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Review article

Lymph node positive head and neck carcinoma after curative radiochemotherapy: A long lasting debate on elective post-therapeutic neck dissections comes to a conclusion

Carcinome épidermoïde des voies aérodigestives supérieures avec des métastases ganglionnaires au moment du diagnostic après la chimioradiothérapie : le débat du curage ganglionnaire vient à son terme

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ABSTRACT

There has been a long lasting debate, whether planned neck dissections after curative radio(chemo)therapy for locally advanced head and neck squamous cell carcinomas offer some benefit in tumor control or survival. We did a thorough literature research on that topic. The results of several recently published studies are described, summarized, and reviewed. Patients with residual disease in clinical or radiographic examinations (CT or MRI scans) up to 3 months after completion of radiochemotherapy profit from neck dissections. In patients with an initial or delayed clinical complete remission after completion of radiochemotherapy, a neck dissection can be safely omitted. In conclusion, there is no longer evidence for a benefit of prophylactic post-radiochemotherapy neck dissections, but strong evidence for a therapeutic post-radiochemotherapy neck dissection in this group of patients.

Mots clés :
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RÉSUMÉ

Un débat datant des années 1980 concernait la question de l'effet du curage ganglionnaire après une chimioradiothérapie pour un carcinome épidermoïde des voies aérodigestives supérieures sur le contrôle régional du cancer et même la survie. Le sujet a été soumis à une recherche minutieuse de la littérature concernée. Nous décrivons, résumons et évaluons les publications scientifiques les plus récentes. Les patients en situation de réponse incomplète sur l'examen clinique et la scanographie ou l'IRM trois mois après la chimioradiothérapie profitent du curage ganglionnaire. En revanche, le curage ganglionnaire peut être omis pour les patients en situation de réponse complète immédiate ou dans les trois mois qui suivent la chimioradiothérapie. En conclusion, dans le traitement des carcinomes épidermoïdes des voies aérodigestives supérieures, le curage ganglionnaire prophylactique n'apporte pas d'avantage. En revanche, il mène à une amélioration significative dans le cas d'une rémission incomplète.

1. Background

Due to their association with alcohol- and tobacco-consumption and human papilloma virus, head and neck squamous cell carcinomas are among the major oncological burdens. In 2008 they accounted for over 170,000 new male cases and about 80,000 deaths worldwide [1].

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Traditionally, primary radiotherapy is considered as a treatment option for patients with unresectable locally advanced head and neck squamous cell carcinomas. Nowadays, the treatment paradigm of locoregionally advanced head and neck squamous cell carcinomas has evolved from radical surgery followed by adjuvant radiotherapy to nonsurgical organ preserving strategies with surgery reserved as a salvage procedure [2]. However, 5-year overall survival rates after radiotherapy alone are only about 30%, as up to 50% of local and regional failures will occur during the later course [3]. A meta-analysis of individually updated data of over 16,000 patients showed that the addition of cisplatin-based chemotherapy simultaneously to normofractionated radiotherapy resulted in an increase of cure rates of about 5–8% independent of the tumor site [4]. Altering standard fractionation of radiotherapy does not seem to increase the therapeutic ratio when applied concomitantly to chemotherapy [5]. Another promising approach is the intensification of chemotherapy by means of three taxane-containing cycles prior to radiochemotherapy. In two studies survival rates were increased by about 10% [6,7]. However, as toxicity of this approach is high, only patients with minor comorbidity and in a good clinical condition are suitable for such an aggressive therapy. Alternatively instead of cisplatin the EGFR-antibody cetuximab increases radiosensitivity of head and neck squamous cell carcinomas to a similar extension [8]. Taken together, despite many attempts to increase efficacy of radiochemotherapy, medical progress is slow and cure rates are still disappointing for patients with locally advanced disease.

Cure of these patients is strongly correlated with local control [9]. In a landmark retrospective analysis of the RTOG database, Leibel et al. described a 20% distant metastasis rate for patients who were in locoregional control 6 months after treatment compared to nearly 40% of patients after locoregional failure [10]. For most tumor sites of the head-and-neck region, improvement in local control increased overall survival. Thus, achieving locoregional control is of utmost importance for these patients.

A high rate of about 25% of residually positive neck pathology after radiochemotherapy despite clinical complete responses has been reported. In these cases, salvage surgery often is less successful but associated with higher complication rates, due to fibrosis and rarified vessels developing in irradiated tissues after longer follow-up (e.g. more than 3 months after completion of radiochemotherapy). The first reports of combining radiotherapy with surgical neck dissection in an attempt to control advanced nodal disease ($\geq$ N2) date back into the 1970s, in the era of conventional radiotherapy alone [11]. Thus, planned neck dissection is recommended traditionally as an adjuvant surgical treatment modality, irrespective of whether regional control by primary radiotherapy/radiochemotherapy was achieved in an effort to completely eradicate residual tumor cells [12,13].

On the other hand, post-radiotherapy neck dissection may result in an overtreatment of many patients, who have already been subjected to severe toxicity due to radiochemotherapy but do not profit in terms of overall survival. Furthermore, post-radiotherapy neck dissection may be ineffective, as some patients will still relapse or develop distant metastases despite this surgical procedure. Thus, there is a growing body of evidence that planned neck dissection after radiotherapy is not necessary even in case of extended neck disease. Therefore, a long lasting controversy on this issue appeared which seems to come to a conclusion nowadays.

2. Classification of neck dissections in different oncological settings

At present, the following classification of neck dissections is suggested [12,14,15]:

- the classical “radical neck dissection” means removal of all five ipsilateral neck levels including the internal jugular vein, the spinal accessory nerve, and the strenocleidomastoid muscle. As this procedure is associated with increased morbidity and permanent functional and cosmetic deficits even in non-irradiated patients, it is not routinely performed nowadays by most surgeons but being restricted predominantly to bulky neck disease with huge extracapsular spread. However, the options of radical procedures are limited by infiltration of the carotid artery and/or deep infiltration of cervical tissue;
- “modified radical neck dissection (comprehensive neck dissection)” involves removal of lymph nodes from levels I to V (as in radical neck dissection), but with the preservation of at least one (of all) of the nonlymphatic structures in order to minimize post-surgical functional deficits. This approach is sometimes referred to as “functional neck dissection”;
- “extended neck dissection” refers to removal of additional lymph node levels and/or nonlymphatic structures, such as muscle, blood vessel, and nerve not normally removed by radical neck dissection;
- “selective neck dissection” is based upon a subdivision of the neck into levels and has been introduced as a removal only of high-risk lymphatic levels depending on the primary site with preservation of nonlymphatic structures.

In the context of radiochemotherapy, three different oncological settings have to be distinguished:

- “up-front” neck dissection means removing lymph nodes of a clinically positive neck “before” radiochemotherapy with the advantage of avoidance of surgery on an irradiated neck. This procedure can be performed together with dental extraction before the initiation of radiochemotherapy;
- “elective” post-radiotherapy neck dissection meaning removal of cervical lymphatics “despite a clinical and radiological complete remission after radiochemotherapy” with absence of suspicious cervical lymph nodes (cN0). This surgical procedure is done in order to remove potential subclinical (micrometastatic) disease which may be the origin of subsequent locoregional or even distant failure [16]. It is determined to be performed “after” radiochemotherapy;
- “salvage” post-radiotherapy neck dissection for surgery of residual neck disease or delayed regional recurrence on follow-up.

Only few randomized trials evaluated the value of up-front neck dissections. Patient numbers were rather small; therefore results must be interpreted with caution. Carinci et al. randomized 54 patients between functional ($n = 21$) or comprehensive ($n = 2$) neck dissection followed by radiochemotherapy (60 to 65 Gy normofractionated radiotherapy + cisplatin 100 mg/m^2 + 5-fluorouracil 1000 mg/m^2 for 5 days on days 1, 22, and 43) (group 1) vs. radiochemotherapy alone (group 2) [17]. Two- and 5-year overall survival were 52% and 26% in group 1 vs. 29% and 0% in group 2. The authors concluded that locoregional control was improved by up-front neck dissection, thus curing a subset of patients.

In a series on 55 patients with predominantly advanced head and neck squamous cell carcinomas, Paximadis et al. reported an overall neck control rate of 96.7% and a locoregional control rate of 87.3%, respectively [18]. However, further prospective studies to evaluate the patient groups most appropriate for this approach are needed.

There is no doubt that salvage neck dissection often remains the only treatment option in case of residual neck disease or regional recurrence. In contrast, the role of a prophylactic post-radiotherapy neck dissection as either a planned or an elective procedure still is