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Viable tumor in salvage neck dissections in head and neck cancer: Relation with initial treatment, change of lymph node size and human papillomavirus

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ABSTRACT

Objectives: To identify predictive factors for the presence of viable tumor and outcome in head and neck cancer patients who undergo therapeutic salvage neck dissections.
Materials and Methods: Retrospective analysis of 76 salvage neck dissections after radiotherapy alone (n = 22), radiotherapy in combination with carboplatin/5-fluorouracil (n = 42) or with cetuximab (n = 12).
Results: Viable tumor was detected in 41% of all neck dissections. Univariate analysis revealed initial treatment with radiotherapy without systemic therapy (OR 6.93, 95%CI: 2.28–21.07, p < .001), increased lymph node size after initial treatment compared to pretreatment CT scan (OR 20.48, 95%CI: 2.46–170.73, p = .005), more extensive neck dissections (OR 8.40, 95%CI: 2.94–23.98, p < .001), and human papillomavirus negative cancer (OR 4.22, 95%CI: 1.10–16.22, p = .036) as predictors of viable tumor. Patients with decreased or stable, but persistently enlarged lymph node size after chemoradiation had a significantly lower chance of viable tumor (OR 0.15, 95%CI: 0.05–0.41, p < .001). Disease-specific 5-year survival was 34% in case of viable tumor, and 78% when no viable tumor was found (p < .001).
Conclusions: Viable tumor in salvage neck dissections is associated with reduced survival. Radiotherapy alone, human papillomavirus negative cancer and increase in lymph node size, are associated with viable tumor in salvage neck dissections. In case of decreased or stable lymph node size after chemoradiation, watchful waiting could be considered.

Introduction

Radiotherapy with or without concomitant systemic treatment is one of the main treatment strategies for patients with locally advanced head and neck squamous cell carcinoma (HNSCC).

These patients have high recurrence rates despite the evolution of treatment strategies [1]. In case of persistent enlarged or recurrent lymph nodes after complete response of the primary tumor, a salvage neck dissection is the treatment of choice [1]. However, this treatment has been associated with considerable morbidity like wound complications in more than 30% of the patients. Complication rates are lower after selective salvage neck dissections compared to (modified) radical salvage neck dissections [2].

After (chemo)radiation, the diagnostic value of CT and MRI, and the specificity of ultrasound-guided fine needle aspiration cytology for evaluating lymph node metastases is low [2], which complicates

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decision making about neck dissection.

PET-CT guided surveillance after chemoradiotherapy is advised. The indication for a salvage neck dissection is lymph node size > 1 cm with FDG uptake. In case of lymph nodes > 1 cm without FDG-uptake and FDG-positive lymph nodes < 1 cm a neck dissection can be considered [3]. Therefore, in recent studies, salvage neck dissections are generally performed in patients with enlarged PET-negative lymph nodes or persistent normal-sized PET positive nodes [3,4].

Other studies have shown that 20–68% of the therapeutic salvage neck dissections contain viable tumor [5]. Identification of variables predicting the presence of viable tumor in neck nodes after various forms of treatment (i.e. radiotherapy with or without systemic therapy) would be helpful for selecting the right patients for neck dissection and for avoiding unnecessary surgery.

In this study we aimed to identify clinical, histopathological, radiological and treatment related predictors for the presence of viable tumor in salvage neck dissections. Furthermore we assessed the influence of presence of viable tumor in salvage neck dissections on clinical outcome.

Patients and methods

The study cohort was composed of 76 patients. All patients who were treated with a salvage neck dissection after definitive radiotherapy with or without concomitant systemic treatment for HNSCC between January 2005 and March 2015 at the University Medical Center in Groningen were included in this retrospective analysis.

The indication for salvage neck dissection was residual cervical lymph nodes suspicious for regional metastases in the absence of a residual primary tumor. Patients with distant metastases or surgical treatment of the primary tumor site simultaneously with the neck dissection were excluded from the study. The study was approved by the Institutional Review Board.

Primary treatment regimens and evaluation of treatment response

Of the 76 included patients, 22 were initially treated with radiotherapy alone (without concomitant systemic treatment), 42 with radiotherapy and carboplatin/5-fluorouracil (5-FU) and 12 with radiotherapy in combination with cetuximab.

Patients were treated with definitive conventional three-dimensional conformal radiotherapy (3D-CRT) (n = 14) and since 2007 with intensity modulated radiotherapy (IMRT) (n = 62).

Patients treated with 3D-CRT received 23 × 2 Gy to the indicated elective neck levels and a sequential boost on the primary tumor and lymph node metastases to a total dose of 70 Gy. In patients treated with IMRT a simultaneous integrated boost technique was used. Most patients received bilateral elective irradiation of the neck to a total dose of 54.25 Gy, in fractions of 1.55 Gy, while the primary tumor and lymph node metastases were treated to a total dose of 70 Gy, in 2 Gy fractions.

Patients treated with concomitant chemoradiotherapy were irradiated with a schedule of 35 × 2 Gy, 5 times per week over 7 weeks. Patients not eligible for chemoradiotherapy were treated with an accelerated schedule of 6 fractions per week up to a total dose of 70 Gy, with or without cetuximab. Patients ≥70 years were treated with radiotherapy alone (35 × 2 Gy, 5 times per week over 7 weeks).

Chemotherapy consisted of 3 cycles carboplatin 300–350 mg/m^2 at day 1 in combination with 5-FU 600 mg/m^2 as continues infusion on day 1–4 in 3-week cycles. Cetuximab was given to patients with locally advanced disease < 70 years of age with a contraindication for chemotherapy. Cetuximab was started 1 week before start of radiotherapy with an initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 during radiotherapy.

For evaluation of treatment response, a CT was performed approximately 8 weeks after completion of initial treatment. Lymph nodes exceeding 1 cm in short axis, or with pathological imaging characteristics such as a necrotic or cystic center, heterogeneous enhancement, indistinct margins and/or a round shape were considered suspect for residual or recurrent disease. The post-treatment scans were reviewed in the Multidisciplinary Tumor Board. In case of suspicious lymph nodes in the neck, the involved levels and size of the largest lymph node were recorded. The size of the largest lymph node on post-treatment response imaging was compared to the size on the CT before start of the initial treatment. Change in lymph node size was calculated as a percentage of the lymph node size on CT before initial treatment, and categorized in patient groups with an increased, stable or decreased lymph node size, reflecting the response to initial treatment.

In one patient treated with radiotherapy alone with persistently enlarged lymph nodes at the post-treatment response imaging, the pre-treatment CT was not available at the time of this study; therefore, change in lymph node size could not be assessed and the patient was excluded from the concerning analyses.

Before salvage neck dissection, locally persistent or recurrent primary tumor was ruled out by performing direct panendoscopy under general anesthesia. If suspicious tissue was seen at the initial primary tumor localization, biopsies were taken.

Salvage neck dissections

The extent of neck dissection was based on initial treatment and on the size and location of suspicious lymph nodes on post-treatment response imaging. Patients who were initially treated with radiotherapy alone underwent a (modified) radical neck dissection as standard treatment. Patients who received primary radiotherapy in combination with systemic treatment underwent, if possible, a selective neck dissection of the level(s) of the affected lymph nodes.

Neck dissection specimens were divided into separate levels, sliced and palpated for lymph nodes. Lymph nodes were formalin fixed and paraffin embedded. Standard single level Haematoxylin and Eosin (H&E) sections were cut. All slides were reviewed by a dedicated head and neck pathologist. The oropharyngeal carcinomas were tested for human papillomavirus (HPV) [6]. All other carcinomas were not tested for the presence of human papillomavirus, but were considered to be HPV negative because of the low prevalence of HPV-driven head and neck squamous cell carcinomas among these subsites [6–8], and because HPV positivity in hypopharyngeal carcinomas is not clearly associated with prognosis [9].

Statistical analysis

Logistic regression analysis was used to evaluate predictive factors for presence of viable tumor, and to estimate correlations between variables. A p value < .05 was considered statistically significant. For statistical analysis, extent of lymph node levels resected was dichotomized into 3 or less lymph node levels (reflecting selective neck dissections) and 4 or more levels (reflecting more extensive neck dissections).

Negative and positive predictive values were calculated to analyze the combination of initial treatment and change in lymph node size in relation to presence of viable tumor.

Kaplan-Meier survival plots were constructed to estimate disease-specific survival, which was defined as the duration from the salvage neck dissection to death as a consequence of head and neck cancer or last follow-up of the patient, with evaluation of the differences by the Mantel-Cox log-rank test.

Statistical analysis was performed using SPSS (version 22 for Windows, Armonk, NY: IBM Corp.).