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Long-term results of positron emission tomography-directed management of the neck in node-positive head and neck cancer after organ preservation therapy

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SUMMARY

Objectives: The current study presents the long-term results from a study designed to evaluate a restaging positron emission tomography (PET) directed policy whereby neck dissections were omitted in all node positive head and neck squamous cell carcinoma (N + HNSCC) patients with PET-negative lymph nodes after definitive radiotherapy (RT), with or without chemotherapy.
Methods: A post-therapy nodal response assessment with PET and computed tomography (CT) was performed in patients who achieved a complete response at the primary site after definitive radiotherapy. Patients with PET-negative lymph nodes were observed regardless of residual CT abnormalities.
Results: One hundred and twelve patients, the majority of whom (83 patients, 74%) had oropharyngeal primaries, were treated on protocol. Median follow-up was 62 months. Negative and positive predictive values for the restaging PET was 97.1% and 77.8% respectively, with only one patient who was PET-negative after treatment experiencing an isolated nodal relapse.
Conclusion: PET-guided management of the neck following organ preservation therapy effectively spares neck dissections in patients with N + HNSCC without compromising isolated nodal control or overall survival.

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Introduction

The standard of care for the non-surgical management of patients with node-positive mucosal head and neck squamous cell carcinoma (N + HNSCC) is radiotherapy (RT) with or without chemotherapy, and in many institutions this has traditionally been followed by a planned neck dissection of initially involved nodal regions. Improved imaging modalities are now available to evaluate the response of involved neck nodes and select patients who will potentially benefit from a neck dissection after completion of definitive radiotherapy [1]. In a number of retrospective studies, functional imaging with 18F-fluorodeoxyglucose positron emission tomography (PET) has been shown to have a high negative predictive value (NPV) in nodal assessment after chemoradiotherapy [2–4].

We have previously reported results from a prospective study designed to evaluate a restaging PET policy where neck dissections were omitted in all N + HNSCC patients with PET-negative lymph nodes after definitive RT, with or without chemotherapy, regardless of the presence of residual lymph nodes on clinical examination and contrast-enhanced computed tomography (CT). With a median follow-up of 28 months from commencement of RT, the protocol appropriately spared neck dissections in patients who achieved a complete PET response at the primary and neck, despite residual structural imaging nodal abnormalities without compromising regional control [5].

The purpose of the present analysis is to present the long-term results of this approach and patterns of recurrences, failure free survival and overall survival.

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Patients and methods

The study was approved by the institutional ethics board and written informed consent was obtained from all participants. A thorough description of patients and methods is previously described [5] and will be summarized in the following sections.

Patient eligibility and pathological evaluation

Patients were eligible for treatment on protocol if they had biopsy proven N + HNSCC with no evidence of distant metastasis, and after discussion at our multidisciplinary head and neck clinic were considered eligible for organ preservation therapy with definitive RT. For patients with oropharyngeal tumours and those with involved cervical nodes with unknown primary, biopsy p16 status was determined by immunohistochemical (IHC) staining and considered positive if strong and diffuse (nuclear and cytoplasmic) in $\geqslant$70% of tumour cells.

Only patients who achieved a complete response at the primary site at 12 weeks post-RT were eligible for analysis; primary site response was based on clinical examination, CT and PET findings and a final determination of primary response made at the multidisciplinary team meeting.

Radiotherapy and systemic treatment

All patients were treated with definitive radiotherapy, either with concomitant boost RT or conventionally fractionated RT with or without systemic therapy. Elective sites were treated to a biologically equivalent dose of 50 Gy in 2 Gy fractions. Known sites of gross disease received either 2 Gy/fraction to a total of 70 Gy over 7 weeks or a concomitant boost schedule to a total of 66 Gy over 5 weeks using a morning dose of 2 Gy/day for 5 weeks and an afternoon boost dose of 1.6 Gy/day in weeks 4 and 5.

Selection of systemic therapy was at the discretion of the treating physician but was generally omitted for patients with low-volume disease (T0-2, N1). Concurrent systemic therapy consisted of either high-dose cisplatin (100 mg/m^2) given in weeks 1, 4 and 7 or fractionated weekly cisplatin (40 mg/m^2). Patients with contraindications to cisplatin received either carboplatin/5-flurouracil in the final two weeks of radiotherapy, or cetuximab as a pre-radiotherapy loading dose then weekly during treatment.

Diagnostic CT imaging and definitions

A diagnostic contrast-enhanced CT of the head, neck and chest was performed as a baseline pre-therapy, and with the 12-week restaging PET. A residual nodal abnormality on structural imaging was defined as a node demonstrating necrosis, contrast enhancement or $\geqslant$10 mm in any dimension. Diagnostic CT scans were assessed by a radiologist associated with the multidisciplinary clinic.

PET imaging protocol and definitions

Preparation for imaging was in accordance with the guidelines of the Society of Nuclear Medicine and European association of Nuclear Medicine [6,7]. A Philips Gemini GXL PET/CT system was used and images acquired from skull vertex to mid-thigh, with a low-dose CT for attenuation correction and lesion localization (120 kVp; 30–50 mAs) also acquired.

Two qualified nuclear medicine physicians independently reviewed all the datasets on dedicated MedView display systems (MedImage, Ann Arbor, MI). The PET scans were assessed visually. FDG uptake was considered positive if it was focal, corresponded to a structural abnormality and was of greater intensity than background liver activity. Where focal FDG avidity was below background liver activity, but of greater intensity than adjacent normal-tissue activity this was considered equivocal. No residual FDG avidity above background or diffuse uptake in the absence of a corresponding structural abnormality was considered negative. Standardized Uptake Value (SUV) were recorded for all PET imaging but not used in the assessment of treatment response algorithm.

PET-directed neck policy

The PET protocol (Fig. 1) consisted of a PET-CT scan performed within 3 weeks prior to commencing, and around 12 weeks post therapy. If the post-treatment PET was considered negative in the neck the patient remained on an observation policy regardless of an incomplete response on CT. If the post-treatment PET demonstrated equivocal nodal FDG avidity a repeat PET was performed 4–6 weeks later; if the repeat PET was equivocal or positive a neck dissection was performed. If the 12-week PET was positive a neck dissection was performed.

Follow-up

Following completion of treatment patients were assessed every 3 months for the first year, every 4 months for the next 2 years and every 6 months for another 2 years. Additional re-imaging was performed only if clinically indicated.

Analysis and statistical considerations

In order to analyze long-term results all patients' medical records were reviewed and, when needed, up-to-date information was obtained from treating physicians.

Isolated nodal failure was defined as nodal recurrence in the absence of any other type of failure, primary and/or distant. Composite nodal failure was defined as nodal failure that occurred in the presence of another failure site(s).

Survival analysis data was calculated using Kaplan–Meier methods using the time from the date of completion of RT until failure (defined below), death or the time of last follow-up. Nodal (isolated or composite) failure-free survival (FFS), locoregional (primary site and nodal) FFS, distant metastasis FFS and overall survival were calculated. Life tables were used to calculate actuarial five-year survival and confidence intervals for the proportion of patients surviving nodal-, locoregional- and distant-failure free. Median follow-up time was calculated using the reverse overall-survival Kaplan–Meier method.

Results

Patient and tumour characteristics

Between January 2005 and April 2009, 121 patients with node-positive HNSCC, suitable for organ preservation treatment, were treated according to the protocol. Four patients did not achieve a complete response at the primary site and five patients did not undergo the restaging PET. These patients were excluded; 112 patients were eligible for the primary analysis and all are also included in the present analysis. Patient demographics, tumour characteristics and TNM staging are summarized in Tables 1 and 2.

The median follow-up time for all eligible patients was 62 months (interquartile range (IQR) 54–67), At close-out date for analysis, 78 patients (70%) were alive with no evidence of

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