Post-operative concurrent chemo-radiotherapy versus post-operative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck

Post-Operative Skin Trial (POST study)

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FOREWORD

This document is intended to describe a Trans-Tasman Radiation Oncology Group (TROG) 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 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 Central Operations Office, Newcastle, to confirm the details of the protocol in their possession.
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1. SUMMARY OF TRIAL

Design: This is a two-armed randomised trial in post-operative patients with high-risk cutaneous SCC of the head and neck (above the clavicles).

Main objective: To determine, in patients who have undergone surgery with curative intent for high-risk CSCC of the head and neck, whether there is a difference in time to loco-regional relapse between patients treated with post-operative concurrent chemo-radiotherapy and post-operative radiotherapy alone.

Patient selection: The main eligibility criterion is that patients are post-operative, have a high-risk feature and suitable for weekly carboplatin and 6 weeks of radiotherapy. Patients must have undergone complete resection of all visible, palpable and imageable gross disease, with or without microscopic positive margins.

High-risk features are defined as either High-Risk Nodal Disease or Advanced Primary disease:

**High Risk Nodal Disease**
- Intra-parotid nodal disease (any number or size, with/without extracapsular extension, with/without an identifiable index lesion)
- Cervical nodal disease with a synchronous or previously (≤ 2 years) resected index lesion within the corresponding nodal drainage basin and exclusion of a mucosal primary with at least a CT+/- MRI and panendoscopy*

* For cervical nodal disease to be eligible there must be at least one of the following criteria:
  - ≥ 2 nodes
  - largest node ≥ 3cm
  - Extracapsular extension

**Advanced Primary Disease** (TNM 6th Edition 2002) (Appendix 1)
- T3-4 primary disease (cartilage, skeletal, muscle, bone involvement, >4cm) of the head and neck including lip, nose and external auditory canal with or without nodal disease
- In transit metastases (metastases between the primary site and the adjoining nodal basin)

Randomisation and stratification: Patients will be randomised between the two arms, radiotherapy and chemo-radiotherapy. Allocation to treatment will be balanced according to high-risk nodal disease and advanced primary disease, and institution. If both high risk nodal and primary disease features are present the patient will be stratified according to the nodal disease.

Treatment: Patients will receive 60Gy or 66Gy in 2Gy/fraction 5 days/week with or without weekly intravenous carboplatin (AUC 2).

Follow-up schedule: Patients will be followed up weekly during treatment, 4, 8 and 12 weeks, and then 6,9,12,16,20,24 months from the completion of treatment and then an optional 6 monthly thereafter up to five years.
2. STUDY SCHEMA

Eligible patients
Cutaneous SCC of the head and neck (above clavicles)
Definitive surgery with removal of all macroscopic (gross) disease*

High risk feature

Stratify
High Risk Nodal Disease
Vs.
Advanced Primary Disease
and
Institution

Randomise

Radiotherapy alone
60Gy or 66Gy in 30-33 fractions 5-5/week

Radiotherapy 60Gy or 66Gy in 30-33 fractions 5/week
Carboplatin (AUC 2) intravenously weekly

* Resection of all palpable, visible and/or imageable disease, with or without microscopic residual disease

Note: Patients with residual positive microscopic disease are eligible
3. INTRODUCTION

Two in every 3 Australians will develop a skin cancer. The prevalence of skin cancer continues to increase due to the ageing population and represents a significant problem in our community. Cure of early (T1-2) de novo CSCC treated with either curative intent surgery or radiotherapy is 85-100%. (1) However, cure rates for locally advanced, recurrent, or metastatic disease to regional nodes following surgery alone are much lower, in the order of 20-70%, depending on the clinico-pathological features. (2,3)

Predictors of loco-regional recurrence in CSCC include T stage, local/satellite recurrence, incomplete excision, perineural invasion (PNI), dermal lymphatic spread and poorly differentiated tumours. The presence of these risk factors increases the likelihood of nodal spread and adversely affects survival outcome. Regional node metastasis to intra-parotid and/or cervical lymph nodes is a significant adverse feature, particularly in the presence of multiple involved nodes, large nodes (> 3cm) and extracapsular extension (ECE). (1,2,5)

Metastatic CSCC is the most common malignancy of the parotid region in Australia. (1,6,7) The 5-year loco-regional control (LRC) with surgery alone is in the order of 40%-45%. The addition of post-operative radiotherapy improves loco-regional control by 15-20%, and is therefore considered the standard of care in this group of patients. (1,6,8)

Recent data have shown that synchronous post-operative chemo-radiotherapy is superior to post-operative radiotherapy alone in “high-risk” mucosal head and neck squamous cell carcinoma (HNSCC). (9,10,11) However, to date, there is no evidence from randomised trials that such a benefit exists in CSCC of the head and neck.

At present there is little consensus amongst clinicians in Australia as to who should receive post-operative chemo-radiotherapy in CSCC. Although tumour control rates may be improved, the addition of chemotherapy may also significantly increase treatment related toxicity. Nonetheless, some centres have adopted the use of post-operative chemo-radiotherapy in selected patients with CSCC based on extrapolation from mucosal sites. This has resulted in a wide variability in practice for this disease.

High-Risk Cutaneous SCC

Defining a “high-risk” group is difficult due to a lack of good quality prospective data. The definition we have used is therefore based on retrospective series and extrapolation from prospective results in mucosal HNSCC.

Based on the available data, for the purpose of this trial “high-risk” CSCC has been divided into 2 broad categories: metastatic nodal disease and/or advanced primary disease.

Metastatic Nodal Disease

Prospective data from mucosal HNSCC has demonstrated that the presence of ECE, ≥2 involved cervical nodes and/or ≥3 cm node are high-risk features. (2, 5)

For CSCC, there is evidence that intra-parotid nodal metastases, regardless of number or size, result in a higher risk of regional recurrence, even after post-operative radiotherapy. (12) The presence of any of these features has been defined as “high-risk”.

Advanced Primary Disease

Increasing tumour size is a well-recognised adverse factor. Patients with T3-4 disease are more likely to have involvement of underlying bone, cartilage and muscle. These patients may benefit from the addition of synchronous chemotherapy to radiotherapy and have therefore been included as high-risk.

Microscopic positive margins, as an isolated risk factor in the absence of any other adverse risk factor has not been considered an eligibility criterion for enrolment onto the study as these patients may do well with radiotherapy alone, particularly for T1-2 lesions. Patients who have a positive margin due to extensive disease and invasion into underlying structures will have other adverse features making them “high-risk”.

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Perineural infiltration (PNI) is a well-recognised adverse factor for increased local recurrence and nodal metastases. (13,14) PNI can range from minor to extensive. Most patients with minor PNI are likely to do well with radiotherapy alone, while patients with extensive PNI may benefit from post-operative chemo-radiotherapy. However, there is no universal method of quantifying minor versus extensive PNI. Due to the difficulty in determining a universal objective consensus of what constitutes extensive PNI, this has not been included as a “high-risk” defining feature.

**Benefit of concurrent chemotherapy to radiotherapy**

The addition of concurrent platinum to radiation has been demonstrated to improve outcomes in a number of malignancies and is widely used in clinical practice. In particular, in mucosal HNSCC the addition of concurrent chemotherapy to radiotherapy in both unresected locally advanced disease, and post-operatively, improves LRC by approximately 15%. (9,10,11,15,16,17,18) In a recent update of a meta-analysis published by Pignon et al in the Lancet (2000), Bourhis et al reported the absolute survival benefit of the addition of chemotherapy to radiotherapy for both unresected and post-operative head and neck SCC was 8% at 5 years. (18) A secondary aim of the current study is to determine whether the addition of chemotherapy confers a similar benefit in “high-risk” CSCC.

The experience with post-operative concurrent chemo-radiotherapy in high-risk mucosal HNSCC is probably of most relevance to our proposal to test chemoradiation in postoperative CSCC. Two large trials addressing the role of post-operative concurrent chemo-radiotherapy in high-risk mucosal HNSCC have been published. (10,11) The RTOG 9501/Intergroup trial demonstrated significant improvement in LRC and disease free survival but only a non-significant improvement in OS. (10) The EORTC performed a similar study, with slightly different eligibility criteria, demonstrating a significant improvement, of 10-15%, in LRC, progression free survival and OS in the chemo-radiation arm. (11)

**Choice of chemotherapy**

There is limited data on the use of chemotherapy for cutaneous SCC. There are small series demonstrating activity with the use of neoadjuvant platinum-based chemotherapy. (19,20) The majority of studies demonstrating superiority of concurrent chemo-radiotherapy in mucosal HNSCC have used cisplatin. However, the majority of patients eligible for this study will be elderly and many will have co-existing medical co-morbidities that may preclude the use of cisplatin e.g., hearing impairment, renal impairment, cardiac disease and neuropathy. Hence, we have elected to use carboplatin given once weekly during radiotherapy in the experimental arm. Carboplatin is generally much better tolerated than cisplatin, and can be given safely to many patients who have significant contraindications to cisplatin. The choice of doses and scheduling of platinum when combined with radiation has been largely empirical, but benefit has been seen with schedules ranging from low dose daily to high doses at 3-4 week intervals. With carboplatin, higher doses given 3-4 weekly may be associated with more myelosuppression and delayed recovery of neutrophil and platelet counts, while a weekly schedule using a dose targeting an AUC of 2 has been found to be well tolerated. (21) Synchronous carboplatin and radiotherapy has been used effectively and safely in several head and neck trials. (22, 23, 24) The 94-01 French Head and Neck Oncology and Radiotherapy Group demonstrated improved OS and LRC with concurrent carboplatin/5FU and radiotherapy compared with radiotherapy alone without a significant increase in late morbidity. (23) A randomized phase II trial of chemoradiotherapy using either weekly Carboplatin (100 mg/m²) or daily cisplatin (4 mg/m²) for the initial 4 weeks of radiotherapy demonstrated a significant difference in the 5-year LRC in favour of the carboplatin arm. Haematologic
toxicity was more frequent in the carboplatin-treated arm but there was no difference in radiation-related adverse effects. (24)

We have reported on the use of post-operative radiotherapy and concurrent weekly cisplatin (40mg/m²), or carboplatin (AUC 2) for patients ineligible for cisplatin, in high-risk mucosal HNSCC. Forty-three percent were unfit for cisplatin. Treatment with either chemotherapy type was well tolerated, 96% completed at least 4 of the 6 planned doses of chemotherapy. Toxicity was acceptable with no treatment related deaths. This was a retrospective single institution study with limited numbers, but LRC was comparable to the EORTC and RTOG studies and there was no apparent difference in outcome between the 2 chemotherapy agents. (22)

Dose of radiation therapy
This study is assessing the role of radiotherapy (+/- chemotherapy) in the adjuvant setting. Patients must have undergone complete macroscopic resection (resection of all visible, palpable and/or imageable disease with or without microscopic positive margins).

A choice of 60Gy or 66Gy, conventionally fractionated has therefore been chosen for this study. The trial centre will need to select the total dose, ie, 60Gy or 66Gy prior to randomisation to minimise bias. This range of dose is considered sufficient even in the setting of positive microscopic margins. (5)

4. OBJECTIVES

The primary objective of the trial is:

To determine, in patients who have undergone surgery with curative intent for high-risk CSCC of the head and neck, whether there is a difference in time to loco-regional relapse between patients treated with post-operative concurrent chemo-radiotherapy and post-operative radiotherapy alone.

Secondary objectives are:

1. To compare disease-free survival time
2. To compare overall survival time
3. Compare quality of life - Head and Neck FACT (Appendix 2)
4. Compare acute and late effects of radiotherapy and chemotherapy – Common Terminology Criteria for adverse events Version 3.0 (Appendix 3)

5. PATIENT SELECTION

This study plans to enrol 350 patients.

5.1 Inclusion Criteria

5.1.1 Histologically proven SCC

5.1.2 Complete macroscopic resection of all known disease with or without microscopic positive margins. Surgery may consist of one or more of the following:

- Resection of the primary lesion
- Any type of parotidectomy (superficial, total, partial, etc.)
- Any type of neck dissection(s)
5.1.3 High risk feature(s); High Risk Nodal disease and/or Advanced Primary disease

**High Risk Nodal Disease**
- Intra-parotid nodal disease (any number or size, with/without extracapsular extension, with/without an identifiable index lesion)
- Cervical nodal disease with a synchronous index lesion or previously resected cutaneous primary tumour (<5 years) within the corresponding nodal drainage and a mucosal primary has been excluded with at least a CT +/- MRI and panendoscopy*

* For cervical nodal disease to be eligible there must be at least one of the following criteria:
  - ≥ 2 nodes
  - largest node ≥ 3cm
  - Extracapsular extension

**Advanced Primary Disease** (TNM 6th Edition 2002) (Appendix 1)
- T3-4 primary disease (cartilage, skeletal, muscle, bone involvement, >4cm) of the head and neck including lip, nose and external auditory canal with or without nodal disease
- In transit metastases (metastases between the primary site and the adjoining nodal basin)

5.1.4 Age ≥ 18 years
5.1.5 Written informed consent
5.1.6 ECOG ≤ 2 (Appendix 4)
5.1.7 Absolute neutrophil count ≥ 1.5 X 10^9/L, platelet count ≥ 100 X 10^9/L, and haemoglobin ≥ 10g/dL (pre-radiotherapy blood transfusion to elevate the haemoglobin ≥ 10g/dL is permissible)
5.1.8 Calculated creatinine clearance (Cockcroft-Gault) ≥ 40mL/min (Appendix 5)
5.1.9 Available for follow-up for up to 5 years
5.1.10 Life expectancy greater than 6 months

5.2 **Exclusion criteria**

5.2.1 Intercurrent illness that will interfere with either the chemotherapy or radiotherapy such as immunosuppression due to medication or medical condition
5.2.2 Metastasis(es) below the clavicles
5.2.3 Previous radical radiotherapy to the head and neck, excluding treatment of an early glottic cancer ≥ 2 years ago and superficial radiotherapy to cutaneous SCC or basal cell carcinoma
5.2.4 High risk for poor compliance with therapy or follow-up as assessed by investigator
5.2.5 Pregnant or lactating women
5.2.6 Patients with prior cancers, except: those diagnosed ≥ 5 years ago with no evidence of disease recurrence and clinical expectation of recurrence of less than 5%; or
5.2.7 Low risk cervical nodal disease* without advanced primary disease

*Low risk cervical nodal disease is defined as the presence of all of the following criteria;
- single nodal metastasis,
- ≤ 3 cm,
- no extracapsular extension.

6. REGISTRATION AND RANDOMISATION

6.1 Registration

To randomise a patient, check the eligibility criteria have been satisfied, complete the registration form and telephone the Coordinating Trial Centre on +61 (0)7 3176 5054 and ask for the POST Trial Centre Coordinator.

Eligible patients will be randomised to either radiation alone or concurrent chemoradiotherapy. 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.

6.2 Randomisation and stratification

Patients will be randomised to a treatment arm while maintaining balance with respect to each of the following:
- High risk nodal metastases vs. advanced primary disease
- Institution

Randomisation will be achieved using a permuted block design, stratified by institution and disease category described above. Central telephone randomisation will be used to maintain adequate allocation concealment.

6.3 Recurrence following randomisation and pre-radio(chemo)therapy

In the event a patient develops loco-regional failure following randomisation and prior to radio(chemo)therapy commencing if possible, patients should undergo salvage surgery. If surgery achieves complete macroscopic resection then patients should be treated as per allocated treatment arm. If following surgery there is macroscopic residual disease or patient does not undergo salvage surgery then treat as per investigators choice.

Treatment and subsequent management of these patients will be recorded for the purposes of this trial and all analyses will be based on intention-to-treat.

7. TREATMENT DETAILS

7.1 Initial Surgery
Surgery must involve complete macroscopic resection of all known disease with or without microscopic positive margins. Surgery may consist of one or more of the following:

- Resection of the primary lesion
- Any type of parotidectomy (superficial, total, partial, etc.)
- Any type of neck dissection(s)

Note: Patients with microscopic positive margins are eligible

Patients with advanced local disease with no regional nodal metastases must have undergone complete macroscopic resection of the primary lesion with or without a skin graft or flap repair. Patients may undergo a prophylactic superficial parotidectomy and/or neck dissection.

Patients who present with high-risk intra-parotid nodal disease without a synchronous cutaneous lesion must have undergone a superficial/partial/total parotidectomy with or without a therapeutic or elective neck dissection. The type of neck dissection is at the discretion of the surgeon but must involve removal of clinically and/or radiologically enlarged regional lymph nodes.

7.2 Radiotherapy

Every attempt should be made to commence radiotherapy within 6 weeks (but not compulsory) but no later than 9 weeks following surgery. In the event of wound complications/infection, radiotherapy should not commence until the radiation oncologist is satisfied that the wound has sufficiently healed. In both arms radiotherapy will consist of a conventionally fractionated course of treatment. ICRU 50 and ICRU 62 are to be followed in planning and prescribing treatment. Refer to Appendix 6 for ICRU Guidelines.

7.2.1 Target Volumes

7.2.1.1 Advanced Local Disease with no nodal metastases

Only the Planning Target Volumes (PTV) and the site of resected gross disease, Gross Tumour Volumes (GTV) are required to be outlined. The Clinical Target Volumes (CTV) do not need to be recorded.

Refer to Figure 1 for case example.

PTV 1 (50Gy)

Refer to Figures 1.0, 1.1, 1.2 & 1.3.

Dose: 50Gy in 25 fractions, 2Gy per fraction, 5 per week

Definition: CTV 1 + minimum 0.5 cm margin in all dimensions

CTV 1:
- site of resected gross disease
- surgical bed/scar
- first echelon of clinically uninvolved draining lymph nodes
**PTV 2 (54Gy)**

Refer to Figures 1.4, 1.5, 1.6, 1.7

**Dose:** 54Gy in 27 fractions, 2Gy per fraction, 5 per week

**Definition:** CTV 2 + minimum 0.5 cm margin in all dimensions

**CTV 2:**
- site of resected gross disease
- surgical bed/scar

**PTV 3 (60Gy or 66Gy)**

Refer to Figures 1.8, 1.9, 1.1.1

**Dose:** 60-66Gy in 30-33 fractions, 2Gy per fraction, 5 per week

**Definition:** CTV 3 + minimum 0.5 cm margin in all dimensions

**CTV 3:**
- site of resected gross disease

**Additional points**

1. Appropriate bolus material should be used to achieve full tumour dose on skin at the primary site.

2. As these are high-risk patients, every attempt should be made to treat the first echelon of clinically uninvolved draining lymph nodes and the intervening lymphatics. The corresponding first echelon of draining lymph nodes for cutaneous sites of the head and neck is shown in Appendix 7.

3. Where elective nodal dissection is performed and no disease detected this will be considered part of the surgical bed/scar. **Bolus of the scar is optional.**

4. Elective nodal irradiation may be omitted where it is technically difficult or the toxicity is considered unacceptably high, such as for midline scalp lesions.

5. The surgical scar should be visible on the planning CT scans

**7.2.1.2 High-risk nodal disease or advanced disease with low risk nodal disease**

Only the Planning Target Volumes (PTV) and the site of resected gross disease, Gross Tumour Volumes (GTV) are required to be outlined. The Clinical Target Volumes (CTV) do not need to be recorded.

Refer to Figure 2 & 3 for case example.
**PTV 1 (50Gy)**

*Refer to Figures 2.0, 2.1, 2.2, 2.3*

**Dose:** 50Gy in 25 fractions, 2Gy per fraction, 5 per week

**Definition:** CTV 1 + minimum 0.5 cm margin in all dimensions

**CTV 1:**
- site of resected gross disease
- surgical bed/scar
- first echelon of clinically uninvolved draining lymph nodes

**PTV 2 (54Gy)**

*Refer to Figures 2.4, 2.5, 2.6.*

**Dose:** 54Gy in 27 fractions, 2Gy per fraction, 5 per week

**Definition:** CTV 2 + minimum 0.5 cm margin in all dimensions

**CTV 2:**
- site of resected gross disease
- surgical bed/scar

**PTV 3 (60Gy or 66Gy)**

*Refer to Figures 2.7, 2.8.*

**Dose:** 60-66Gy in 30-33 fractions, 2Gy per fraction, 5 per week

**Definition:** CTV 3 + minimum 0.5 cm margin in all dimensions

**CTV 3:**
- site of resected gross disease

**Additional points**

1. In all cases of intra-parotid or upper cervical nodal metastases the ipsilateral surgically unperturbed lower neck and supraclavicular region will be considered the next echelon of nodes and therefore part of **CTV 1** and treated electively.

2. In the event that the PTV 2(54) is similar to the PTV 3(60-66), omit the PTV 2.

3. When nodal metastases have occurred >12 months following definitive treatment to the index cutaneous lesion, with no evidence of local recurrence, treatment of the primary or intervening lymphatics is optional.

4. Where high-risk nodal metastases have occurred ≤12 months following definitive treatment to the index lesion, it is preferable but not compulsory to include the primary site and intervening dermal lymphatics as part of the **PTV1-3** and treated in continuity to **60-66Gy**.

5. Bolus of the scar is optional.
6. If a named nerve is involved (e.g. facial nerve) the entire nerve back to its exit from the base of skull will be considered part of the PTV1-3 and treated to 60-66Gy.

7. Donor surgical areas of harvesting for rotation flaps, well beyond the target region do not require radiotherapy.

8. If the lower neck/supraclavicular nodes are involved treatment of the next echelon of nodes is not required.

A CT illustration of nodal sites of the neck are described by Nowak et al and is recommended as a guide for determination of the PTV. (25,26)

7.2.2 Immobilisation
Patients should be positioned supine and immobilised using either a thermoplastic mask or a vacuum formed mask. In the case of patients treated with an appositional electron field, an open neck technique as described by Kian Ang et al, is a recommended approach. (27)

In cases where the posterior vertex area of the scalp or sub occipital nodes require irradiation, the patient may be positioned prone if it allows for ease of set-up and treatment.

7.2.3 Simulation and Planning
A pre-treatment dental assessment should be done in all dentate patients.

An intra-oral stent or tongue depressor should be used if this will allow a greater amount of tongue or oral cavity to be excluded from the treatment volume.

Patients should undergo a planning CT for determination of depth of tumour coverage and dose calculation. All surgical scars should be marked (e.g. with radio-opaque wire) for CT planning and visible on the planning images (for QA purposes). The entire volume of interest is required to be scanned preferably with 5mm slice separation but no more than 10mm. Treatment fields should be marked preferably on the planning computer, or clinically.

The use of a junction is permitted to treat PTV1-3. This may be warranted due to physical limitations and sites of disease. The junction should be chosen so as to avoid splitting through sites of resected gross disease.
The upper and lower neck should be marked as a continuous volume as shown in Figure 3. An area that will require 60-66Gy should also have a PTV1 (50Gy) and PTV 2 (54Gy) marked, not just a PTV (60-66Gy). It is preferable that the lower neck be contoured rather than treated to a depth for QA purposes.

The treatment field arrangement is at the discretion of the participating centre. The dose received by the PTV must satisfy ICRU 50 requirements for dose homogeneity, i.e. a minimum of 95% of the prescribed dose encompasses the PTV and the maximum clinically significant isodose (minimum diameter >15mm) does not exceed 107% of the prescribed dose.

The dose received at, and close to the junction is unlikely to achieve ICRU50 recommendations for dose homogeneity due to physical limitations. This is accepted provided that the dose received 1cm (or other appropriate distance from the junction) either side of the junction satisfies homogeneity requirements.
Every attempt should be made to use techniques to avoid unnecessary irradiation of the larynx or dose exiting through the orbits.

7.2.4 Dosimetry
The dose variation across the PTV should not exceed +7% and -5% of the prescription point (ICRU reference point) dose. Missing tissue compensation should be available to provide dose homogeneity within the PTV. Where an electron beam abuts a photon beam overlying a site that contained disease, a small volume hot spot of up to 120% is permissible.

For electron fields the dose will be specified to the depth of the 90% isodose line and the energy will be chosen to deliver this dose to the volume of interest.

Where there are > 2 fields junctioning through sites of resected gross disease and/or scar a mono-isocentric technique should be used.

Maximum Doses to Normal Tissue:
Spinal Cord: The total dose shall not exceed 45Gy to the spinal cord. (If the location of previous gross disease mandates a higher cord dose to achieve adequate tumour coverage, a dose of up to 48Gy to the spinal cord is permitted).

Brain Stem and Optic Chiasm: The total dose shall not exceed 54Gy to the brainstem and optic chiasm.

7.2.5 Field verification
For patients receiving photon beams a portal film/image of each field should be taken weekly.

Portal images should be taken on the first day of treatment for each field.

For electron fields, a simulation film, photograph or digitally reconstructed radiograph (DRR) should be available as a reference image to demonstrate the planned location of the treatment field in relation to the surgical scar.

7.2.6 Fractionation
If radiotherapy is interrupted the chemotherapy will also be delayed.

For both arms of the trial, conventional once daily fractionation of 2Gy, 5 fractions per week are specified. In the event of public holidays, missing treatment(s) should be made up in the same way as for treatment interruptions (see below).

Treatment interruptions should be avoided unless there is severe acute toxicity which cannot be managed conservatively. In the event of a treatment interruption for any reason, the missing dose fraction(s) should be made up by either treatment on a weekend, giving a second treatment on one or more of the remaining treatment days with a minimum 6-hour interfraction interval provided that no more than 6 fractions are given in any one week or adding the missed fraction on at the end.

The reason for any treatment interruption must be documented.

In the event of significant early skin reaction the bolus may be removed at the recommendation of the radiation oncologist. The dose at which the bolus was removed must be recorded.
7.2.7 Dose calculation and reporting

Prescription point

The dose should be prescribed and isodose normalized to a reference point which satisfies ICRU50 criteria. (Appendix 6)

The reference point or points should be clearly defined and labeled according to local protocols. If there are multiple points the label should include an anatomical description of the reference point. (e.g. upper face Ref. Pt., lower neck Ref. Pt.).

Location of the reference point or points should be recorded e.g. x, y, z co-ordinates in relation to the CT data-set/ or depth within tissue.

Dose reporting

1. Dose uniformity: The maximum and minimum clinical isodoses in the PTV shall be calculated and reported as per ICRU50. These may be extracted from isodose distributions, calculated separately or derived from the dose-volume-histogram (DVH).

2. Isodose distribution: An isodose plot of dose distribution in the central transverse plane through the prescription point/s and 1 cm inside the upper and lower margins of the fields shall be recorded.

3. The monitor units required to deliver the prescribed dose to the prescription point shall be calculated and submitted for each field.

4. Organs at Risk: The maximum dose to the spinal cord, brainstem and optic chiasm shall be recorded when in the field.

7.3 Chemotherapy

7.3.1 Chemotherapy administration

Carboplatin will commence with a dose calculated to target an AUC of 2.0. Chemotherapy will commence on either day 1, 2 or 3 of the radiation and preferably repeated on the same day of each week. A maximum of 6 doses of weekly Carboplatin will be given. Carboplatin will be administered intravenously over 20-30 minutes prior to radiation therapy, and radiation therapy on the day of chemotherapy should be delivered within 4 hours of completion of chemotherapy. Note patients treated to 66Gy still receive a maximum of 6 doses of weekly Carboplatin.

7.3.2 Calculation of carboplatin dose

Carboplatin dose will be calculated according to Calvert formula:

Carboplatin dose (mg) = (Glomerular filtration rate [GFR] + 25) x target AUC 2.

GFR will be estimated using the Cockcroft-Gault formula. (Appendix 5) (28,29)

In general, the calculated dose of carboplatin according to the Calvert formula at baseline should be used in all cycles unless there is a weight change of > 10% from baseline or serum creatinine changes by > 0.02 mmol/L.
7.3.3 Dose modification for toxicity and delays

Blood counts are required weekly during the chemo-radiotherapy and weeks 3 & 6 in the radiotherapy alone patients.

The ANC count must be $\geq 1.0 \times 10^9$/L and the platelet count $\geq 90 \times 10^9$/L prior to the administration of weekly carboplatin in weeks 1 - 4 of radiation. In weeks 5-6 chemotherapy can be given if the ANC count is $\geq 1.0 \times 10^9$/L and the platelet count $\geq 75 \times 10^9$/L. If the blood counts are below these cut-off criteria, treatment will be delayed one week. If the blood count has then recovered, treatment will be administered with a 20% dose reduction.

A 30% dose reduction is required following grade 4 neutropenia, grade 3 or 4 thrombocytopenia or febrile neutropenia.

<table>
<thead>
<tr>
<th>Time</th>
<th>Grade</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir</td>
<td>Febrile neutropenia, or ANC &lt;0.50 x $10^9$/L</td>
<td>Reduce subsequent doses by 30%</td>
</tr>
<tr>
<td>On treatment day</td>
<td>ANC 0.50-0.99 x $10^9$/L</td>
<td>Omit dose and reduce subsequent doses by 20% if ANC recovers to $\geq 1.0$</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir</td>
<td>Platelets &lt;50 x $10^9$/L</td>
<td>Reduce subsequent doses by 30% if platelets recover to $\geq 90$ (75 – weeks 5+6)</td>
</tr>
<tr>
<td>On treatment day</td>
<td>Platelets &lt;90 x $10^9$/L (weeks 2-4)</td>
<td>Omit dose and reduce subsequent doses by 20% if platelets recover to $\geq 90$ (75 – weeks 5+6)</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt;75 x $10^9$/L (weeks 5-6)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-haematological toxicities outside the radiation field (except alopecia and emesis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst grade</td>
<td>Grade 4</td>
<td>Cease chemotherapy</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Omit next dose and reduce subsequent doses by 30% if recovers to grade 1</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Dose modifications for concurrent chemotherapy

Grade 3 non-haematological toxicity (apart from alopecia and emesis) due to the carboplatin will require omission of chemotherapy until it resolves to $\leq$ grade 1, and then a 30% dose reduction is required for the next cycle. Concurrent chemotherapy will be ceased for patients who experience grade 4 carboplatin related non-haematologic toxicity. In general, radiation related toxicities will not require modification of carboplatin dose or timing. (Table 1)

If radiotherapy is interrupted then chemotherapy will also be delayed. No weekly carboplatin doses will be administered after completion of radiation. In cases where the chemotherapy is delayed or ceased the radiotherapy will continue according to protocol.

8. DEFINITIONS OF OUTCOME MEASURES

8.1 Primary Outcome

The primary outcome is time to loco-regional relapse, measured from the date of randomisation. Loco-regional relapse is defined in section 8.3 below.
If distant relapse occurs, the patient will continue to be followed for subsequent loco-regional relapse. Therefore, distant relapse will not be treated as a censoring event in the analysis. Only loco-regional relapse and death from disease will be treated as failure events. Patients who die with no evidence of disease will be treated as censored as of the date of death. Similarly, patients who are lost to follow-up will be treated as censored at their last known follow-up date. Patients who are alive at the defined study close-out date will be treated as censored at that date.

### 8.2 Secondary Outcomes

Secondary outcomes are:
- Disease free survival time
- Overall survival time
- Treatment related morbidity
- Quality of life

#### 8.2.1 Disease free survival time

This is defined as the time from randomisation to the first relapse of any type (local, regional or distant) or death from any cause. These are the failure events. Patients who are lost to follow-up will be treated as censored at their last known follow-up date. Patients who are alive at the defined study close-out date will be treated as censored at that date.

#### 8.2.2 Overall survival time

This is defined as the time from randomisation to death from any cause. Patients who are lost to follow-up will be treated as censored at their last known follow-up date. Patients who are alive at the defined study close-out date will be treated as censored at that date.

#### 8.2.3 Treatment-related morbidity

Treatment-related acute and late toxicity will be monitored by the radiation and medical oncologists and recorded at regular intervals. The Common Terminology Criteria for adverse events Version 3.0 (which includes both acute and late toxicity) will be recorded (Appendix 3). Toxicity will be recorded weekly during radiation therapy and 4, 8, 12 weeks and then 6, 9, 12, 24 months following completion of treatment and then 6 monthly thereafter.

#### 8.2.4 Quality of Life

The FACT instruments have been chosen to assess quality of life (QoL). The FACT-G consists of 27 questions in 4 domains. The 38-item FACT- H&N also includes an 11-item head and neck cancer specific subscale. Each response is rated from 0-4 on a Likert index, considering the past 7 days. (refer to Appendix 2)

To maximise the validity and generalisation of QoL results all eligible patients should participate in the QoL component of the study. The QOL scores will be compared between the 2 arms.

Eligibility for QoL assessment will be determined prior to randomisation.

Patients excluded from completing the QoL questionnaire will be those that meet the following criteria:
1) Inability to comprehend English
2) Inability to comprehend QoL questions due to cognitive or psychiatric deficits

In blind or illiterate patients the questionnaire should be administered verbally.
**Timing of assessment**

QoL assessment is to be performed at baseline (pre-randomisation), then at 12 weeks, 6 months, and 1 & 2 years from the date of completion of treatment, even in the event of relapse of any type. QoL will also be recorded at the time of any type of relapse.

### 8.3 Types of Relapse

The following three types of relapse will be recognised:
- local or *in transit* relapse
- Ipsilateral or contralateral regional (nodal basin) relapse
- distant relapse

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.

**Local or *in transit* relapse**

Local relapse will be defined as any relapse occurring within 1 cm of the scar of the index lesion. *In transit* relapse will be defined as dermal or subcutaneous relapse between the primary site and the adjoining nodal basin.

A relapse occurring along the scar of the primary site will be considered a local relapse.

**Regional relapse**

Ipsilateral regional relapse will be defined as any nodal relapse or relapse within the nodal basin above the clavicles on the ipsilateral side.

A relapse occurring along the scar over a nodal basin will be considered an ipsilateral regional relapse. In the event where it is difficult to distinguish between a local or regional scar relapse regional relapse will take precedence.

Contralateral nodal relapse will be defined as any nodal relapse occurring on the contralateral side to the index lesion or dissected neck.

In the event where there is a relapse in the contralateral neck which was electively irradiated due to the fact it was a midline lesion (e.g. vertex lesion) will be considered an ipsilateral regional relapse.

**Distant relapse**

This will be considered as any relapse that occurs below the clavicles.

### 9. MONITORING PROCEDURES AND TESTS

#### 9.1 SCHEDULE

##### 9.1.1 Pre-randomisation

Eligibility investigations should be performed within 6 weeks prior to randomisation. These investigations are:
- History and clinical examination
- Disease status
- Full blood count and differential (FBE)
- Urea, creatinine and electrolytes (U&E)
- LFT’s
- CT head and neck
• CT chest or CXR chest
• QoL assessment
• Pregnancy Test (women of child-bearing potential)

9.1.2 On Treatment

Treatment related toxicity should be recorded weekly. Full blood counts are required weekly for patients randomised to the chemo-radiotherapy arm and in weeks 3 & 6 in the radiotherapy alone arm. U&E’s and creatinine to be recorded weekly before each dose of Carboplatin.

9.1.3 Scheduled follow-up visits

Follow-up visits are to be scheduled at 4, 8 and 12 weeks then 6, 9, 12, 16, 20 and 24 months from the completion of treatment. Then optional follow-up visits are to be scheduled at 6 monthly intervals up to 5 years or until the close-out date. Investigations at these visits are to include:

• History and clinical examination
• Disease status
• Treatment-related toxicity
• QoL assessment (12 weeks and 6, 12 & 24 months following completion of treatment and then annually until the close-out date)

9.1.4 Summary of monitoring schedule

A summary of the monitoring schedule required for this study is provided (Appendix 8).

9.1.5 Documentation required upon relapse

Careful documentation upon identification of first relapse is required. Document whether relapse is local or in transit, regional, distant, or a combination of these.

(i) Local or in transit and regional disease status. If disease is present or suspected on clinical examination:
   a. Confirm with FNA cytology or biopsy.
   b. Ideally record with a second observer.
   c. CT image area of interest
   d. Photo-documentation (preferably digital) and/or a tumour diagram (supplied by trial centre with study forms) documenting location of relapse is required. Whether the relapse has occurred within or outside the radiation field must be stated. Refer to Quality Assurance 12.4.

(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 chest and abdomen to ascertain presence of other possible distant metastases.

(iii) If the patient fails with local or in transit or regional relapse, follow up should continue according to protocol or until death. Any salvage treatment and its outcome, should be recorded.

(iv) 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.
Quality of Life (QoL) is required at first relapse but should continue to be recorded according to protocol regardless of the type of relapse.

10. SERIOUS ADVERSE EVENT REPORTING

10.1 Adverse Event (AE) Reporting

An adverse event is defined in Good Clinical Practice (GCP) guidelines as an untoward medical occurrence in a clinical trial patient. AEs are signs (including an abnormal laboratory finding), symptoms or diseases that are ‘temporally associated’ (occur within a related time period) to a medical treatment or procedure. There may or may not also be a causal relationship.

AEs can be significant enough to lead to important changes in a trial. Therefore sites participating in this trial will be required to report adverse events in accordance with TROG policy. The documentation of an adverse event requires specific information regarding the sign, symptom or disease. AEs must be reported on the relevant trial forms and the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) must be used to grade the severity of an event.

10.2 Serious Adverse Event (SAE) Reporting

10.2.1 SAE Definitions

Adverse events are considered ‘serious’ if they threaten life or function. Due to the significant information they provide, serious adverse events require expedited reporting.

Serious Adverse Events (SAEs) are defined as any AE which:
- Results in death (i.e. fatal/grade 5 CTC AE)
- Is life-threatening (i.e. grade 4 CTC AE)
- Requires In-Patient Hospitalisation or Prolongation of Existing Hospitalisation
- Results in Persistent or Significant Disability/Incapacity, or
- Is a Congenital Anomaly/Birth Defect

The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was immediately at risk of death at the time of event. It does not refer to an event which hypothetically might have caused death if it were more severe. However, important medical events may be considered a serious adverse experience if they require medical or surgical intervention to prevent one of the listed definitions, e.g. an ‘allergic bronchospasm’ which required intensive treatment in an emergency room or at home.

An event that results in hospitalisation or prolongs an existing hospitalisation will not be considered a serious adverse event if the only reason for the hospitalisation or prolongation was:
- administration of chemotherapy
- administration of trial procedures
- placement of a permanent intravenous catheter
- hospice placement for terminal care
- pre-trial scheduled elective surgery
- outpatient hospitalisation for procedures such as:
  - elective day surgery
  - convenience purposes (eg. transportation difficulties)
- admission for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding

Overdoses (drug or radiation) should be reported in an expedited fashion if the events associated with the overdose meet the SAE definitions listed above. If no serious adverse events are experienced the overdose must be reported on the relevant trial forms.

The development of new cancers at any time during the trial follow-up period should be reported on the relevant trial forms. If any events associated with the new cancer meet the SAE definitions listed above, then they should also be reported in an expedited fashion.

### 10.2.2 SAE Reporting

SAE reports are required at the following points:

<table>
<thead>
<tr>
<th>SAEs should be reported from the time a patient is registered/randomised on the clinical trial, until 30 days after their last protocol treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Report [S1]</strong></td>
</tr>
<tr>
<td><em><em>Completed Report</em> [S1]</em>*</td>
</tr>
<tr>
<td><strong>Updated Report# [S1]</strong></td>
</tr>
</tbody>
</table>

SAEs are required to be reported whether or not considered related to the treatment under investigation. The TROG SAE form requires the investigator to define the attribution to protocol treatment (not related, possibly related, definitely related), and the nature of the event (expected or unexpected). An ‘expected SAE’ is a known possible toxicity consistent with current available information (eg. drug product information or investigators brochure). An ‘unexpected SAE’ is the occurrence of an unknown toxicity or an event of greater severity or specificity than indicated in the available information (including the protocol or informed consent form).

An Investigator at the site must sign all reports. All SAE forms must include the TROG trial and patient registration numbers. The investigator may be asked to provide follow-up information.

Copies of all SAE reports must be FAXED to the following addresses:

<table>
<thead>
<tr>
<th>Fax To:</th>
<th>Fax Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-ordinating Trial Centre (Trial Centre Co-ordinator)</td>
<td>+61 7 3176 2252</td>
</tr>
<tr>
<td>TROG Central Operations Office</td>
<td>+61 2 4921 1465</td>
</tr>
</tbody>
</table>

### 10.2.3 SAE Responsibilities

The Investigator at each treatment site is responsible for ensuring that the conduct of the study at their site complies with the protocol, including monitoring the safety of patients treated according to this protocol and ensuring that any serious adverse events are reported in the required timeframes. The Investigator is also responsible for ensuring that serious adverse events are reported to their Institutional Ethics Committee in accordance with local notification requirements.

The Co-ordinating Trial Centre will maintain up to date records of all. The Trial Management Committee (TMC) will ensure serious adverse events (both expected and unexpected) are regularly reviewed. Consideration will also be given to information provided by (non-serious)
adverse event data. Participating sites will be advised of any safety issues that arise during the review process. In the event of a significant incidence of SAEs, consideration will be given to amending the trial. Summary reports will be presented to the TROG Scientific Committee at least 6 monthly.

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 initialled and dated by an authorised person.

Source data, including medical histories, radiological imaging, laboratory tests, chemotherapy and 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 surgical/operative notes, pathology reports, CT reports, blood test results, and radiotherapy treatment details) will be requested, if necessary, for CRF edit checks and source data verification.

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 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 Technical Review will be conducted in 2 stages:

Level 1: The first five radiotherapy patients from each treatment centre will be reviewed by designated review radiation oncologists and the TROG QA Office. If major violations are identified, then a further two patients will also be reviewed. Once an acceptable quality level is achieved, sites then progress to Level 2 auditing.

Level 2: All centres will continue to be audited with one in every three patients from each treatment centre 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 a checklist of information required for RT QA review will be provided by the TROG QA Office. Review material will be required within four weeks of treatment completion.

The Trial Centre Data Manager and Trial Chairperson will coordinate the review in consultation with the TROG QA Office and report to the Trial Management Committee. Results will be reported to the TMC at least 6 monthly, and to the TROG Trials Review meeting biannually.

12.3 Chemotherapy Treatment Delivery

For each patient, a checklist of information required for chemotherapy review (i.e. treatment charts/’flowsheets’) which clearly demonstrate the prescription and administration of chemotherapy drugs will be provided by the TROG QA Office. Review material will be required at the end of treatment.

Case Record Forms (CRF) and the copies of chemotherapy records (‘source data’) will be reviewed for each patient to assess and verify compliance with the protocol. Audits will focus on delivered dose, method of administration, treatment timing and dose modifications.

12.4 Reporting of local and/or regional recurrence

All relapses must be reported to the Trial Centre immediately at the time of detection (refer to section 8.3: Types of Relapse and section 9.1.5 Documentation Required Upon Relapse).

Relapse reports must clearly state whether loco-regional recurrence has occurred within or outside the radiation field. If the relapse is close to a radiotherapy field border, the investigator should review the radiotherapy treatment and planning information to verify the location of the relapse relative to the treatment field borders.

Location of relapse will be recorded via photo-documentation and/or tumour diagram for QA purposes.

Photos may be sent electronically. Photographs of palpable and/or visible local and regional relapses should be taken perpendicular to the skin with the palpable extent of all nodal relapse clearly marked.

A blank tumour diagram form will be provided with the study forms and must be completed by the radiation oncologist for documentation of all relapses.

The first 5 relapses from each centre will be reviewed by designated review radiation oncologists and the TROG QA Office.

For all cases selected for relapse reviews, reviewers will require:
- Radiotherapy treatment and planning information (as per the checklist section 12.2)
- Tumour diagram form
- Photo-documentation (if possible)
- CT images and report (relapse site/s)
- FNA cytology or biopsy report (relapse site/s)
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.

13. STATISTICAL CONSIDERATIONS

13.1 Trial Design

This is a two-armed randomised trial in post-operative patients with high-risk cutaneous SCC of the head and neck. The purpose of this study is to test the hypothesis that there is an improvement in time to loco-regional relapse for patients who undergo post-operative concurrent chemo-radiotherapy compared with post-operative radiotherapy.

13.2 Randomisation and Stratification

Patients will be randomised between the two arms, radiotherapy and chemo-radiotherapy. Allocation to treatment will be balanced according to high-risk nodal disease and advanced primary disease, and institution.

A choice of dose is permitted, either 60 Gy or 66 Gy. In order to avoid bias resulting from the confounding of dose with treatment arm, the radiation oncologist will be required to nominate the total dose prior to randomisation. Stratification according to total dose will not be performed because of the potentially low numbers using the higher dose of 66 Gy.

13.3 Statistical Methods

The original target sample size for the trial was based on detecting a clinically important difference in the time to LRR that was feasible to achieve with the addition of CT. The targeted difference was a 15% improvement in the LRR-free rate with CT-RT at 2 years (70% to 85%), corresponding to a hazard ratio of 0.46. It was assumed that the time to LRR curve for the RT group exhibits an exponential decline to a plateau at 40% and that LRR’s occur by 12 months. With an accrual rate of 45-50 patients per year, a further 2 years of follow-up after accrual, a power of 80% and significance level of 5%, 237 patients were required. However, to allow for some censored observations due to competing risks and for a 5% loss to follow up in the cohort, 265 patients were planned to be recruited.

Following an observation by the trial investigators that the LRR rate appeared to be lower than expected, data relevant to the primary outcome for the PORT arm only were extracted for the purpose of a sample size reassessment. Based on these data, an assumed accrual rate of 45 per year, and an unchanged clinically important hazard ratio of 0.46, the sample size was re-calculated to a total of 350 patients. Based on these results the IDMC recommended that the trial continue with the revised target accrual.

The date of primary outcome analysis will occur when the final patient has reached a minimum 2 years follow-up.

The Kaplan Meier method will be used in the primary analysis to estimate the rate of loco-regional control over time in the two arms of the study. The two arms will be compared through the log rank test, stratified for type of high-risk disease. Total dose of radiation (60 or 66 Gy) and phase of trial (pre-amendment; post-amendment) will be included as covariates in preliminary analyses comparing arms, along with other potential risk factors, in order to assess whether these need to be accounted for in subsequent analyses.
Secondary analyses of disease free and overall survival will also use the Kaplan Meier method. The primary outcome will be analysed on an intent-to-treat basis, using data from all randomised patients, in the group to which they were randomised, irrespective of treatment actually received.

Quality of life will be compared between the two arms at 12 weeks and, 6, 12 & 24 months following completion of treatment.

13.4 Interim Analyses and Early Closure Criteria

Accrual rates and acute radiotherapy and chemotherapy toxicities will be assessed as part of routine interim annual reporting. Approximately 50 patients are expected to be accrued in the first 12 months. Consideration will be given to stopping the trial early if any of the following occur:

- Unacceptable radiotherapy acute toxicity (any Grade 4 toxicity)
- Unacceptable chemotherapy acute toxicity (any non-haematological Grade 4 toxicity) in the chemo-radiotherapy arm
- Accrual is less than 30% of the expected number of patients in the first 12 months from launching the trial.
- A clearly more effective therapy becomes available.

A formal safety analysis will be performed by an Independent data Monitoring Committee (IDMC) when the target accrual has reached the half way mark.

No formal interim analyses of the primary endpoint will be performed.

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. (Appendix 9)
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 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 ≥ 15% accrual and three authors for ≥ 25% accrual).

Acknowledgement of TROG 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. In addition, publications must be reviewed by the TROG Publications Committee prior to submission.
16. TRANSLATIONAL STUDY (OPTIONAL)

Given the potential toxicity of chemoradiation in patients with high risk cutaneous Squamous cell carcinoma it is highly desirable to prospectively identify which patients are most likely to benefit from this approach. We wish to perform molecular studies on tumour tissue from patients on the POST study in order to identify predictive markers for outcome and for response to chemoradiation in high risk cutaneous SCC.

New patients will be asked for consent at the time of enrolment. Patients already on study will also be given the opportunity to consent for the use of their tissue for translational studies.

Once consent has been provided, requests will be made for tissue blocks where possible, or for 20 unstained sections (if tissue blocks are not available) to be sent to Peter MacCallum Cancer Centre. While tissue submission for translational studies is strongly encouraged it is not required. Unavailability of tissue is not a criterion for exclusion.

Given the well documented role of the epidermal growth factor receptor in the biology of epithelial tumours and response to radiation, the role of hypoxia in radioresistance, and the role of the DNA repair enzyme ERCC1 in sensitivity to platinum compounds and radiation the following studies will be performed:

1. Immunohistochemistry for EGFR protein
2. Chromogenic In Situ Hybridization (CISH) for EGFR gene copy number
3. Excision repair cross-complementing group 1 (ERCC1)
4. Hypoxia markers (HIF-1alpha and CAIX )

In addition to the above, other putative biomarkers for outcome in these patients may be explored in future studies. Results of these molecular analyses will be correlated with clinical outcome both in the control and treatment groups to identify potential prognostic and predictive markers for high risk cutaneous SCC treated with radiation or chemoradiation.
17. REFERENCES:


18.  APPENDICES INDEX

Appendix 2:  FACT-Head and Neck QOL
Appendix 3:  Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0
Appendix 4:  ECOG Performance Status
Appendix 5:  Cockcroft-Gault Formula for Calculating Creatinine Clearance
Appendix 6  Radiotherapy Guidelines
Appendix 7:  Lymphatic Drainage of the Head and Neck
Appendix 8:  Summary of Monitoring Schedule
Appendix 9:  Patient Information Sheet & Consent Form: Template

Figure 1.  Advanced Local Disease
Figure 2.  High Risk Nodal Disease
Figure 3.  High Risk Nodal Disease Summary

T – Primary Tumour

T0  no evidence of primary tumour
T1  ≤ 2 cm
T2  > 2 to 5 cm
T3  > 5 cm
T4  Tumour invades deep extradermal structures, i.e., cartilage, skeletal muscle, or bone

N – Regional Lymph Nodes

NX  regional lymph nodes cannot be assessed
N0  no regional lymph node metastasis
N1  Regional lymph node metastasis

M – Distant Metastasis

M0  No distant metastasis
M1  Distant metastasis
Appendix 2: FACT-Head and Neck QOL

Below is a list of statements which 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.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1 I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP2 I have nausea ..............................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3 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>GP4 I have pain ...................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP5 I am bothered by side effects of treatment ..</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP6 I feel ill ........................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP7 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>Some what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1 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>GS2 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>GS3 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>GS4 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>GS5 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>GS6 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>
<tr>
<td>Q1 Regardless of 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.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am satisfied with my sex life</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.

### EMOTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing hope in the fight against my illness ..................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to work (include work at home).....</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am enjoying the things I usually do for fun ........................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am content with the quality of my life right now ..................................</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.

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Some what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;N1 I am able to eat foods that I like ...................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N2 My mouth is dry ...........................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N3 I have trouble breathing.................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N4 My voice has the usual quality and strength ................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N5 I am able to eat as much food as I want.......</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N6 I am unhappy with how my face and neck look..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N7 I can swallow naturally and easily ..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N8 I smoke cigarettes or other tobacco products ................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N9 I drink alcohol (e.g. beer, wine, etc) .............</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N10 I am able to communicate with others..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N11 I can eat solid foods .................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;N12 I have pain in my mouth, throat or neck .......</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
### Appendix 3: Common Terminology Criteria for adverse events (CTCAE) Version 3.0

#### AUDITORY/EAR

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing: patients without baseline audiogram and not enrolled in a monitoring program¹</td>
<td>Hearing (without monitoring program)</td>
<td>—</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Profound bilateral hearing loss (&gt;90 dB)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Remark:** Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.

**Also consider:** Hearing: patients with/without baseline audiogram and enrolled in a monitoring program¹; Hearing: patients without baseline audiogram and not enrolled in a monitoring program¹.

#### BLOOD/BONE MARROW

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Hemoglobin</td>
<td>—</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&lt;LLN – 10.0 g/dL</td>
<td>&lt;10.0 – 8.0 g/dL</td>
<td>&lt;8.0 – 6.5 g/dL</td>
<td>&lt;8.0 – 6.5 g/dL</td>
<td>&lt;6.5 g/dL</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;LLN – 6.2 mmol/L</td>
<td>&lt;6.2 – 4.9 mmol/L</td>
<td>&lt;4.9 – 4.0 mmol/L</td>
<td>&lt;4.9 – 4.0 mmol/L</td>
<td>&lt;4.0 mmol/L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;LLN – 100 g/L</td>
<td>&lt;100 – 80 g/L</td>
<td>&lt;80 – 65 g/L</td>
<td>&lt;80 – 65 g/L</td>
<td>&lt;65 g/L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Leukocytes (total WBC)</td>
<td>Leukocytes</td>
<td>—</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&lt;LLN – 3000/mm³</td>
<td>&lt;3000 – 2000/mm³</td>
<td>&lt;2000 – 1000/mm³</td>
<td>&lt;2000 – 1000/mm³</td>
<td>&lt;1000/mm³</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;LLN – 3.0 x 10⁹ /L</td>
<td>&lt;3.0 – 2.0 x 10⁹ /L</td>
<td>&lt;2.0 – 1.0 x 10⁹ /L</td>
<td>&lt;2.0 – 1.0 x 10⁹ /L</td>
<td>&lt;1.0 x 10⁹ /L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td>Neutrophils</td>
<td>—</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&lt;LLN – 1500/mm³</td>
<td>&lt;1500 – 1000/mm³</td>
<td>&lt;1000 – 500/mm³</td>
<td>&lt;1000 – 500/mm³</td>
<td>&lt;500/mm³</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;LLN – 1.5 x 10⁹ /L</td>
<td>&lt;1.5 – 1.0 x 10⁹ /L</td>
<td>&lt;1.0 – 0.5 x 10⁹ /L</td>
<td>&lt;1.0 – 0.5 x 10⁹ /L</td>
<td>&lt;0.5 x 10⁹ /L</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>Platelets</td>
<td>—</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&lt;LLN – 75,000/mm³</td>
<td>&lt;75,000 – 50,000/mm³</td>
<td>&lt;50,000 – 25,000/mm³</td>
<td>&lt;50,000 – 25,000/mm³</td>
<td>&lt;25,000/mm³</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&lt;LLN – 75.0 x 10⁹ /L</td>
<td>&lt;75.0 – 50.0 x 10⁹ /L</td>
<td>&lt;50.0 – 25.0 x 10⁹ /L</td>
<td>&lt;50.0 – 25.0 x 10⁹ /L</td>
<td>&lt;25.0 x 10⁹ /L</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Death**
### CONSTITUTIONAL SYMPTOMS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>Fatigue</td>
<td>Mild fatigue over baseline</td>
<td>Moderate or causing difficulty performing some ADL</td>
<td>Severe fatigue interfering with ADL</td>
<td>Disabling</td>
<td>—</td>
</tr>
<tr>
<td>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10^9/L)</td>
<td>Fever</td>
<td>38.0 – 39.0°C (100.4 – 102.2°F)</td>
<td>&gt;39.0 – 40.0°C (102.2 – 104.0°F)</td>
<td>&gt;40.0°C (&gt;104.0°F) for ≤24 hrs</td>
<td>&gt;40.0°C (&gt;104.0°F) for &gt;24 hrs</td>
<td>Death</td>
</tr>
</tbody>
</table>

Remark: The temperature measurements listed are oral or tympanic.

Also consider: Allergic reaction/hypersensitivity (including drug fever).

| Weight loss                                    | Weight loss  | 5 to <10% from baseline; intervention not indicated | 10 – <20% from baseline; nutritional support indicated | ≥20% from baseline; tube feeding or TPN indicated | —                                            | —                                            |

### DERMATOLOGY/SKIN

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy, skin</td>
<td>Atrophy, skin</td>
<td>Detectable</td>
<td>Marked</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atrophy, subcutaneous fat</td>
<td>Atrophy, subcutaneous fat</td>
<td>Detectable</td>
<td>Marked</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Also consider: Induration/fibrosis (skin and subcutaneous tissue).

| Dry skin                          | Dry skin                                | Asymptomatic             | Symptomatic, not interfering with ADL | Interfering with ADL    | —                        | —                        |
### DERMATOLOGY/SKIN

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair loss/alopecia (scalp or body)</td>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Hyperpigmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Hyperpigmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration/fibrosis (skin and subcutaneous tissue)</td>
<td>Induration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Also Consider:** Fibrosis:cosmesis; Fibrosis-deep connective tissue.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telangiectasia</td>
<td>Telangiectasia</td>
<td>Few</td>
<td>Moderate number</td>
<td>Many and confluent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### GASTROINTESTINAL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Anorexia</td>
<td>Loss of appetite without alteration in eating habits</td>
<td>Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated</td>
<td>Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated</td>
<td>Life-threatening consequences</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Also Consider:** Weight loss.
## GASTROINTESTINAL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth/salivary gland (xerostomia)</td>
<td>Dry mouth</td>
<td>Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow &gt;0.2 ml/min</td>
<td>Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min</td>
<td>Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva &lt;0.1 ml/min</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Remark:** Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient’s participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow.

**Also Consider:** Salivary gland changes/saliva.

| Dysphagia (difficulty swallowing) | Dysphagia | Symptomatic, able to eat regular diet | Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs | Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs | Life-threatening consequences (e.g., obstruction, perforation) | Death |

**Remark:** Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilatation is graded as Stricture/stenosis (including anastomotic), GI – Select.

**Also Consider:** Dehydration; Esophagitis.

| Mucositis/stomatitis (clinical exam) – Select: Anus, Esophagus, Large bowel, Larynx, Oral cavity, Pharynx, Rectum,Small bowel, Stomach, Trachea | Mucositis (clinical exam) – Select | Erythema of the mucosa | Patchy ulcerations or pseudomembranes | Confluent ulcerations or pseudomembranes; bleeding with minor trauma | Tissue necrosis; significant spontaneous bleeding; life-threatening consequences | Death |

**Remark:** Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.
## Gastrointestinal

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1: Slightly thickened saliva; slightly altered taste (e.g., metallic)</th>
<th>Grade 2: Thick,ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL</th>
<th>Grade 3: Acute salivary gland necrosis, severe secretion-induced symptoms interfering with ADL</th>
<th>Grade 4: Disabling</th>
<th>Grade 5:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary gland changes/saliva</td>
<td>Salivary gland changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Also Consider:** Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – Select; Mucositis/stomatitis (functional/symptomatic) – Select; Taste alteration (dysgeusia).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1: 1 episode in 24 hrs</th>
<th>Grade 2: 2 – 5 episodes in 24 hrs; IV fluids indicated ≤ 24 hrs</th>
<th>Grade 3: ≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥ 24 hrs</th>
<th>Grade 4: Life-threatening consequences</th>
<th>Grade 5: Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Vomiting</td>
<td>1 episode in 24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Also Consider:** Dehydration.
### INFECTION

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC &lt;1.0 x 10^9/L, fever ≥38.5°C)</td>
<td>Febrile neutropenia</td>
<td>—</td>
<td>—</td>
<td>Present</td>
<td>Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)</td>
<td>Death</td>
</tr>
</tbody>
</table>

**ALSO CONSIDER:** Neutrophils/granulocytes (ANC/AGC).

**Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) — Select**

- Select AEs appear at the end of the CATEGORY.

**Remark:** Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection).

**ALSO CONSIDER:** Neutrophils/granulocytes (ANC/AGC).

| Infection (documented clinically) — Select | Localized, local intervention indicated | IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated | Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis) | Death |

| Infection with normal ANC or Grade 1 or 2 neutrophils — Select | Localized, local intervention indicated | IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated | Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis) | Death |

**Remark:** Infection with unknown ANC — Select is to be used in the rare case when ANC is unknown.
### Lymphatics

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema: head and neck</td>
<td>Edema: head and neck</td>
<td>Localized to dependent</td>
<td>Localized facial or neck</td>
<td>Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)</td>
<td>Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

### Musculoskeletal/Soft Tissue

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis-deep connective</td>
<td>Fibrosis-deep connective tissue</td>
<td>Increased density, “spongy”</td>
<td>Increased density with</td>
<td>Increased density with fixation of tissue; operative intervention indicated; interfering with ADL</td>
<td>Life-threatening; disabling; loss of limb; interfering with vital organ function</td>
<td>Death</td>
</tr>
<tr>
<td>tissue</td>
<td></td>
<td>feel</td>
<td>limness or tethering</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Also Consider:** Induration/fibrosis (skin and subcutaneous tissue), Muscle weakness, generalized or specific area (not due to neuropathy) – Select: Neuropathy: motor; Neuropathy: sensory.

| Osteonecrosis (avascular necrosis) | Osteonecrosis                        | Asymptomatic, radiographic findings only | Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy) | Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated | Disabling | Death |

**Also Consider:** Induration/fibrosis (skin and subcutaneous tissue), Muscle weakness, generalized or specific area (not due to neuropathy) – Select: Neuropathy: motor; Neuropathy: sensory.
## OCULAR/VISUAL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eye syndrome</td>
<td>Dry eye</td>
<td>Mid, intervention not indicated</td>
<td>Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated</td>
<td>Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

## PULMONARY/UPPER RESPIRATORY

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)</td>
<td>Voice changes</td>
<td>Mild or intermittent hoarseness or voice change, but fully understandable</td>
<td>Moderate or persistent voice changes, may require occasional repetition but understandable on telephone</td>
<td>Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication</td>
<td>Disabling; non-understandable voice or aphonie; requires voice aid (e.g., electrolarynx) for &gt;50% of communication</td>
<td>Death</td>
</tr>
</tbody>
</table>

*ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).*
## Appendix 4: ECOG 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 5: Cockcroft-Gault Formula for Calculating Creatinine Clearance

Women:

Creatinine clearance in mL/min = \( \frac{1x (140 - \text{age [yr]} ) \times \text{body wt [kg]}}{\text{Serum creatinine [umol/L]}} \)

or

Creatinine clearance in mL/min = \( \frac{0.85 \times (140 - \text{age [yr]} ) \times \text{body wt [kg]}}{72 \times \text{serum creatinine [mg/dL]}} \)

Men:

Creatinine clearance in mL/min = \( \frac{1.23 \times (140 - \text{age [yr]} ) \times \text{body wt [kg]}}{\text{serum creatinine [umol/L]}} \)

or

Creatinine clearance in mL/min = \( \frac{1x (140 - \text{age [yr]} ) \times \text{body wt [kg]}}{72 \times \text{Serum creatinine [mg/dL]}} \)
Appendix 6: Radiotherapy Guidelines

ICRU Reference Point

Photon Beams:

The present system of recommendations for reporting is based on the selection of a point within the PTV, which is referred to as the ICRU Reference point. The ICRU Reference point shall be selected according to the following general criteria:

The dose at the point should be clinically relevant and representative of the dose throughout the Planning Target Volume (PTV),

The point should be:
- easy to define in a clear and unambiguous way
- selected where the dose can be accurately determined (physical accuracy)
- selected in a region where there is no steep dose gradient.

These recommendations will be fulfilled if the ICRU Reference point is located firstly, at the centre, or in the central parts of the Planning Target Volume, and secondly, on or near the central axis of the beam(s).

In some situations, it is not possible to define the ICRU Reference Point at the centre of the Planning Target Volume. In these conditions, one has to select the ICRU Reference Point inside the tissues represented by the PTV, and in a place where dose specification is considered to be meaningful. Such a place could be the region where the tumour cell density is considered to be at its maximum. (ICRU Report 50, 1993).

Electron Beams:

Single electron beam: a point should be on the 90% isodose line near the geometrical centre of the field.
Appendix 7: Lymphatic Drainage of the Head and Neck

(Adapted from Cunningham’s Textbook of Anatomy, GJ Romanes 1972 pp 961-962)
## Appendix 8: Summary of Monitoring Schedule

<table>
<thead>
<tr>
<th>Pre-randomisation (≤6 weeks of randomisation)</th>
<th>On Treatment</th>
<th>Follow-Up Visits † (Post Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly</td>
<td>Week 4</td>
</tr>
<tr>
<td>Initial Surgery 1</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CT Head &amp; Neck 2</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CT chest or Chest X-ray 2</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>History &amp; Clinical exam</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disease Status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AE assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QoL assessment 3</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>FBE</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ELFT 7</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1. Every attempt should be made to commence radiotherapy within 6 weeks but no later than 9 weeks following surgery.
2. CT of Head & Neck, and CT of Chest or Chest X-ray is to be done within 6 weeks of randomisation.
3. QoL also performed at first relapse.
4. Dates for follow up visits (post treatment) are to be calculated from the day of treatment completion.
5. Weekly for Chemo-radiotherapy arm and weeks 3 & 6 for radiotherapy alone arm.
7. Weekly U&E, creatinine for chemo-radiotherapy arm.
8. Up to 5 years or the close-out date (optional).
Appendix 9: Patient Information Sheet & Consent Form: Template

Patient Information Sheet & Consent Form: Template

Post-Operative Concurrent Chemo-Radiotherapy versus Post-Operative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck The ‘POST’ Study

PATIENT INFORMATION SHEET AND CONSENT FORM

Version 4: 18 October 2011

A SIGNED COPY OF THIS FORM MUST BE PROVIDED TO THE PATIENT PRIOR TO STUDY ENTRY

[Name of Treatment Centre/s] Research Team:

Name of Institutional Investigator/s
Name of Research Nurse / Trial Coordinator

An overview of this study

You are being invited to take part in a research study for patients with a skin (cutaneous) cancer called squamous cell carcinoma.

a) The staff at this hospital study the nature of cancer and try to develop better methods of diagnosis and treatment. The aim of this study is to try to determine the most effective treatment to control your cancer. We are also looking at how your quality of life is affected. In order for you to decide whether you should agree to be part of this study, you should understand enough about its risks and benefits to make an informed decision. This process is known as informed consent.

b) Your doctor has explained to you that a squamous cell skin cancer or a skin cancer that has spread to your lymph nodes has been removed with surgery. It is usual to have an operation to remove all the lymph nodes in the region where the cancer has spread. This operation is called a “lymph node dissection” or “lymphadenectomy.” In some cases the cancer spreads to lymph nodes that lie within your parotid gland (a major salivary gland that lies on either side of your jaw). Removal of this gland is known as a “parotidectomy”.

c) Even after such an operation, the cancer sometimes grows back again in the area of the operation. The surgeon at the operation, and the pathologist who looks at the tissue removed at operation are able to see if there are signs that you may be at risk of this. Skin cancers that have a high likelihood of returning are known as a “high-risk” skin cancer.

d) Your cancer has been identified as being a “high-risk” skin cancer.

e) There is good evidence that radiotherapy following surgery for these cancers reduces the risk of the cancer returning. The use of post-operative radiotherapy reduces the risk of the cancer coming back by 15-30%.

f) There is some preliminary evidence in other cancers that giving a chemotherapy drug known as carboplatin in a low dose once a week during the radiotherapy may improve the chance of cure. However at present there is no definite evidence that the use of this agent with
radiotherapy given at the same time following surgery for “high-risk” skin cancer improves cure.

g) Carboplatin added to radiotherapy in the treatment of other cancers has been shown to be safe and effective. However, the addition of carboplatin to the radiotherapy may increase the rate of side effects during treatment.

h) It is planned that approximately 350 patients will participate in this study. This is a Trans-Tasman Radiation Oncology Group (TROG) study and many treatment centres from Australia and New Zealand will be involved. Patients participating in this study will be divided into 2 groups. After the operation one group (half of the 350 patients) will receive radiation treatment and the other half, radiation and carboplatin, after the operation. A ‘randomisation’ procedure is used to decide which patients are in each treatment group, that is, a computer will decide at random which group you are in. This means that if you agree to participate in the trial you have a random 50:50 chance (like tossing a coin) of being given radiotherapy or carboplatin/radiotherapy after your operation. The radiotherapy would commence around 6 weeks after your operation and usually no earlier than 4 weeks.

i) Should you decide not to participate in this study, your doctor will discuss details of your treatment options with you. Your decision not to participate would not affect how you would be treated.

j) It is important to tell your doctor about any treatments or medication that you are currently taking.

1. Treatment schedule and follow up program

a) You will have had other tests, such as CT scans and blood tests to find out if the skin cancer has spread to other parts of your body and how well your various organs are performing. You should know the results of these tests before considering this clinical trial.

b) You will be required to attend a radiotherapy planning appointment and undergo a CT scan prior to starting treatment. This is to obtain measurements necessary for planning your radiation treatment. A doctor will draw on your skin an area in the region of surgery. A photograph may be taken of this outline and then the pencil marks removed. The treatment is given by a large x-ray machine (linear accelerator) which uses high energy x-rays directed at the site of the operation to kill any possible remaining cancer cells. You will have to come to hospital for 30-33 treatment visits, five days per week over a maximum of 47 days. Most treatment appointments take around 15-30 minutes in total.

c) If you have been randomised to receive carboplatin in addition to radiotherapy you will need to attend the chemotherapy day-ward once a week for 6 weeks (6 visits) for approximately one hour. The chemotherapy is given over 30 minutes through a drip inserted in your arm (intravenous infusion).

d) During your treatment you will be reviewed weekly by your doctor. Following radiation treatment you will have regular follow up visits, monthly for the first 3 months, and then every 3 months up to the 1st year and then every 4 months in the 2nd year and then 6 monthly until the completion of the trial. You will have complete clinical examinations and will be monitored for the effect of the treatment. Some of your medical information and test results will be recorded by your doctor on special study forms.

e) To assess how you are feeling, you will be asked to fill in a quality of life assessment questionnaire at the beginning of the study, and then at 3, 6, 12 and 24 months following completion of treatment. This questionnaire is designed to determine how the treatment affects you and to record any symptoms you may have. It takes about 10 minutes to complete the questionnaire.

f) You will be participating in the trial for at least 2 years.
2. **Possible side effects from radiotherapy and carboplatin**

a) Radiotherapy and carboplatin may add to the side effects you already feel from your operation.

b) Radiotherapy is a localized treatment to the face and neck. The side effects of radiotherapy depend on the area being treated. Your doctor will discuss the potential side-effects that may occur during and shortly after treatment and long-term effects which may appear months or years after treatment.

c) Women who are pregnant or uncertain if they are pregnant must not participate in this trial. Women who are of child-bearing potential will need to have a pregnancy test before being included in this trial. Both men and women are strongly advised to practice effective contraception during, and for at least 6 months following treatment. You should discuss methods of effective contraception and your individual circumstances with regard to family planning with your doctor.

d) The acute side effects of radiotherapy depends on what area of the head and neck is being treated, and commonly include skin redness and peeling, loss of taste, sore throat, hair loss within the treated area, lack of appetite, weight loss and lethargy. Common permanent long term side-effects include thinning of skin, thickening of the neck tissues, hair loss or thinning, hearing loss and dry mouth. Rare complications which can develop years after treatment include damage (necrosis) of the mandible (lower jaw bone) which can lead to fractures, nerve damage and cataract formation.

e) If you receive carboplatin with radiotherapy you will undergo weekly blood tests. This drug is used in many other cancer and its side effects are well known. The common side-effects with this drug are nausea, vomiting and diarrhoea. The other potential side effect is that it can reduce the level of white cells (help fight infections), platelets (help blood clot) and haemoglobin (helps carry oxygen in your blood). If the white cells or platelets fall to a low level, carboplatin will either not be given that week or the dose will be reduced. If the white cells fall to a low level there is a risk you may develop a serious infection (febrile neutropenia) and you will require urgent hospitalization and antibiotic treatment. In very rare cases if the treatment is not commenced urgently death can occur. Your doctor will discuss with you the potential risks of the chemotherapy.

3. **Possible benefits**

It is not possible to predict if participating in this study will have any personal benefit for you. This study is trying to find out if giving chemotherapy with radiotherapy following surgery is more beneficial to radiotherapy alone. If one of the treatment programs proves to be superior to the other, you may benefit from your involvement in this trial. Benefit cannot be guaranteed, however other patients may benefit in the future from knowledge gained in this trial.

4. **Your rights**

a) You may ask questions regarding this trial and can expect clear and understandable answers in return.

b) Participation in the study is voluntary, and you are not obliged to participate if you do not wish to do so. You may withdraw from this study at any time you wish without jeopardizing further treatment at this hospital. Your doctor may withdraw you from this study at any time if it felt that continuing would incur a serious risk to you. If you wish to withdraw from the study at any time, you can notify Dr _________by calling the hospital on telephone number __________.

c) If any new information becomes available that may influence your decision to continue in this trial, such information will be given to you.
d) Any information obtained in connection with this trial and that can identify you will remain confidential. It will only be disclosed with your permission, except as required by law. If you give us your permission (by signing the attached Consent Form), you also consent to the release of your medical records to the Trans-Tasman Radiation Oncology Group (TROG), its employees or agents, to the regulatory authorities here and overseas and the institutional Ethics Committee with the understanding that these records will be used only in connection with carrying out our obligations relating to this study (such as verification of the accuracy of study information and compliance with research guidelines). You will not be identified as an individual in any reports or subsequent publications.

e) In the unlikely event that you suffer an injury as a result of participating in this trial, hospital care and treatment will be provided at no extra cost to you.

f) Your participation in this study will not influence the amount of money (if any) you have to pay for your treatment.

g) Although you will not receive payment for participation in a clinical trial, you may be reimbursed for expenses incurred beyond what is related to routine management of your disease.

h) This study will be conducted in accordance with the Australian National Health & Medical Research Council’s National Statement on Ethical Conduct in Research Involving Humans (June 1999) and the New Zealand Interim Good Clinical Research Practice Guidelines (Medsafe, August 1998) developed to protect the interests of research participants. The ethical aspects of this research project have been reviewed by the Research Ethics Committee of this hospital and the project has been duly approved. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study or your rights as a participant, or should you wish to make an independent complaint, you can contact the Secretary, Research Ethics Committee, (details provided by the participating centre)

5. Whom to call

The doctor you should contact should any problems arise is Dr______________. The hospital telephone number is ______________. If at any time during your treatment you require urgent medical assistance after-hours, contact [insert relevant details for hospital emergency department or on-call Radiation Oncologist]. You should inform the medical staff that you are participating in this clinical research study.
PATIENT CONSENT FORM

A SIGNED COPY OF THIS FORM MUST BE PROVIDED TO THE PATIENT PRIOR TO STUDY ENTRY

Dr……………………………….has discussed this trial with me. I have had the opportunity to ask questions and I have received answers that are satisfactory to me.

• I have been informed of the possible risks or side effects of the procedures being conducted.

• I understand that a ‘randomisation’ procedure will determine my treatment group and that there is a 50:50 chance of being given radiotherapy or carboplatin / radiotherapy after my operation.

• I understand that I can withdraw from this trial at any time without affecting my further management.

• I consent to the publishing of results of the study provided my identity is not revealed.

• I have read and kept a copy of the attached Patient Information Sheet and understand the general purposes and methods of this trial.

• I agree to participate in this trial.

• I hereby give permission for medical practitioners, other health professionals, hospitals or laboratories outside this hospital, to release information concerning my disease and treatment which is needed for this trial and understand that such information will remain confidential.

• I authorize TROG auditors and regulatory authorities access to my medical records for purposes of data verification and verification of compliance with research guidelines.

PATIENT’S NAME   ………………………………………

Please print

PATIENT’S SIGNATURE   ………………………………………    DATE   ……………….
Please print

I, the supervising physician, confirm that I have fully explained the nature, purpose and reasonably foreseeable risks to the patient taking part in the study. I confirm that he/she been given a copy of the Patient Information Sheet.

Please print

Please print
OPTIONAL TRANSLATIONAL STUDY CONSENT

The researchers doing this study are also interested in doing research studies on tissue samples from your diagnostic cancer specimen to better understand the nature of the type of cancer you have and how patients like you respond to treatment. We are requesting your consent to allow us to use, for research purposes, any tissue samples that may have been taken from you previously as a biopsy or during surgery. These tissue samples are routinely stored in pathology laboratories.

The samples will be kept until the research studies are completed. They will then be returned to the hospital where you had your surgery or biopsy. The samples will be used for research purposes only and will not be sold.

The collection of these samples is an optional part of this study. The tumour sample would come from your squamous cell cancer that has already been removed by surgery or biopsy. You may choose not to take part, or may at any time withdraw your consent for this portion of the study and ask that the collected tissue samples not be used. Deciding not to take part, or deciding to withdraw your consent for this portion of the study later, will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating, and no longer want your tissue samples to be used in this research, you should tell your doctor.

By signing this consent section, I agree to the use of tissue samples obtained previously from my previous biopsy or surgery for the purposes of additional testing for markers that can predict response to treatment.

PATIENT'S NAME ..................................................  
Please print

PATIENT'S SIGNATURE ........................................ DATE ......................

WITNESS' NAME ..................................................  
Please print

WITNESS' SIGNATURE ........................................ DATE ......................

PHYSICIAN’S NAME ..................................................  
Please print

PHYSICIAN’S SIGNATURE ........................................ DATE ......................

Note: All parties signing the consent section must date their own signature.
Figure 1. Advanced Local Disease

Phase 1 – PTV50

CTV 1 (50Gy):
- site of resected gross disease
- surgical bed/scar
- first echelon of clinically uninvolved draining lymph nodes

PTV 1 (50Gy): CTV 1 + minimum 0.5 cm margin in all dimensions
Phase 1 – PTV50 cont.

Fig. 1.3
Phase 2 – PTV54

CTV 2 (54Gy):
- site of resected gross disease
- surgical bed/scar

PTV 2 (54Gy): CTV 2 + minimum 0.5 cm margin in all dimensions
Phase 2 – PTV54 cont.

Fig. 1.7
Phase 3 – PTV60-66

CTV 3 (60-66Gy):
- site of resected gross disease

PTV 3 (60-66Gy): CTV 3 + minimum 0.5 cm margin in all dimensions
**Figure 2. High Risk Nodal Disease**

**Phase 1 – PTV50**

CTV 1:
- site of resected gross disease
- surgical bed/scar
- first echelon of clinically uninvolved draining lymph nodes

PTV 1 (50Gy): CTV 1 + minimum 0.5 cm margin in all dimensions

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Phase 1 cont.
Fig. 2.3
Phase 2 – PTV54

CTV 2:
- site of resected gross disease
- surgical bed/scar

PTV 2 (54Gy): CTV 2 + minimum 0.5 cm margin in all dimensions
Phase 3 – PTV60-66

CTV 3 (60-66Gy):
- site of resected gross disease

PTV 3 (60-66Gy): CTV 3 + minimum 0.5 cm margin in all dimensions
Figure 3. High Risk Nodal Disease Summary

GTV - Red

PTV50 - Orange

GTV - Red

PTV50 - Orange

PTV54 - Magenta

GTV - Red

PTV50 - Orange

PTV54 - Magenta

PTV60-66 - Red

Fig. 3.1

Fig. 3.2

Fig. 3.3