

Protocol 24021: Sentinel Node Biopsy in the Management of Oral and Oropharyngeal Squamous Cell Carcinoma

Outline Submitted by D. Lacombe for M. Mc Gurk
Center: 7013
Modified by lacombe
Final: Yes

Participating group(s)

EORTC Group: Head and Neck (single group study)

Full Protocol already available

No

Study already running

No

Date of activation

NA

Number of patients already included

NA

Eortc Coordinator

NA
NA
NA
NA
select

Leading Coordinator

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DC approved

yes, EORTC Data Center
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Trial Design

Observational non randomized trial

Objectives

1. To establish that sentinel node biopsy (SNB) markedly reduces the incidence of elective neck dissection required in the management of the N0 neck.
2. To describe the survival of SNB+ patients treated by neck dissection and relate it to that of SNB- cases with subsequent treatment for recurrent cervical disease. [descriptive only]
3. To establish if histological evaluation of the sentinel node by immunochemical and H&E section taken at 2.5mm intervals is adequate to detect tumor, or a more detailed evaluation by serial section is more appropriate

Rationale

Sentinel node biopsy is based on the assumption that a primary tumor drains to one (or more) discrete lymph nodes before disseminating to the remaining local nodal field. It is also assumed that if metastatic disease is found in the sentinel node there is an increased likelihood that other nodes will be involved. This in turn argues for the elective treatment of the affected nodal area. There is also a corollary in that if no disease is identified in the sentinel node the remaining lymph nodes can be presumed free of disease. Thus the hypothesis is that, in the context of oral cancer, the status of the sentinel node can be taken as indicative of the status of the entire neck. (For the purposes of this protocol oral cancer will be defined as squamous cell carcinoma of the mouth and oropharynx). If this premise is substantiated then a more conservative approach to head and neck surgery can then be adopted.

There is a powerful rationale for sentinel node biopsy in the management of oral cancer as the status of the neck has a significant impact on outcome [1] and cervical metastasis is relatively common (30%) for tumors stage II or greater [2] but systemic dissemination is infrequent [3]. Control of loco-regional disease (neck and primary site) is therefore often commensurate with cure. Consequently a policy has been adopted to eliminate occult metastasis by elective neck dissection in all patients in whom this is felt to be likely. This policy means that up to 80% of patients with N0 necks have unnecessary operations. Oral cancer is eminently suitable for sentinel node evaluation as metastasis takes place down lymphatic corridors to specific areas of the neck, which depend on the site of the primary tumor [2,4].

The technique of sentinel node biopsy has been established in the field of breast cancer [5] and malignant melanoma [6] and more recently for head and neck cancers [7-9]. The technique described using a vital dye [10] was modified [11] to incorporate a radioactive tracer. The combined technique involves injecting a radiolabelled tracer around the periphery of the tumor in the 24-hour window prior to surgery. During this period the migration of tracer can be followed with a gamma camera and the position of the sentinel node(s) marked on the skin of the neck. At the commencement of surgery a blue dye is injected around the tumor in a similar manner. Over a period of 20 minutes it passes along lymphatic channels to accumulate in sentinel node(s) giving them a blue hue. At surgery the node(s) are identified by the radioactive signal detected with a hand held gamma probe and by the blue colour. Once identified the node(s) can be sent for histological examination. In a multi institutional study by Ross et al, the sensitivity of this technique in head and neck cancer has been estimated as 94% in those centres that have performed more than 10 SNB procedures. However, the sensitivity of the technique falls to 57% with less experienced operators [12].

Experience in melanoma and breast cancer has shown that routine pathology alone involving limited sampling of nodes is not sufficient in assessing sentinel nodes.

Detailed step serial sectioning and immunohistochemistry in melanoma and breast have shown upstaging of disease between 3-33% [13]. Gershenwald [14] looked at recurrences following 243 melanoma sentinel node biopsies and found that 80% would have been prevented had immunohistochemistry and step serial sectioning been used. Immunohistochemistry has been previously shown to upstage disease between 8-23% of clinically N0 necks in SCC of the head and neck [13,15,16]. Our studies have shown an upstaging of almost 20% in sentinel node biopsy within the clinically N0 neck [17]. Definitive pathological assessment of sentinel nodes will therefore involve the use of step-serial sectioning and immunohistochemistry.

References

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Investigational agents

Name: NA
Origin: NA
Type: NA

Further plans

Historical data exist for both elective neck dissection and a "wait and see" policy in which no treatment for the N0 neck is undertaken until clinically apparent metastasis is found. A prospective randomized trial of sentinel node versus conventional practice is not practical due to the number of patients required to confirm survival advantage

Eligible patient population

- Primary biopsy proven oral/oropharyngeal squamous cell carcinoma.
- T1 > 1cm, T2 tumors or T3 tumors that can be locally resected.
- Tumors that can be treated by local resection alone or iridium implants and are amenable to injection of dye/radioactive markers. (It is envisaged that the vast majority of primary tumors will be treated by surgical excision).
- Negative neck nodes (N0) based on imaging by either CT or MRI scans (ultrasound evaluation of the neck is operator dependent and not universally available). The standard of assessment for entry to the study is a N0 neck based on CT/MRI imaging. Radiological evidence suggestive of cervical metastasis (cystic degeneration or lymph nodes >2cm in diameter will be interpreted as N+ and the case will fall out of the study). This will be an uncommon event with early cancers (T1, T2 N0). It is estimated that CT/MRI evaluation will reduce the incidence of positive nodes in the study population from 30% to 25%. Patient accrual will be adjusted accordingly.
- Patients must be preoperatively fit enough to withstand a neck dissection prior to

inclusion into this trial.

- No previous neck pathology or treatment to the primary tumor or neck (surgery, radiotherapy or chemotherapy) that may alter lymphatic drainage channels.*
- Age limit 18 – 75.
- WHO PS 0-2
- Written informed consent.

* During and after SNB (i.e.: after registration), local treatments that do not affect the neck such as small needles brachytherapy or intra-arterial chemotherapy are allowed. Loco-regional treatment such as external beam radiotherapy through-and-through radioactive wires are not allowed.

Treatments

In the 24-hr period prior to surgery the patients will be injected at as many sites as required to completely surround the tumor with 10-40 MBq of 99mTc labelled nanocolloid. The colloid distributes along the lymphatics and localizes in draining nodes. It is helpful (but not essential to the study) that the signal is imaged with a gamma camera until sentinel lymph nodes are detected. These node(s) are usually identified between 15 minutes and one hour after injection. The positions of the sentinel nodes can then be marked on the skin to help localise them at surgery. Either static or dynamic lymphoscintigraphy may be used depending on each member State's regulations.

This study will focus on the ipsilateral neck. If more than one sentinel node is identified or more than one site contains a sentinel node, then these will be harvested for histopathological examination. Contra-lateral sentinel nodes will be investigated only in cases of probable nodal metastasis of the contra-lateral neck (mid-line cancers).

The status of the contra-lateral neck will be determined through follow-up for the duration of the trial. (In this context, if postoperative radiation should include the contra-lateral neck, then this will be recorded on the proforma.)

At the commencement of surgery, 1-2 ml of Patent Blue V dye, diluted 1:3 in water, will be injected at 4 equally spaced points to completely surround the tumor. The neck will then be approached by a neck incision of the surgeon's choice that will aid a subsequent neck dissection should it be required. The sentinel node(s) (on average 2.0 per case) will be identified using the gamma probe and blue dye.

Anatomopathologic assessment should be undertaken in two parts. The first involves fixing the nodes in 10% neutral buffered formalin and after fixation bisecting them through the hilum, if this is identifiable, or through the long axis of the node. If the thickness of the halves is more than 2.5mm the slices are further sectioned to provide additional 2.5mm thick blocks. Two histological sections should be taken from each 2.5mm slice: one to prepare for H&E, the other for cytokeratin antibody.

Part two: if the sentinel node is microscopically free from tumor after H&E then step-serial section is mandatory. The blocks are cut at approximately 150µm and stained alternately with H&E and multi cytokeratin antibody (AE 1/3). All positive immunocytochemistry (ICC) will be compared with the H&E serial section to confirm positive findings. Centres that are not able to undertake the second detailed evaluation of the node can forward the blocks to a central quality control laboratory for preparation (see quality control).). All tissues will be stored in airtight containers for translational research projects and appropriate informed consent obtained from the patients for this work.

In a study of 125 successful sentinel node biopsies at Canniesburn in clinically N0 necks the upstaging of disease occurred in 34% of cases (42 out of 125). The upstaging occurred in 32 cases using H&E and 10 cases using additional serial sections and immunohistochemistry. The upstaging of data in this study resulted in a reported incidence of occult metastasis of around 30% for T1 and T2 tumours. A micrometastasis could be defined as a nodal deposit 2mm or less in greatest diameter. An isolated tumour cell cluster = 0.2mm or less in diameter.

A positive sentinel node will lead to a neck dissection within 28 days (type in accordance with each cancer centre's protocols). Positive nodes in level IV warrant a modified radical neck dissection – type of neck dissection employed should be recorded). Delay from positive sentinel node to surgery should not exceed 28. One of the objectives in this study is to describe the survival of SNB+ patients with neck dissection, as well as survival of SNB– patients that subsequently develop recurrent disease. There will be a delay between SNB+ cases being identified and subsequent neck dissection of approximately 4 weeks. There is anecdotal evidence that delay makes it difficult to control the neck. Unless data is recorded on this issue it will be held as a criticism of the study. The specimen from the therapeutic neck dissection will be formalin fixed and the nodes assessed in accordance with The Royal College of Pathologists Guidelines [18]. In the event of nodal disease where there are >2 positive nodes or extra-capsular spread then postoperative radiotherapy is indicated. Suggestion for radiation protocol to be used will be detailed in the full protocol (details of histological assessment of nodes is contained in the next section).

References:

20 Minimum dataset for head and neck carcinoma. Royal College of Pathologists 1998.

Added investigations

Factors in the patient's history or on clinical examination that may predict for abnormal paths of lymph drainage will be recorded ie scar formation, previous surgery, Tumor Biopsy, etc.

The study will be undertaken in conjunction with the Nuclear Medicine Departments of participating hospitals. The medical physics expert (radiation protection officer) at each centre will coordinate the study in accordance with the member State's regulations.

For the sentinel node biopsy, see treatment details above.

Imaging by CT Scans or MRI must be done prior to surgery. For follow up of patients, Imaging is the only reference for this study. The investigative criteria used for entry to the study will be based on CT/MRI assessment and will be used for follow-up every 3 months up to 3 years and then every 6 months up to 5 years after entry. Patients with suspected recurrence are to be evaluated as deemed necessary by the attending doctor. If recurrent disease is detected at any site (local, contralateral regional, distant) the patient will be investigated and treated according to the institution's best preference and will be treated as competing risk events in the analysis of the primary endpoint. A second primary tumor will also be treated as a competing risk. These patients should be followed up to chart the subsequent course of the disease. This is especially the case in patients with isolated regional recurrence.

Endpoints

Primary: Cervical recurrence-free rate 3 years after registration in the cohort of patients who are SNB- at registration

Secondary: 1. Overall survival collectively, and by SNB status (SNB- or SNB+) but only descriptive.

2. PFS in the SNB- cohort

3. Salvage rate of the SNB- patients who had a cervical recurrence during the first 3 years after registration. Patients should be followed up for five years or to death in order to establish survival.

4. QA endpoint: false negative rate for part I and II of the pathology assessment

Randomized

No

Justification: A randomized trial would have to test a non-inferiority hypothesis and would require over 1000 patients

Design parameters

Other statistical design

After registration of a patient in this trial, a sentinel node biopsy (SNB) technique is performed.

Based on the SNB procedure, a patient is classified as either SNB positive (SNB+) or SNB negative (SNB-).

An elective neck dissection will be performed on the SNB+ patients, while the SNB- cases will be followed up during five years. The validity of the SNB procedure will be assessed by investigating whether SNB- patients are still cervical neck recurrence-free 3 years after registration in the study.

Based on this evaluation, patients can be classified as cervical recurrence-free 3 years after registration (rec-) or not (rec+).

It is expected that in 75% of the registered patients, there is no spread from the primary tumor site to the cervical nodes at the enrolment in the study. One assumes that all these cases will be rec-. Furthermore, since false positive results of the SNB procedure are not expected, it is assumed that all these patients will be SNB-.

The SNB technique will only be considered worthwhile if more than 2/3 of the rec+ patients are evaluated as SNB+ at registration. Hence, in order to have evidence that in future practice SNB should be used instead of elective neck dissection, less than 8.33% (i.e. 1/3 of 25% rec+) of the registered patients should be both rec+ and SNB-. It follows that in the cohort of SNB- patients, the cervical recurrence-free rate at the sentinel node(s) 3 years after registration should be more than $75/83.33=0.90$. This is expressed in the null hypothesis of the one-sided statistical test:

H0: $p=0.90$ versus H1: $p = 0.9474$, where p is the true recurrence-free rate at the sentinel node(s) in SNB- patients 3 years after registration of the patient in the trial.

This study is designed to have 80% power to detect that the SNB technique allows to evaluate 5/6 of the rec+ cases as SNB+ at registration. Hence, the sample size of this study is based on a true cervical recurrence-free rate at the sentinel node(s) in SNB- patients 3 years after enrolment being 75/79.17 ($p=0.9474$ under H1, i.e. 75% rec- out of a SNB- cohort of 75% rec- and 1/6 of 25% rec+). Considering a one-sided significance level of 5% implies that 203 SNB- patients are required. This sample size still needs to be inflated for several reasons:

- It is assumed that the SNB procedure cannot be done on 10% of the registered patients.

- 25% of the patients who can be assessed by SNB are expected to be SNB+.

- One assumes that 30% of the SNB- cases will drop out because of being lost to follow-up, other failure, during the first 3 years after registration. Taking into account these reasons for inflating the sample size, it follows that a total of 430 patients need to be enrolled in this study. It is estimated that this patient number can be recruited over a period of 3 years. The cervical recurrence free rate in the SNB- cohort will be assessed using cumulative incidence techniques.

Stopping rule

We assume that the SNB procedure will fail in only 10% of the cases and that the overall failure rate (rate of all events whether neck recurrence (i.e. local and cervical recurrence) or distant metastasis or death after 3 years) is not higher than 25% (16.7% for local and distant failures, and 8.3% for cervical recurrence). Translating this to one year rates, there should not be more than 9% (6%+3%) failures of all types (neck recurrence or distant metastasis or death) per year. The stopping rule will be based on the test for the one year PFS, with $P_0=0.91$ (corresponding to 9% failure) and $P_1=0.81$ (corresponding to 19% failure), with one-sided $\alpha=0.10$ and 80% power. Then, 59 SNB- patients should be followed-up during one year or until death or progression, whichever comes first. If 51 or more SNB- patients are free of progression at one year, the recruitment would be prolonged to achieve the target defined for the main objectives. Taking into account the 10% percentage of patients with unfeasible SNB, 25% being SNB+ and 10% discontinuations during the first year, approximately 98 patients should be accrued at the moment of the interim analysis. As stopping the trial at the interim look will result in acceptance of the final null hypothesis, the alpha level of the final test does not need to be adjusted.

Monitored by an IDMC

Yes. IDMC Role: An IDMC review will be done after 1.5 years of recruitment, checking the rate of the various types of failures and the rate of SNB procedures that fail

PK - PD

No. Justification: NA

Translational research

Objective: The trial presents a unique opportunity to ascertain a closely stratified cohort of well-characterised squamous cell carcinomas of the oral cavity and oropharynx with matched sentinel lymph nodes. Tissue collection will be prospective and properly layered informed consent from patients will be obtained that will allow rigorous translational research to be performed. Another advantage of collecting tissues prospectively is that the ascertained samples are quality assured for uniform handling and storage. Problems relating to obtaining release of tissues used for routine diagnosis in pathology laboratories will be overcome.

TR project 1 Identification of genes and pathways regulating invasion and metastasis that predict local spread to the neck.

The clinical trial will identify matched primary operable T1-T3 squamous cell carcinomas of the oral cavity and oropharynx that differ only in having spread to the neck (~30%) or not. Distant spread will be a rare event in the cohort. Microarray platforms will be used to identify constellations of gene expression associated with invasion and metastasis including cell adhesion molecules such as E-cadherin,

integrins, proteolytic factors and their regulatory molecules in their respective pathways. The aim of the translational research is to identify specific and sensitive markers that could be applied to the primary lesion that predict negative or positive sentinel node in the N0 neck. The secondary aim is to identify gene differences between primary lesions and metastatic deposits in the sentinel nodes to determine the pattern of molecular evolution of the tumor during progression to local spread. Several array based comparative genomic hybridisation (CGH) studies of oral cancer are in progress worldwide and these will identify amplicons that are important to the biology of the disease. The tissues collected in this EORTC trial will enable application of these future molecular targets to the clinical situation in drug development programmes.

TR project 2 Innate immune responses as predictors of spread of squamous cell carcinoma to the neck and clinical outcome.

Studies of sentinel nodes in melanoma have shown that accumulation of DC-Lamp+ dendritic cells [23] and a range of other markers of active and innate immunity including Toll receptors are associated with efficient antitumor responses and the control of dissemination within the sentinel node. The ascertained tissues from the head and neck squamous carcinoma study will be an invaluable resource for determination of the role of the immune response in regulation of cell spread in a different system.

TR project 3 Role of hypoxia in the evolution of metastatic cell populations.

Recently published studies of GLUT-1 staining in oral cancer funded by TRAC, showed that chronic hypoxia, indicated by peripheral staining, was predictive of adverse outcome [24]. The tissue ascertained by the trial will permit a more comprehensive study of hypoxia markers in the matched primary tumours with SNB+ and SNB- nodes. It is likely that a microarray platform will be available at reasonable cost to identify hypoxia induced genetic drifts and angiogenic pathways, with findings confirmed by immunohistochemistry. Current studies by the head and neck group and others have identified predictive and prognostic markers that co-localise with pimonidazole in squamous cell carcinomas and that could be used to map hypoxia in early stage oral and oropharyngeal carcinomas.

TR project 4 Alcohol and smoking polymorphisms

The reference laboratory hosts the UK DNA bank for the ARCAGE study[25] that will complete recruitment of 4,000 head and neck cancers and case controls across the EU by July 2004. The study will provide major epidemiological results and will identify polymorphisms in alcohol and smoking regulatory genes that predispose to the development of head and neck cancer. Prospective collection of a simple venous blood specimen with appropriate layered consent will provide the opportunity to extend the ARCAGE study using a highly stratified sample of early stage oral cancers, where local action of alcohol may be a significant factor in the pathogenesis of oral cancer. The ARCAGE study will provide an extensively characterised reference population for the sentinel node study.

It is envisaged that the tissue collected by this trial will be an attractive resource enabling the Group to seek major external funding to undertake this research.

Material: Will be described in the full protocol

LRD Group contacted: This has been done in cooperation with TRAC (Sloan)

Quality of life

No.

Economics

No

Sponsor

No

Number of centers

18

Total yearly accrual

120

List of centers

The list hereunder indicates the EORTC site number, the name of the investigator, the location, the number of patients expected on a yearly basis / the number of SNB cases performed.

3060 Werner-Marburg, Germany: 20/ 150

101 Dequanter-Brussels (Bordet), Belgium: 15-20/11

121-Mahy-Brussels (St Luc) Belgium: 10/5 (in the process of doing additional ones)

123-Lawson-Yvoir, Belgium: 10-20/49

453-Stoeckli-Zurich, Switzerland: 20/60

225-Mamelle Paris (France): 20/60

851-Remenar-Budapest (hungary): 10/15

169-Grandi-Trento (Italy): 5/6 (additional 4 completed in the enxt 2 months)

696-Poli-Parma(Italy): 5-10/27

745-Barzan-Pordenone (Italy):10/110

Foreign: Vigili-Roma (Italy): 10/10

308- Leemans-Amsterdam (NL): 10/?

804-Machado-Lopez-Porto (Portugal) : 10/10

6231-Barbier-Bilbao(Spain): 10/50

6239-Villareal-Badajoz (Spain): 10-15/17

6961-Hyde-London (UK):5/20

7013-McGurk-London (UK):20/20

7091-Soutar-Glasgow (UK): 30/40

7110-Newman –London (UK) 5/20

Comments

1) Quality Assessment (QA)

The study will be restricted to centres that have the necessary probe together with the radiobiology facilities for sentinel node detection and the pathological resources to perform pathological assessment of sentinel nodes.

2) Surgery

Experience has shown that lymphatic mapping in the neck can be difficult [19] and there is a learning curve [20] [12]. Only centers that have previously performed the sentinel node procedure in at least 10 patients will be allowed to enter patients in

the trial. A quality assurance committee will verify the 10 cases from each unit using records from scintigraphy and sentinel node pathology reports as evidence. A video based training programme (CD ROM) will be provided to all the participating centres. It will detail each step in the process of sentinel node biopsy and include a) preoperative injection and tracing of radiolabelled marker, b)operative sequence including injection of blue dye, c) a protocol for recording of gamma counts and criteria for identification of the sentinel node. Quality control will be monitored by centre by failure to identify SN. It seems impractical to evaluate the proficiency of sentinel node biopsy in each centre, but it is possible for the two coordinators to visit each unit if this is deemed important to the study

Similarly the pathology quality assurance panel will provide (in the same CD ROM) consensus criteria and exemplar images to participating centres regarding immunohistochemistry and H&E criteria for the diagnosis of micro-metastasis.

Centers that not yet have this experience, should first validate the technique by performing sentinel node biopsy followed by a neck dissection and compare the pathological results in 10 patients. An overall sentinel node identification rate of 90% in ten consecutive cases should be achieved before patients are entered into the trial. Failure to identify any nodal tissue should not exceed 10% in this study.

3) Pathology

A random sample of 25% of cases will be reviewed by an expert panel in the UK and Belgium (Professor Sloan, University of Manchester & Dr Silvana Di Palma, Guildford, Dr Brigit Weynand, St Luc Brussels) by consensus reporting. The case material from all suspected false/positive and false/negative reports (ascertained by unexpected clinical behaviour) will also be reviewed. A standard operating procedure (SOP) document will be issued to all participating centres which details all aspects of tissue handling including fixation, processing and technical methods for immunohistochemistry. Unstained sections of a reference lymph node containing metastatic squamous cell carcinoma will be forwarded to each participating laboratory with the SOP and thereafter at 6 monthly intervals. The participating laboratory will stain the reference section by H&E and anticytokeratin antibody methods and make an assessment of quality on a 4 point scale and then return the reference slides to the quality control laboratory in Manchester for assessment by a biomedical and pathology staff panel. The participating laboratory will also stain sections from their last positive sentinel lymph node in parallel (when the study is running) and forward these to the reference laboratory. Scores and the slides will be returned to the participating laboratory along with an anonymised data set for all participating centres. The quality assurance process will follow the procedures used in the well-established UK NEQAS system for immunohistochemistry. As indicated above a CD-ROM containing exemplar images will be distributed to participating centres to aid the pathologist's interpretation of the immunohistochemistry. Individual cases may be referred to the reference laboratory for advice where results are equivocal. Calibration of participating centers will be required. Two members of the pathology sub-committee will undertake a central pathological review of 25% of the pathology material. The blocks and slides from the first case at each participating centre should be forwarded to the quality assessment pathology unit. In addition, 25% of treated cases, should be randomly selected each year for review. False negative/positive cases should also be reviewed centrally. If any centre has recurrence rate of >10%, then all the pathological material should be reassessed. To facilitate this quality assessment consent for the study should include permission for material to be reassessed at the central laboratory.

References:

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Can be circulated

Yes/No: yes

Justification: NA