landmarks on the
upper arm and thigh respectively.
      ▪ for any palpable disease indicate the surface location of the disease using
wire on the skin;
      ▪ for the impalpable component of disease, locate the site and size of the
disease by drawing onto the radiograph, using transferred information from
CT relapse documentation.
   f. Report any regional relapse to the Trial Centre immediately so that any further
investigations to confirm the diagnosis can be requested.
   g. Forward the following documentation the Trial Centre:
      i. photograph of local or in transit or regional relapse
      ii. a copy of the CT scan highlighting the site of recurrence and a copy of the CT
  scan report
      iii. FNA or biopsy pathology report
      iv. where applicable, a copy of the plain radiograph
      v. If surgery is performed, a copy of the operation and pathology report
   h. Investigate the patient for disease outside the nodal basin (local, in transit or distant
relapse) by full clinical examination, FBE, LFTs and LDH, and CT scan of brain and
whole body, to be completed within one month of the diagnosis of the nodal basin relapse.

(ii) When distant metastases are the obvious first indication of relapse the patient must be examined for any local or in transit or regional disease, and if such disease is found, documentation is to be provided as described above in (i). Full documentation of distant disease status is to be completed with CT of brain, chest, abdomen and pelvis to ascertain presence or absence of all possible distant metastases

9.3.2 Beyond first relapse.

If the patient fails with local or in transit or regional relapse, the patient should be followed according to the scheduled follow-up visits stipulated in the protocol until distant relapse or death occurs. After distant relapse, follow-up for survival only is required. Any salvage treatment of isolated regional relapse, and its outcome, should be recorded.

9.3.3 At death

Disease status at death will be recorded as disease present or absent and, if present, sites of local or in-transit or regional or distant disease will be recorded, where possible.

10 SERIOUS ADVERSE EVENT REPORTING

A serious adverse event (SAE) is any untoward medical occurrence which occurs during or within 30 days of completing a course of radiotherapy which:

- is fatal;
- is life-threatening;
- requires unanticipated in-patient hospitalization or prolongation of hospitalization;
- results in persistent or significant disability or incapacity;
- is a grade 4 toxicity;
- is a radiation therapy overdose.

The term “life threatening” in the definition of SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

SAEs which occur during or within 30 days of a study participant completing a course of radiotherapy must have an initial report sent by fax WITHIN ONE WORKING DAY of detection of the event to the Trial Centre at +61-3-9656-1420, the TROG Central Operations Office at +61-2-4921-1465 and the Chair of the ANZ MTG at +61-2-9550-6316. If all details are not available at the time of the initial report, a completed report must be sent within the next 10 days. If the event is not resolved at the time of the initial report, a continuation form must be sent within 30 days.

All SAE forms should be signed by the Principal Investigator at the treatment site. Each investigator is also responsible for ensuring that SAEs are reported to their Institutional Ethics Committees in accordance with local notification requirements.

SAEs are to be reviewed by the Trial Management Committee and then reported to the TROG Scientific Committee and the Chairman of the ANZ MTG.
11 FORMS AND DATA HANDLING

Case record forms (CRFs) will be supplied by the Trial Centre. Research nurses or data managers, and Principal Investigators at participating institutions should record data on CRFs as soon as they are collected. Completed forms should be returned to the Trial Centre at times requested by the Trial Centre data manager (refer to CRFs) and a copy of each CRF should be kept at the participating centre.

Subjects are to be identified by initials, UR number and trial registration number.

All case record forms should be completed in black ink and never in pencil.

All requested information must be entered on the CRFs. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. A correction should be made by striking through the incorrect entry with a single line and by entering the correct information adjacent to it. The correction must be initialed and dated by an authorized person.

Source data, including medical histories, radiological imaging, laboratory tests, radiotherapy treatment records and verification films and portal images, must be retained for 15 years after completion of the trial and be available for checking or clarification of queries by the Trial Centre if required.

12 QUALITY ASSURANCE

12.1 Data management and verification

The Trial Centre will conduct eligibility checks for all patients during telephone registration and prior to randomisation.

Throughout the study, copies of relevant documents (such as pathology and CT reports, blood test results, and radiotherapy treatment details) will be requested, if necessary, for CRF edit checks.

The Trial Centre will issue data queries as required to clarify CRF data and will report to the Trial Chairperson regarding form return and protocol compliance.

12.2 Surgery

Refer to Appendix 5, item 1.6.

12.3 Radiotherapy treatment delivery

In accordance with TROG policy (Section 8, Policy & Procedures Manual: Quality Assurance Statement of Minimum Requirements for Clinical Trials) a technical review will be conducted for this study.

The first radiotherapy patient for each nodal region from each treatment centre will be reviewed. If major violations are identified, then a further two patients will also be reviewed. Once an acceptable quality level is achieved, one in every three patients for each nodal region from each treatment centre will be randomly selected for technical review. If a continued level of acceptable quality is maintained, the rate of sampling may be decreased at the discretion of the Trial Management Committee.

For patients selected for technical review: copies of the case history, treatment prescription, treatment administration sheet, isodose plans and portal and simulator images will be requested by the Trial Centre within two weeks of treatment completion.

The Trial Centre Data Manager and Trial Chairperson will coordinate the review in consultation with the TROG QA Coordinator and report to the Trial Management Committee.

12.4 Treatment morbidity

Measurement of lymphoedema will be undertaken and funding for data management will be sought.
12.5 Site visits and monitoring

The QA program for this study will be amended (at the discretion of the Trial Management Committee) to include site visits if funding becomes available.

13 STATISTICAL CONSIDERATIONS

13.1 Trial design

This is a two-arm, randomised trial whose main aim is to determine whether the addition of radiotherapy to surgery is effective in decreasing the incidence of regional relapse in patients with macroscopic nodal metastatic melanoma. Secondary aims are to compare arms with respect to morbidity of treatment, quality of life, overall survival, failure-free survival and patterns of relapse. A secondary aim also is to assess the effects of several potential prognostic factors on each outcome.

13.2 Randomisation and stratification

Patients will be randomised in the ratio of 1:1 between the two arms, radiotherapy and no radiotherapy. Allocation to treatment will be balanced by institution, nodal basin site (3 levels) and number of involved nodes (2 levels), maximum node diameter (2 levels), and extent of extra-capsular spread (3 levels) using the minimisation technique.

13.3 Statistical methods

Regional failure is one of the four competing events of interest. The other three events are distant relapse, local or in transit relapse, and death without previous relapse. Follow-up beyond any of these events, for the purpose of answering the main aim of this trial, is not considered relevant. Therefore, a competing risks analysis will be undertaken in which the cumulative incidence curves corresponding to each of these four types of events will be calculated. However, the main aim of the trial will be evaluated by a logrank comparison of hazard functions (equivalently, Kaplan-Meier time-to-relapse curves) for regional relapse, as a first event, between the two treatment groups. A regional relapse occurring simultaneously with a local, in transit or distant relapse, or death as a first event, will be counted in the estimation of the regional relapse rate.

All analyses will be carried out on an intention-to-treat basis; i.e., all patients randomised will be included in the analysis and will be analysed according to the treatment arm randomised to, irrespective of the treatment actually received. The primary analysis comparing treatment arms will be performed after adjusting for nodal basin region; that is the logrank test over strata will be used. Secondary analyses will adjust for number of involved nodes, maximum node diameter and extranodal spread, as used in the stratified allocation of patients to treatment arms. Ninety-five percent confidence intervals (95% CI) for differences between treatment arms with respect to all important outcome variables (regional relapse rate, overall survival rate, failure-free survival rate, morbidity, quality of life measures) will be calculated. A close-out date will be determined, at the time of final analysis, as the earliest of the dates of last follow-up of patients alive and not lost to follow-up; any follow-up beyond this date will be ignored in order to minimize bias.

Failure-free survival (i.e. time to the first of any one of these events) will be compared between treatment arms. A competing risks analysis will be undertaken in which, for each arm, the cumulative incidence curves corresponding to each of the four types of events will be calculated. Cox regression adapted to the simultaneous assessment of the effects of covariates on multiple types of failure will be used. 54

13.4 Sample size required

The following calculations are based on information obtained from the sample size reassessment from pooled data as planned for this trial and, as such, incorporates data from patients in this trial.

Sample size calculations are based on the following assumptions:
The expected accrual rate to the trial is about 38 patients per year.

The time to regional relapse (Kaplan-Meier) curve for the control arm plateaus at 60% and patients susceptible to regional relapse fail exponentially with a median time to relapse of 0.3 years.

The hazard ratio to be detected is 0.437, corresponding to plateau regional relapse-free rates of 60% and 80% in the control and experimental arms, respectively.

Competing events (non-regional relapse and death without preceding relapse) occur exponentially at a rate of 0.45 per year.

A follow-up time of 1 year following end of accrual.

The above Kaplan-Meier regional relapse-free rates correspond with cumulative incidence rates approximately the same as those targeted in the initial sample size calculation (30% versus 15%).

For a power of 80% (and using a two-sided test at the 5% level of significance), 46 regional relapses are required to be observed. This can be achieved by accruing 210 patients, over 5.6 years. To allow for losses to follow-up and ineligible patients it is aimed to accrue 250 patients (over 6 years).

The above sample size will enable a difference of 15% in the 1-year failure-free survival rates (e.g. 35% versus 50%) to be detected with a probability (power) of 82%, or a 10% difference in overall survival rates (e.g., 75% vs 85%) with a power of 90%.

13.5 **Interim analyses and early closure criteria**

Accrual rates and acute radiotherapy toxicities will be assessed as part of routine interim annual reporting.

Formal interim analyses comparing regional relapse rates of the two arms will be performed after approximately half (23) of the expected total number of regional relapses have been reported in patients. Arms will be compared using the logrank test. Critical alpha levels used will be those determined by the O'Brien-Fleming alpha-spending function \( \Phi^{-1} \left( \frac{1}{2} - \Phi \left( z_{0.975} \sqrt{t} \right) \right) \), where \( \Phi \) is the cumulative normal distribution function and \( t \) is the number of regional relapses at interim analysis as a proportion of the total number expected for the trial.

Consideration will be given to stopping the trial early if any of the following occur:

- the comparison of regional relapse rates at interim analysis is significant at the alpha level specified.
- unacceptable radiotherapy acute toxicity.
- accrual is less than 30% of the expected number of patients in the first 24 months from launching the trial.
- a clearly more effective therapy becomes available.

### 14 ETHICAL CONSIDERATIONS

14.1 **Ethical principles**

This protocol has been designed to comply with TROG guidelines (incorporating both the Declaration of Helsinki and ICH Harmonized Tripartite Guidelines for Good Clinical Practice).

Each investigator is responsible for ensuring that this study is conducted in accordance with any applicable guidelines and the laws and regulations of the country in which the trial is performed to provide the greatest protection of the patient.
14.2 Informed consent
Before recruitment and enrolment into the study, each prospective candidate will be given a full explanation of the study. The informed consent form will be submitted for approval to the Ethics Committee of each participating institution.

Once this essential information has been provided to the subject and the investigators have been assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent to participate in the study. For subjects who cannot give informed consent (e.g., mentally incompetent, or physically incapacitated and unable to sign), a parent or legal guardian must give the informed consent; however, the subject’s consent should also be obtained if the subject is able to understand the nature, significance and extent of the risks associated with the clinical trial.

14.3 Institutional ethics committee
The Institutional Investigator must submit this protocol to the Institutional Ethics Committee and is required to forward a copy of the written approval or advice signed by the Chairman to the Trial Centre.

The date of the review, the trial identifiers (title, protocol number and version) and the documents studied (protocol and informed consent material) should be clearly stated on the approval or advice sheet.

14.4 Confidentiality
All patient information must be treated in strict confidence. Data, which identify any study subject, must not be revealed to anyone not directly involved in the research project or the clinical care of that subject.

An exception is where the patient has provided written consent for his/her records to be subject to source document verification. In this instance, the records may be inspected by (a) a representative of TROG and the ANZ MTG for the purposes of source document verification or quality audit as stipulated in the Guidelines for Good Clinical Research Practice, or (b) a representative of a government regulatory authority for the purposes of official inspection. Records must be made available for inspection on the understanding that all information relating to study subjects will be treated in strict professional confidence.

14.5 Adherence to protocol
Except for an emergency situation in which proper care for the protection, safety and well being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must be recorded and explained.

15 PUBLICATION AND PRESENTATION POLICY
The trial management committee will be responsible for decisions regarding presentations and publications arising from this study.

Authorship credit should be based on the Vancouver statement by the International Committee of Medical Journal Editors, i.e. substantial contribution to all three of the following criteria –

- conception and design OR analysis and interpretation.
- drafting article OR critically revising it for intellectual content.
- final approval of version to be published.

or, a fourth criterion is

- contributors who register 5% or more (accrual by institution) of the evaluable cases on a study will be listed as authors. The designated author is the choice of the institution’s principal
investigator and in most cases would be the investigator with the highest accrual. If an institution places a large number of cases on the study, that institution will get an additional author for every 10% of the patients accrued, not to exceed a total of three authors (i.e. two authors for \( \geq 15\% \) accrual and three authors for \( \geq 25\% \) accrual).

Acknowledgement of TROG and the ANZ Melanoma Trials Group is required in all publications, abstracts and presentations. Publications and abstracts must be presented to the Trial Management Committee for review and approved prior to submission.
16 REFERENCES


17 APPENDICES

Appendix 1: Prognostic Variables Predictive of Regional Relapse
(after lymphadenectomy for nodal metastatic melanoma)

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>% regional relapse</th>
<th>No. of patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Node Mets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELND +ve &amp; -ve histo, sentinel node +ve</td>
<td>5-10%</td>
<td>26-29</td>
<td></td>
</tr>
<tr>
<td>TLND +ve Histo by Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid / Neck Dissection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34%</td>
<td>150</td>
<td>O'Brien 30</td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>44</td>
<td>Byers 7</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>287</td>
<td>Singletary/Calabro 31,32</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>48</td>
<td>Monsour 33</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>15</td>
<td>Bowsher 34</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>56</td>
<td>Lee 35</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>168</td>
<td>Gibbs 36</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axilla Dissection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>438</td>
<td>Calabro 32</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>15</td>
<td>Monsour 33</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>24</td>
<td>Bowsher 34</td>
</tr>
<tr>
<td></td>
<td>28%</td>
<td>160</td>
<td>Lee 35</td>
</tr>
<tr>
<td>Groin Dissection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>276</td>
<td>Calabro 32</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td>25</td>
<td>Monsour 33</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>37</td>
<td>Bowsher 34</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td>122</td>
<td>Lee 35</td>
</tr>
<tr>
<td>All sites</td>
<td>18%</td>
<td>55</td>
<td>Miller 26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Positive Nodes</th>
<th>% Regional Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Node</td>
<td></td>
</tr>
<tr>
<td>1-2 to 3 nodes</td>
<td></td>
</tr>
<tr>
<td>16%</td>
<td>53%</td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>1-2 to 3 nodes</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>1-2 to 3 nodes</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt;4 or 4 to 10 Nodes</td>
<td></td>
</tr>
<tr>
<td>16%</td>
<td>53%</td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>&gt;10 Nodes</td>
<td></td>
</tr>
<tr>
<td>16%</td>
<td>53%</td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>&gt;10 Nodes</td>
<td></td>
</tr>
<tr>
<td>16%</td>
<td>53%</td>
</tr>
<tr>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>25%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Matted Nodes

<table>
<thead>
<tr>
<th>Extracapsular Extension</th>
<th>% Regional Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td>28%</td>
</tr>
<tr>
<td>23%</td>
<td>63%</td>
</tr>
<tr>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td>28%</td>
</tr>
<tr>
<td>23%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Size of Node

<table>
<thead>
<tr>
<th>Size of Node</th>
<th>% Regional Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-5cm</td>
<td></td>
</tr>
<tr>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>3-6cm</td>
<td></td>
</tr>
<tr>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>&gt;6cm</td>
<td></td>
</tr>
<tr>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>

Extent of Operation

<table>
<thead>
<tr>
<th>Extent of Operation</th>
<th>% Regional Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Neck Dissection</td>
<td>14%</td>
</tr>
<tr>
<td>Radical Neck Dissection</td>
<td>11%</td>
</tr>
<tr>
<td>Modified Neck Dissection</td>
<td>9%</td>
</tr>
<tr>
<td>Belli 21</td>
<td></td>
</tr>
</tbody>
</table>

No benefit has been shown (in neck, inguinal / ilioinguinal dissections) for radical versus conservative surgery impacting on node basin recurrence.7,21,22,26,50-52

* All relapse rates were reported as crude rates from studies with long accrual periods (10-30 years), with the exception of Lee 35 who reported actuarial rates at 10 years.
### Appendix 2: AJCC Staging for Melanoma: TNM Classification

*Journal of Clinical Oncology, August 15, 2001 Vol 19 No16: pp 3635-3648*

<table>
<thead>
<tr>
<th>T classification</th>
<th>Thickness</th>
<th>Ulceration Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>≤ 1.0 mm</td>
<td>a: without ulceration and level II/III</td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td>b: with ulceration or level IV/V</td>
</tr>
<tr>
<td>T2</td>
<td>1.01 – 2.0 mm</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td>b: with ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01 – 4.0 mm</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td>b: with ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.0 mm</td>
<td>a: with ulceration</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td>b: without ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N classification</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1 node</td>
<td>a: micrometastasis	extsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: macrometastasis	extsuperscript{b}</td>
</tr>
<tr>
<td>N2</td>
<td>2 – 3 nodes</td>
<td>a: micrometastasis	extsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: macrometastasis	extsuperscript{b}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: in transit met(s)/satellite(s) without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M classification</th>
<th>Site</th>
<th>Serum Lactate Dehydrogenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal LDH</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal LDH</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal LDH</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated LDH</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Micrometastases are diagnosed after sentinel or elective lymphadenectomy.  
\textsuperscript{b}Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.
### Appendix 3: WHO Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to do light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Appendix 4: FACT G – Functional Assessment of Cancer Therapy - general

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.** The information that you provide will remain strictly confidential.

Please fill in your initials:.............................................

Your birth date (day, month, year):............................

Today's date (day, month, year):...............................

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I am bothered by the side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL/FAMILY WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

Regarding your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.

14. I am satisfied with my sex life

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**EMOTIONAL WELL-BEING**

15. I feel sad

16. I am satisfied with how I am coping with my illness

17. I am losing hope in the fight against my illness

18. I feel nervous

19. I worry about dying

20. I worry that my condition will get worse

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**FUNCTIONAL WELL-BEING**

21. I am able to work (include work at home)

22. My work (include work at home) is fulfilling

23. I am able to enjoy life

24. I have accepted my illness

25. I am sleeping well

26. I am enjoying the things I usually do for fun

27. I am content with the quality of my life right now

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
The following questions are about any symptoms you may have that are associated only with the region where you first had lymph node surgery.

By circling either Yes or No, please indicate how true each statement has been for you during the past 7 days.

1. I have skin ulceration (scabbing, unhealed or broken skin) in the area of my lymph node surgery
   Yes  No

2. I have used dressings or bandages on the skin where I had my lymph node surgery
   Yes  No

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. My arm/ leg/ neck is swollen or tender</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Movement of my arm/ leg/ neck on the side of my operation is painful</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I have a poor range of arm/ leg/ neck movements on the side of my operation</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. My arm/ leg/ neck on the side of my operation feels numb</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I have stiffness of my arm/ leg/ neck on the side of my operation</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. The changes that have occurred in the area of my lymph node surgery have affected my daily living</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thank you for taking the time to answer these questions
Appendix 5: Surgical and Pathologic Techniques and Synoptic Pathology Report

SURGERY

Ideally all lymphadenectomy operative beds should be clipped to indicate the extent of the operation to the treating radiation oncologist (especially proximal margin).

Parotid/neck Dissection

Therapeutic superficial parotidectomy is indicated for involved nodes in the parotid bed. A comprehensive (classic radical or modified radical) neck dissection is usually required when macroscopic melanoma metastases are present in the neck. Where made possible by the location of the tumour, the spinal accessory nerve should be preserved to minimise morbidity. In certain circumstances, selective neck dissection may be appropriate as a therapeutic procedure. For example, in the setting of a primary on the face with an isolated nodal metastasis in the submandibular triangle, dissection of level V may be avoided. Similarly, in the setting of an isolated posterior triangle metastasis from a posterior scalp or lower neck primary, dissection of level I may be avoided, and in the setting of an isolated posterior triangle metastasis from an infraclavicular primary, both levels I and II may be left. Selective neck dissection may also be performed in a clinically negative neck in association with therapeutic superficial parotidectomy, with the extent of the neck dissection determined by the location of the primary.

The extent of neck dissections and their classification should be in accordance with the Neck Dissection Classification proposed by the American Head and Neck Society and the American Academy of Otolaryngology – Head and Neck Surgery.\(^60\)

This classification uses the well-established system of neck node ‘levels’ as follows:

Level I – submental and submandibular triangle nodes

Levels II to IV – upper, middle and lower jugular nodes respectively

Level V – posterior triangle nodes

Level VI – anterior compartment nodes

The anatomical boundaries of the neck levels are described in detail by Robbins et al\(^60\).

The different neck dissections are classified according to the extent of the nodal resection, and by the sacrifice or preservation of major non-lymphatic structures, with reference to the classical radical neck dissection. Neck dissection reports should clearly state details of the node levels removed and the major non-lymphatic structures sacrificed or preserved. Node fields outside the 6 levels should be separately described (e.g. occipital, postauricular, parotid).
Comprehensive neck dissection

Radical
Dissection of levels I to V, sacrificing sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve

Modified radical
Dissection of levels I to V, preserving one or more of SCM, IJV, or CN XI

Selective neck dissection
Each variation is depicted by “SND” and the use of parenthesis to denote the levels or sublevels removed

Extended neck dissection
Comprehensive or selective dissection, resecting additional non-lymphatic tissues not resected in a RND (e.g. skin, major carotid branches, hypoglossal nerve etc.)

The required minimum numbers of nodes removed from the neck region are as follows:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minimum Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial parotidectomy</td>
<td>2</td>
</tr>
<tr>
<td>Neck dissection</td>
<td></td>
</tr>
<tr>
<td>Comprehensive (levels I-V)</td>
<td>25</td>
</tr>
<tr>
<td>Selective</td>
<td></td>
</tr>
<tr>
<td>4 levels (e.g. SND (I-IV) or SND (II-V, ±postauricular/occipital)</td>
<td>20</td>
</tr>
<tr>
<td>3 levels (e.g. SND (I-III) or SND (III-V)</td>
<td>15</td>
</tr>
</tbody>
</table>

Axillary Dissection

A complete axillary lymph node dissection includes all three levels of axillary nodes. The superior border of dissection is along the axillary vein from the thoracic inlet (Halsted’s ligament) to the latissimus dorsi tendon. The medial border is the intercostal and serratus anterior muscles on the chest wall. The lateral border is the edge of the latissimus dorsi muscle, and the inferior border is the fourth intercostal space. The dissection should extend to the sub-scapular muscle. All fat and lymphatic tissue should be resected from the axilla and the long thoracic and thoracodorsal nerves should be preserved. The pectoralis minor muscle may be transected or removed if necessary to assure complete dissection of Level III nodes. The required minimum number of nodes to be assessed from the axillary region is 10.

Inguinal Dissection

A femoral lymph node dissection should be performed according to the standard technique. The borders of dissection should be: superiorly along the lower abdomen 5 cm above and parallel to the inguinal ligament, inferior to the femoral triangle, medially along the medial border of the adductor magnus muscle, and laterally to the sartorius muscle. The fatty tissue and lymphatic tissue overlying the femoral vessels and nerve are removed up to the inguinal ligament. The required minimum number of nodes to be assessed from the superficial inguinal region is 6.

Therapeutic deep groin dissection of iliac, hypogastric, and obturator nodes should be performed by entering the retroperitoneal space either through a separate incision through the abdominal musculature above and parallel to the inguinal ligament, or by transecting the inguinal ligament. The recommended minimum number of nodes to be assessed from the deep groin region is 4.

Presentation of Specimen to the Pathologist

Resection specimens should be oriented by the surgeon and pinned to cork or polystyrene blocks. The surgeon should indicate surgically critical margins and identify the general territories of node groups in neck dissection specimens by placing markers such as metal tags or sutures at the centre of each anatomical group. For whole neck dissection specimens, suspension of the tissue from a floating cork board is useful. Alternatively, neck dissection
specimens can be divided by the surgeon into the nodal groups prior to placement in separate specimen containers which have been appropriately labelled. Fixation is in a formaldehyde-based solution for 24 to 48 hours in a container of adequate size (the volume of the fixative should be ten times that of the tissue).

Surgical margins should be painted with Indian ink or an appropriate dye to facilitate the later recording of proximity of tumour to the margin.

The surgeon should indicate to the pathologist whether he or she has noted:

(i) the presence of malignant matted nodes,
(ii) visible macroscopic tumour outside nodes or
(iii) close margins, e.g. tumour adherence to major vessels or nerves, involved nodes at the apex of the axilla or proximal inguinal dissection.

**Harvested Node Count**

A surgical operation report is essential to confirm that standard procedure has been followed and an adequate lymphadenectomy has been performed.

The total minimum number of nodes removed can refer to the sum of nodes removed at an initial biopsy or sampling followed by a complete node dissection (must be performed within an eight week period - see Eligibility criteria on 5.1.1).

The number of harvested nodes can vary widely, but serves as an objective guide. When the total node number is unexpectedly low, immediate discussion with the participating pathologist is advised to check the accuracy of the node count or to re-examine the surgical specimen to search for further nodes.

**Surgical Quality Assurance**

This will comprise:

Collection of copies of lymphadenectomy surgical reports, and the histopathology report of lymphadenectomy.

Adherence to pathology criteria and randomization and stratification check.

Review audit by the surgical component of the Trial Management Committee twice yearly.

**PATHOLOGY**

**Pathological Aspects for the Pathologist**

(a) Specimen handling including fixation, dissection, block selection, processing and staining should be performed in the normal routine fashion.

(b) Unless it is regarded as not indicated, specimens should be orientated and pinned out on a cork board or similar for fixation and ease of dissection.

(c) Where indicated, surgical margins should be painted with Indian ink, or a suitable dye or silver nitrate, to facilitate the recording of the proximity of the carcinoma to the margin.

(d) Harvest of lymph nodes from specimens should follow routine practice. Each discrete node should be dissected out with its attached pericapsular adipose tissue. Larger nodes should be bisected or sliced. If there is obvious metastatic tumour, the half slice with the more extensive tumour should be processed, together with the perinodal tissues, to show the extent of extracapsular spread. If the node appears negative, all slices should be processed. Small flat nodes should be processed whole, and several nodes (from the same anatomical level) can be processed in the same cassette.

(e) Harvest of lymph nodes from radical neck dissections should follow standard practice with reference to the described major anatomical groups of lymph nodes. Six major anatomical groups of lymph nodes are described.
• Level I: nodes of the submandibular and submental triangles.

• Levels II, III and IV: nodes of the upper, middle, and lower jugular chain. These nodes lie deep to the upper, middle and lower thirds of the sternocleidomastoid muscle, respectively. The point at which the omohyoid muscle crosses deep to the sternocleidomastoid muscle is a useful landmark for separating levels III and IV. Level IV extends from the omohyoid muscle to the clavicle.

• Level V: nodes of the posterior triangle, behind the posterior border of the sternocleidomastoid muscle.

• Level VI: nodes of the anterior compartment, around the midline viscera.

Pathology Definitions

Extraneodal spread (ENS) is defined as unequivocal involvement by tumour of extranodal connective tissues. This spread encompasses nodal-based transcapsular invasion into surrounding adipose connective tissues, non-nodal-based metastatic involvement of adipose connective tissues, and lymphovascular space invasion.

Lymphovascular space invasion (LVSI) is defined as the presence of tumour within an endothelial-lined space, as assessed by the pathologist at microscopy.

Extensive extranodal spread is defined as the presence of one or both of the following:

a) as noted by surgeon or pathologist, matted lymph nodes forming a significant mass accepted as evidence of gross extranodal tumour on macroscopic examination.

b) as noted by the pathologist at microscopy, defined as the presence of any one or more of:

(i) multiple node extracapsular spread;

(ii) multiple deposits of LVSI;

(iii) multiple deposits of tumour in fat or connective tissue unrelated to nodes or vessels and

(iv) two or more of the following: a single node with extracapsular extension; a single instance of LVSI; a single instance of tumour present in fat or connective tissue unrelated to nodes or vessels.

Pathology Report of Lymphadenectomy

This should indicate, for any region:

- a histological diagnosis of metastatic malignant melanoma (including positive S100 immunohistochemical staining),

- a macroscopic description of tumour identified within the lymphadenectomy specimen,

- total number of nodes sampled,

- total number of positive nodes,

- presence or absence of extranodal spread, and if present whether limited or extensive,

- presence or absence of limited or extensive LVSI,

- maximum diameter of the largest metastatic lymph node in the dissection.

- completeness or quantitative closeness of the surgical excision (ideally in consultation with the surgeon).

Pathology Quality Assurance

All participating Australian and New Zealand pathology laboratories will require NATA and IANZ accreditation, respectively.
## Synoptic Pathology Report

<table>
<thead>
<tr>
<th></th>
<th>Number of nodes harvested</th>
<th>Number of nodes containing metastatic melanoma</th>
<th>Maximum dimension of largest node in cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid/neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial parotidectomy Y / N</td>
<td>Parotid ≥2</td>
<td>Parotid</td>
<td>□</td>
</tr>
<tr>
<td>Neck dissection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical</td>
<td>I</td>
<td>I</td>
<td>□</td>
</tr>
<tr>
<td>Modified radical</td>
<td>II</td>
<td>II</td>
<td>□</td>
</tr>
<tr>
<td>Selective</td>
<td>III</td>
<td>III</td>
<td>□</td>
</tr>
<tr>
<td>Occipital / Postauricular</td>
<td>IV</td>
<td>IV</td>
<td>□</td>
</tr>
<tr>
<td>Other</td>
<td>V</td>
<td>V</td>
<td>□</td>
</tr>
<tr>
<td>Extended Y / N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structures taken</td>
<td>Other</td>
<td>Other</td>
<td>□</td>
</tr>
</tbody>
</table>
Appendix 6: Parotid/Neck Radiotherapy

48 Gy to a reference point as per ICRU 50 in 20 fractions at 5 fractions per week, maximum overall treatment time of 30 days. CT planning is preferred. Dose at any point (including the junctional dose) should not exceed 55 Gy.

A pre treatment dental assessment and dental treatment should be done in all patients.

Recommended treatment volume is to encompass the ipsilateral

- parotid bed
- level I, II, III, IV and V neck nodes
- lymphadenectomy surgical scars (and primary site when included) to tumour dose on skin

Primary site may also be considered for inclusion in the treatment volume if primary site is:

- Stage III
- excised < 1 year before nodal recurrence
- abutting or overlying RT node fields

In the unusual case of supraclavicular fossa nodal involvement alone from upper trunk primary or unknown primary, the supraclavicular fossa nodal basin alone is to be treated with a 5 cm margin (proximally into ipsilateral neck and distally into adjacent proximal axilla) on operative bed.

Isodoses should be generated (for both CT and non-CT planning) at the level of

- central axis (middle of field)
- orbit
- temporo-mandibular joint (TMJ)
- mid-point of the angle of mandible
- mid-point of cricoid cartilage
- supraclavicular fossa (ie. 2cm above the superior aspect of the medial head of the clavicle)
- 3cm above the Inferior field border
- 3cm below the Superior field border

Dose constraints:

Maximum dose variation in the clinically determined PTV should be between 90% and 105% of the reference dose (ie. between 43.2 Gy and 50.4 Gy). Doses outside the PTV should not exceed 52.5Gy (where isodose >2cm²) and dose at any point should be \( \leq 55 \text{Gy} \).

Maximum dose to normal tissue:

- Brain dose 40 Gy
- Spinal cord 40 Gy
- Mandible 45 Gy
- Larynx 45 Gy
- Maximal dose at any point \( \leq 55 \text{Gy} \)

SAMPLE TECHNIQUES

a) Appositional electron field(s) - usually 9 or 12 MeV - with head rotated to fully expose neck and flatten contour from zygoma to clavicle

b) Personalized head & neck rest (polyurethane setting foam)

c) Fill external ear canal with water

d) CT planning in treatment position with 1 cm slices

e) Outline field marked on skin with radio-opaque plastic “wire” during CT.

f) Crafted bolus to attenuate dose at depth where required, for (i) variation in contour and (ii) dose reduction to spinal cord, brain and larynx.

g) If 2 or 3 junctional electron fields are used to vary energy of electron beam, for ≥1 cm junction movement for half treatment course.

Technique 1 has advantages of treating node basins while avoiding contralateral salivary glands, majority of oral cavity, oropharynx and often larynx (need extra care to add correct thickness of crafted wax buildup overlying larynx and beyond profile of larynx), while delivering near TD to skin.

**Technique 2.** As per standard H&N techniques

a) Multiple 6MV photon fields ± junctional electron fields when required.

b) Cast immobilization.

c) Add full build-up to all surgical scars and any encompassed primary site.

d) CT plan.

Maximum spinal cord dose not to exceed 40 Gy in 2 Gy fractions

**SAMPLE CASE STUDY - Technique 1.**
Parotid/Neck Radiotherapy – continued

Isodosing – 12 MeV electrons

Isodosing: 100%, 90%, 70%, 50%, 20% (refer to colour scale)

Level of orbit

Crafted bolus

Level of larynx

SCF region
Appendix 7: Axilla/Supraclavicular Radiotherapy

48 Gy to a reference point dose as per ICRU 50 in 20 fractions at 5 fractions per week, maximum overall treatment time of 30 days. CT planning is preferred. Dose at any point (including the junctional dose) should not exceed 55 Gy.

- when using mono-isocentric techniques the reference point should reflect a clinically relevant site within the PTV and (as per ICRU 50) should not be at a site of steep dose gradient
- a PTV should be marked on the planning CT

Recommended treatment volume to encompass ipsilateral:
- Axillary nodes Levels I, II and III.
- Supraclavicular fossa in continuity (5 cm margin on proximal operative clip.)
- Skin dose to surgical scars and any encompassed primary site.

Field limits on surface anatomy

Upper level profile of medial trapezius muscle.
Lower level 8th or 9th rib on chest wall.
Lateral edge junction of proximal 1/3rd and distal 2/3rds of humerus.
Medial edge 1 to 2 cm ipsilateral to midline. If clinical situation demands coverage to midline, then maximum spinal cord dose is to be less than 40 Gy.

Isodoses should be generated (for both CT/non CT planning techniques) at the level of:
- central axis (middle of field)
- mid point of the clavicle (brachial plexus dose estimate)
- 3cm below the Superior field border
- 3cm above the Inferior field border

Dose constraints:

Maximum dose variation in the clinically determined PTV should be between 90% and 105% of the reference dose (ie. between 43.2 Gy and 50.4 Gy). Doses outside the PTV should not exceed 52.5Gy (where isodose >2cm²) and dose at any point should be <55Gy.

Maximum dose to normal tissue:
- Brachial Plexus 45Gy
- Spinal cord 40Gy (generally exclude spinal cord from field)
- Maximal dose at any point ≤55 Gy

SAMPLE TECHNIQUE

**Technique 1**

1a) Patient to lie supine with arm abducted 20 to 45 degrees. Hand near side and arm position secured by personalized polyurethane foam support.

1b) Parallel opposed anterior and posterior axilla/SCF fields of MVT photons, ideally 6MV anteriorly and 18MV posteriorly.
1c) Shielding to lung, deltoid, superior shoulder joint, larynx and spinal cord (spinal cord dose not to exceed 40 Gy in 2 Gy fractions or equivalent dose reduction for higher fraction size).

1d) 1 to 1.5 cm buildup on scars and any encompassed primary site.

1e) Simulation and CT contour planning.

1f) PTV dose maximum 48 Gy with brachial plexus receiving 45 Gy.

Axilla/Supraclavicular Radiotherapy - continued

Isodosing - Central Axis. (6 MV photons ant. 18 MV photons post.)
Isodosing – Upper Level (6 MV ant. 18 MV post.)
Appendix 8: Inguinal/Iliac Radiotherapy

48 Gy to a reference point as per ICRU 50 in 20 fractions at 5 fractions per week, maximum overall treatment time of 30 days. CT planning is preferred. CT planning is preferred. Dose at any point (including the junctional dose) should not exceed 55 Gy.

Recommended treatment volume to encompass ipsilateral:

- femoral and inguinal and ext. iliac nodes (or 5 cm margin on cephalic clipped surgical bed).
- surgical scars with full skin dose using buildup.

Primary site (+3cm normal tissue margin) may also be considered for inclusion in the treatment volume if primary site is:

- within 5 cm of defined field limits
- excised at or within a year of nodal metastases, and
- ideally treated with a junctional electron box

Fields limits on anatomical boundaries

Upper level: inferior sacro-iliac joint (true pelvic brim) (or 5 cm margin cephalic margin on clipped operative bed).

Lower level: junction proximal ¼ to distal ¾ femoral shaft or to cover inferior extent of surgical scar with minimum 2 cm margin.

Medial edge: midline or 1 cm ipsilateral to midline (to cover medial groin).

Lateral edge: minimally anterior superior iliac spine and maximally inside lateral body profile (pending leg position).

Isodoses should be generated (for both CT/non CT planning techniques) at the level of:

- central axis (middle of field)
- mid-point of Femoral Neck
- inferior aspect of Sacro-Iliac Joint
- 3cm below the Superior field border
- 3cm above the Inferior field border

Dose constraints:

Maximum dose variation in the clinically determined PTV should be between 90% and 105% of the reference dose (ie. between 43.2 Gy and 50.4 Gy). Doses outside the PTV should not exceed 52.5Gy (where isodose >2cm²) and dose at any point should be < 55 Gy.

Maximum dose to normal tissue:

- Bowel - small volume or reduced field volume 45 Gy
- Bowel – large volume 35Gy (maximum bowel volume 1000 cm³)
- Femoral neck 40 Gy
- Maximal dose at any point ≤55 Gy

Technique 1

1a) 3 field technique anterior, posterior and lateral fields with CT planning using MV photons.
1b) 1 to 1.5 cm buildup on scars.
1c) CT planning with serial volume marking required.
Technique 2

2a) Using MV photons anterior field covering whole volume. Posterior field on superior (pelvic) portion of volume with lower level at inguinal ligament, being central axis of posterior field (1/2 beam block or independent diaphragm).

2b) Anterior portion of field opposite posterior field to be attenuated such that prescription is: 45 Gy midplane dose where anterior and posterior parallel opposed fields. 48 Gy peak dose where anterior field only.

2c) 1 to 1.5 cm building on scars.

Hip abduction is helpful for:
- flexible, co-operative patients.
- for reducing skin fold on medial groin crease and thus intensity of skin reaction.
- allowing effective shielding of perineum and anus whilst not compromising groin coverage.
- allowing rotation of long axis of fields to follow lymphatic pathway and reduce femoral neck dose with technique 2.
  - too much hip abduction can be unstable and should be stabilized with bilateral personalized thigh, knee and lower leg support to ensure reproducible knee separation while still allowing comfortable passage through the CT aperture.

SAMPLE CASE for Techniques 1 and 2

Patient positioning

Hip abduction
Inguinal/Iliac Radiotherapy (cont’d)

3 field technique – field placement

2 field technique – field placement
3 field technique – isodosing (6MV photons. Viewed from the medial aspect.)

1 field technique – isodosing (Ant. Beam partially attenuated, 6 MV photons)
## Appendix 9: Surgical and Radiotherapy Morbidity Scoring System

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>None</td>
</tr>
<tr>
<td>early surgical – all sites</td>
<td></td>
</tr>
<tr>
<td>Wound necrosis/healing</td>
<td>Normal healing</td>
</tr>
<tr>
<td>early surgical – all sites</td>
<td></td>
</tr>
<tr>
<td>Seroma</td>
<td>None</td>
</tr>
<tr>
<td>early surgical – all sites</td>
<td></td>
</tr>
<tr>
<td>Nerve damage</td>
<td>None</td>
</tr>
<tr>
<td>early and late surgical and late RT – all sites</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>None</td>
</tr>
<tr>
<td>surgical and RT - early and late – all sites</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Event</strong></td>
<td><strong>GRADE</strong></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Subcutaneous tissue</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>early and late surgical and late RT – all sites</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Joint</strong></td>
<td></td>
</tr>
<tr>
<td><strong>early and late surgical and late RT – all sites</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Acute radiation dermatitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>early RT – all sites</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Acute mucositis due to radiation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>early RT – parotid/neck</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Mouth dryness</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>early RT – parotid/neck</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Salivary gland changes</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Adverse Event</strong></td>
<td><strong>GRADE</strong></td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Inner ear/hearing</strong>&lt;br&gt;early and late RT – parotid/neck</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Middle ear/hearing</strong>&lt;br&gt;early and late RT – parotid/neck</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Skin</strong>&lt;br&gt;late RT - all sites</td>
<td>No change from baseline</td>
</tr>
<tr>
<td><strong>Bone</strong>&lt;br&gt;late RT- all sites</td>
<td>No change from baseline</td>
</tr>
<tr>
<td><strong>Mucous membrane</strong>&lt;br&gt;late RT - parotid/neck</td>
<td>No change from baseline</td>
</tr>
<tr>
<td><strong>Salivary glands</strong>&lt;br&gt;late RT - parotid/neck</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>GRADE</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>late RT - parotid/neck/axilla</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>Lung</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>late RT - axilla</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>Small/large intestine</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>early/late RT - groin</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>Brain</td>
<td>No change from baseline</td>
</tr>
<tr>
<td>late RT – head and neck</td>
<td>No change from baseline</td>
</tr>
</tbody>
</table>

Appendix 10: Measurement of Lymphoedema in a Limb

The method of quantifying limb lymphoedema in patients treated for nodal melanoma in the axilla or groin in this study will be based on a calculation of limb volume using serial circumferential measurements at 10 cm intervals and adding the volumes of truncated cones.

**Technique for limb circumference measurement**

An Australian standard for the measurement of limb circumference was recently adopted at a meeting of the Australian Lymphology Association (N Piller, April 2000).

For both arm and leg measurement a narrow tape should be used and marks made every 10 cm along the limb on the proximal side of the tape. No indent mark should appear on the skin.

Circumference measurements are conducted on both the treated and unaffected limb to allow for calculation and comparison of limb volumes.

**Body mass index (BMI)**

The patient’s weight in kilograms and height in metres should be documented pre-intervention and at six monthly intervals to allow calculation of BMI \[\text{Weight}/(\text{Height})^2\]. This is important as it may effect limb assessment.

**Axilla patients – upper limb measurement**

The patient may be lying or sitting with the arm out straight. Use the tip of the middle finger as a starting point and mark the limb every 10 cm at six points, that is at 10, 20, 30, 40, 50, 60 cm from the tip of the middle finger. Then make a circumferential measurement at right angles to the limb at each of these six marks. These measurements will be recorded on the case record form as C1, C2, C3, C4, C5 and C6. Record all measurements in millimetres. This will result in five segments for each arm (from C1 to C6 inclusive). Diagrams are included on the Case Record Forms to assist in the documentation of lymphoedema.

**Groin patients – lower limb measurement**

Ideally the patient should be lying and rested. Use the sole of the foot as a starting point (this may be placed up against the end of a measuring board with the bottom of the sole firmly against it). Mark the limb, on its anterior surface, every 10 cm at seven points, that is at 10, 20, 30, 40, 50, 60 and 70 cm from the base of the heel. Then make a circumferential measurement at right angles to the limb at each of these seven marks. These measurements will be recorded on the case record form as C1, C2, C3, C4, C5, C6 and C7. Record all measurements in millimetres. This will result in six segments for each leg (from C1 to C7 inclusive). Diagrams are included on the Case Record Forms to assist in the documentation of lymphoedema.

**Assessment of upper and lower limb volume**

The method to calculate limb volume in this study is based on the above measurements of hand and arm or leg circumference (in millimetres) taken at 10 cm intervals from the tip of the middle finger up the arm or from the sole of the foot up the leg. Note: the 0 to C1 component is excluded from the volume calculation.

The volume of each segment is estimated by the formula for the volume of a truncated cone, e.g. the volume for the first segment from C1 to C2,

$$V_1 = \frac{h \left( C_1^2 + C_1 \times C_2 + C_2^2 \right)}{12 \pi}, \text{ where } h = 100 \text{ mm}$$

The volume of each arm and leg will be estimated by summing the five and six truncated cones, respectively.