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Review Article

Treatment of the neck in residual/recurrent disease after chemoradiotherapy for advanced primary laryngeal cancer☆

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ABSTRACT

Concomitant chemoradiotherapy (CRT) is extensively used as primary organ preservation treatment for selected advanced laryngeal squamous cell carcinomas (LSCC). The oncologic outcomes of such regimens are comparable to those of total laryngectomy followed by adjuvant radiotherapy. However, the management of loco-regional recurrences after CRT remains a challenge, with salvage total laryngectomy being the only curative option. Furthermore, the decision whether to perform an elective neck dissection (END) in patients with rN0 necks, and the extent of the neck dissection in patients with rN + necks is still, a matter of debate.

For rN0 patients, meta-analyses have reported occult metastasis rates ranging from 0 to 31 %, but no survival advantage for END. In addition, meta-analyses also showed a higher incidence of complications in patients who received an END. Therefore, END is not routinely recommended in addition to salvage laryngectomy. Although some evidence suggests a potential role of END for supraglottic and locally advanced cases, the decision to perform END should weigh benefits against potential complications.

In rN + patients, several studies suggested that selective neck dissection (SND) is oncologically safe for patients with specific conditions: when lymph node metastases are not fixed and are absent at level IV or V. Super-selective neck dissection (SSND) may be an option when nodes are confined to one level.

In conclusion, current evidence suggests that in rN0 necks routine END is not necessary and that in rN + necks with limited nodal recurrences SND or a SSND could be sufficient.

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1. Introduction

Concomitant chemoradiotherapy (CRT) has emerged as a standard of care for the initial treatment of selected patients with advanced laryngeal squamous cell carcinomas (LSCC), namely patients with large T2, all T3 and T4 tumors with minimal cartilage invasion [1,2]. For patients with other T4 tumors, total laryngectomy followed by radiotherapy or chemoradiotherapy remains the first option in most guidelines [3]. The advantages of CRT over total laryngectomy include preservation of the larynx, improved functional outcomes, and a reduced risk of acute complications. However, it is important to acknowledge that approximately 30–50 % of patients with stage III and IV LSCC will experience a loco-regional recurrence following primary non-surgical treatment. This may reflect variability in T-classification and other selection factors [4–7]. In such cases, salvage surgery (mainly total laryngectomy) becomes crucial as it often represents the sole remaining curative option. Compared with tumors of other head and neck sites (oropharynx and hypopharynx), laryngeal cancer recurrence is associated with more favorable survival outcomes. 5-year overall survival (OS) rates after salvage total laryngectomy range from 57 % to 70 % [8].

It should also be acknowledged that managing recurrent LSCC with surgery poses significant challenges. The extent of the surgical resection required to achieve clear margins is difficult to delineate in recurrent tumors. An additional challenge is the management of the neck. On the one hand, it is generally agreed that patients with local recurrence and resectable lymph node metastases should undergo lymph node dissection, although the extent of lymph node dissection is controversial. On the other hand, the benefit of an elective neck dissection (END) in patients with an rN0 neck is still vigorously debated. Furthermore, the combination of treatment-related toxicity and patients' underlying health conditions raises the risk of postoperative complications and morbidity. Not only because of the risk of complications due to the neck dissection itself, but also the increased risk of a pharyngocutaneous fistula after laryngectomy when a neck dissection is performed [9]. Therefore, the decision to proceed with salvage surgery, and especially the addition of a neck dissection, must be carefully weighed considering potential side effects versus the prospects of achieving a cure. The benefits of a potential cure do not always justify excessive morbidity and an impaired quality of life. Needless to say, it is important to prioritize the patient's condition and preferences when making decisions about salvage surgery [8,10].

Adequate selection of patients suitable for salvage laryngectomy is critical. To that end, objective criteria based on functional and oncologic outcomes are ideal. Predictive modeling based on preoperative information allows to better select patients having a good chance to be successfully treated with salvage surgery. In 2010, the Head and Neck Service at The Institute Gustave Roussy (Villejuif, France) developed a model stratifying patients into distinct prognostic groups that predict survival after salvage surgery. Initial stage IV disease and local and regional recurrence were independent prognostic factors. Two-year OS rates for patients with none, one or two of these predictive factors were 83 %, 49 %, and 0 %, respectively, suggesting that patients with initial stage IV and concurrent local and regional recurrence should not be candidates for salvage surgery [11]. In 2017, Hamoir et al. proposed another survival predictive score incorporating three independent preoperative factors: local and regional recurrence, tumor site (larynx vs. non-larynx), and initial stage (stage I/II vs. stage III/IV). Patients with none, one, two, and three predictive factors of outcome had successful salvage rates of 96.2 %, 62.5 %, 35.5 %, and 28.6 %, respectively [12]. This "easy to apply" predictive model was validated by Quer et al. in a large series of 577 patients [13]. All these results confirm that salvage laryngectomy after CRT failure should be offered only to patients with limited and resectable recurrence in the neck.

The aim of this paper is to review the treatment of the neck in patients with locally advanced LSCC treated with CRT that present with persistent or recurrent local disease amenable to surgical salvage in order to establish recommendations based on the best available evidence.

2. Management of residual/recurrent laryngeal cancer with rN0 neck

2.1. Oncologic results of elective neck dissection versus observation

The efficacy of END in the management of patients with primary LSCC and a clinically N0 neck has been demonstrated [14]. Based on the decision-analysis model published by Weiss et al. [15], most clinicians consider an END in patients with a clinically N0 neck when the likelihood of subclinical nodal metastases exceeds 20 %. In LSCC, this recommendation applies to patients with supraglottic T2-4 tumors, and glottic T3-T4 tumors [16].

In contrast, management of the cN0 neck during salvage surgery after primary CRT is still controversial. Several studies have addressed this issue and three meta-analyses summarizing the results of these studies have been published [17–19] (Table 1). Obviously, most of the studies included in these meta-analyses are the same, although there are small differences based on the inclusion criteria used in each of them. The meta-analyses found considerable variation in the rate of occult metastases among studies, ranging from 0 % to 31 %, with a mean rate of 14 %, 11 %, and 13.7 % in the meta-analysis of Davies-Husband et al., Gross et al., and Lin et al., respectively [17–19]. These rates of subclinical metastases are lower than the 20 % rate used as a cutoff for END in previously untreated head and neck cancer [15]. Such variability in the rates of occult metastasis may be due to factors such as pretreatment T and N classification, diagnostic modalities used for N classification, and the T classification and sub-site at the time of recurrence. Each meta-analysis showed a trend towards higher rates of occult metastases

Table 1
Summary of the meta-analyses analyzing elective neck dissection versus observation in recurrent laryngeal cancer after chemoradiotherapy.

	Davies-Husband et al. [17]	Gross et al. [18]	Lin et al. [19]
Year	2020	2020	2019
Number of studies	19	18	17
Number of patients			
Total	1353	1141	1083
END	872	799	775
Observation	481	350	310
% Occult metastasis (range)	14 % (0–31.1 %)	11 % (0–27 %)	13.7 % (0–29.8 %)
Regional recurrence (%)	8 studies	NA	5 studies
END	8.26 % (0–18.8 %)		7.72 % (0–15 %)
Observation	9.4 (0–30.8 %)		11 % (3.1–18 %)
P	>0.05		NA
DSS	5 studies		5 studies
END	64.9 %	56 % (8 studies)	55 %
Observation	70.5 %	60 % (6 studies)	54 %
P	>0.05	NA	>0.05
OS	5 studies		6 studies
END	60 %	46 % (10 studies)	57 %
Observation	60 %	56 % (7 studies)	52 %
P	>0.05	NA	>0.05
Complications	8 studies		5 studies
END	44.8 %	41 % (10 studies)	44 %
Observation	32.3 %	28 % (9 studies)	31.4 %
P	<0.05	NA	NA

END: Elective neck dissection; OS: overall survival; DSS: disease-specific survival; NA: Not available.

in patients with advanced primary recurrent tumor (T3/T4), those with a supraglottic or transglottic sub-site, and those with node-positive disease prior to primary CRT, but the differences were not statistically significant [17–19]. Interestingly, the reported rates of regional-only recurrences in necks that are observed (without END) are low (0–30.8 %, mean 9.4 %) and are not significantly different from the regional recurrence rates after END (0–18.8 %, mean 8.26 %) (Table 1).

In addition, the reported studies have shown inconsistent results regarding the benefits of END in terms of OS or loco-regional control when done in conjunction with a salvage laryngectomy. Again, the three meta-analyses did not show a statistically significant advantage in disease-specific survival (DSS) or OS in those patients who underwent an END during salvage laryngectomy (Table 1); however, a trend towards a better survival in the END group was observed in T3, T4 and supraglottic tumors [17–19].

The survival outcomes notwithstanding, the morbidity associated with an END in cases of local recurrence alone can be considerable, given its adverse effects on healing, including the increased risk of pharyngo-cutaneous fistula and the higher incidence of postoperative complications and long-term sequelae. The meta-analysis by Davies-Husband et al. [17] confirmed a significant increase in the complication rate associated with performing END compared to neck observation ($p < 0.05$). However, the relative risk of developing complications was 1.29 (CI 0.86–1.92) when END was performed concurrently with salvage laryngectomy, compared to observation of the neck alone, which did not reach statistical significance. The other two meta-analyses also showed an increased frequency of complications in the patients undergoing an END (Table 1), although they did not perform a statistical analysis. Thus, although all three meta-analyses demonstrated an increase in surgical complications associated with END, it is not clear if this increase is significant. However, the possibility of an increased risk of complications must be balanced against the possible benefit in disease control. These findings support those of three prospective trials conducted by the Radiation Therapy Oncology Group (RTOG 91-11, 97-03, and 99-14), which, in a multivariate analysis, found that salvage END was an independent prognostic factor for an increased risk of severe late toxicity [20].

The divergence in opinion regarding the need for END in different studies appears to stem, at least in part, from differing perspectives about the significance of occult metastases in the salvage laryngectomy setting. Some view END as a last opportunity to eradicate occult cancer, while others consider the presence of nodal metastases to be an independent, unfavorable predictor of DSS. Consequently, some studies have shown a statistically significant difference in DSS based on the presence or absence of nodal metastases, which was unaffected by the inclusion of END in the treatment [21,22]. The results of the meta-analyses of Davies-Husband et al. [17] and Lin et al. [19] also support this phenomenon, suggesting that END may reduce the rate of regional recurrence without improving DSS or OS. Although this may seem counterintuitive, it is important to recognize that the rates of occult metastases, regional recurrence in the observed neck, and “cure” rates with END are not congruent in recurrent or persistent laryngeal cancer after CRT.

To shed further light on this, Hilly et al. [23] approached the question differently by using a decision analysis model to compare the outcomes of patients undergoing salvage total laryngectomy with and without concurrent END. Their Monte Carlo simulation of a virtual cohort of 10,000 patients showed an expected mortality rate of 33.4 % in the salvage laryngectomy and neck observation group, with 53.7 % cured without complications and 12.9 % cured with complications. In the salvage laryngectomy with END group, the mortality rate was slightly higher at 35.5 %, but with fewer patients cured without complications (29.8 %) and more cured with complications (34.7 %). Their analysis identified two key factors that influenced the decision to add END to a salvage laryngectomy: the probability of cure with END, and the probability of regional-only recurrence after salvage laryngectomy with neck observation. They concluded that concurrent END became the preferred option when the probability of cure exceeded 82 %. Hilly et al. also recommended concurrent END when the risk of regional-only recurrence exceeded 20 % [23]. The reported neck recurrence rates ranging from 0 % to 30.8 % (mean, 9,4 %) for salvage laryngectomy alone and the cure rates of 46%–60 % for salvage laryngectomy with or without neck dissection (Table 1), do not support routine END in salvage laryngectomy.

A higher rate or regional recurrences could be observed in rT3-T4 tumors, which is the usual presentation stage in CRT failures, or supraglottic tumors. Therefore, an END could be justified in these cases. A selective neck dissection (SND) including levels II-IV or even a super-selective neck dissection (SSND) including levels II-III should be sufficient. However, such recommendations should be applied with caution, especially in patients with more locally advanced, supraglottic tumors, as this presentation is associated with a poor prognosis regardless of intervention. Performing an END in this cohort assumes that there is no occult distant disease at the time of restaging/treatment and that the benefits of END outweigh the increased risk of complications. We agree with Hilly et al. that the decision-making process should focus on the probability of cure, which is more clinically relevant than the risk of occult metastases (currently the most common indication for END). Therefore, based on the results of the above-mentioned meta-analysis, it seems that routine END in salvage laryngectomy after CRT is not justified.

However, this recommendation is not universally accepted due to the limitations of these studies. They include significant biases in patient selection, varying criteria for choosing a treatment modality, lack of standardization of the extent of neck dissection, unclear reporting of data, and considerable heterogeneity among the included studies.

2.2. The role of imaging methods in the decision-making process in rN0 necks

Furthermore, the meta-analyses above mentioned included studies that were conducted from 1999 to 2019, a period marked by remarkable advances in diagnostic techniques, particularly in the field of positron emission tomography/computed tomography (PET/CT). As a result, making informed decisions about whether to perform concurrent END remains challenging.

It is reasonable to speculate that the percentage of true rN0 patients might have been greater if an imaging modality with an improved negative-predictive value had been used. This brings up the question about the current role of different imaging modalities (CT, MRI, PET/CT) in detecting persistent or recurrent disease in lymph nodes. In that regard, a systematic review and meta-analysis highlighted the superior accuracy of PET compared with CT or MRI alone [24]. Several series have been reported with similar outcomes, highlighting the improved specificity of PET in the identification of neck metastases [25,26]. Yao et al. [25] conducted a study that demonstrated that FDG-PET imaging had a remarkable negative predictive value of 100 %, along with sensitivity rates of 100 % and specificity rates of 94 % twelve weeks after definitive RT, in patients with stage N2a disease or higher, regardless of whether or not they had received chemotherapy. Conversely, Rosko et al. [26] published a review of 46 patients with clinically and radiographically staged N0 recurrent laryngeal cancer. They found that PET/CT imaging prior to salvage laryngectomy had a sensitivity of 16.7 %, a specificity of 97.1 %, a positive predictive value of 66.7 %, and a negative predictive value of 76.7 %. These authors concluded that the value of PET/CT has limitations as a predictor of nodal disease in cases of recurrent laryngeal cancer. Therefore, while PET/CT imaging is increasingly being used to improve the accuracy of staging in recurrent cases, caution must be exercised when interpreting imaging findings to determine the need for END in rN0 scenarios.

2.3. Novel techniques to improve preoperative identification of lymph node metastasis

Given the inconsistent performance of current imaging studies, other techniques for the preoperative detection of lymph node metastases have been explored [27].

A recent systematic review and meta-analysis showed that sentinel node biopsy to detect occult lymph node metastases is also very reliable in laryngeal carcinoma: a pooled sensitivity of 94 % and negative predictive value of 97 % [28]. Although the value of sentinel node biopsy in an untreated neck of laryngeal cancer patients is higher, in the near future this diagnostic technique may be also used more often in the previously treated neck [29]. Sentinel node biopsy may have added value in personalized treatment of the clinically negative neck in patients who will undergo salvage laryngectomy.

Finally, there is an emerging role for artificial intelligence in neck node imaging that has shown promising results in untreated necks [30]. If artificial intelligence could also help to predict the presence of occult lymph node metastasis in the treated neck, the risk of metastases in a clinically negative neck will decrease and the need for END will diminish even further.

3. Management of residual/recurrent laryngeal cancer with rN + neck

Few would deny the need to perform a neck dissection in addition to salvage laryngectomy in the presence of clinically or radiologically resectable lymph node metastasis. For a long time, comprehensive neck dissections including levels I–V (radical neck dissection, RND, or modified radical neck dissection, MRND) were considered the primary surgical option for treating clinically positive necks in patients with recurrent HNSCC [31]. However, it is important to highlight that when dealing with clinically positive necks, usually, not all neck levels are involved. Consequently, RND or MRND may be an overtreatment in many instances. The same rationale that led to the adoption of SND for elective treatment of cN0 necks could be applied to cN + necks. This is particularly important in patients with poor prognosis and increased risk of surgical complications as frequently observed in patients with combined loco-regional recurrences following CRT. It is well-known that both RND and MRND are frequently associated with surgical complications, particularly frozen shoulder syndrome and pain due to spinal accessory nerve dysfunction [32]. These complications become more severe when the neck is pre-treated with RT, mainly due to issues such as tissue fibrosis and poor wound healing. In addition, RND and MRND result in longer operative times than SND and are associated with a higher likelihood of postoperative complications. Therefore, opting for less extensive neck surgery, such as SND and SSND, may help to reduce these complications [33].

3.1. Selective neck dissection in the management of rN + necks

In recurrent HNSCC, there is emerging evidence that most patients with cN + neck can be effectively treated with a SND. In a retrospective study of patients with squamous cell carcinoma of the pharynx and larynx who had undergone primary radiation and subsequently undergone salvage neck dissection, a total of 29 neck dissection cases were examined [34]. Among these, viable metastases were identified in 17 of the neck sides (58 %), while the remaining 12 specimens showed no viable metastases. In 16 out of these 17 cases (94 %), metastases were in either level II, III, or IV or a combination of these three levels. Level V was involved in only one case (6 %). Therefore, it would seem justified to consider performing a salvage SND targeting levels II, III, and IV in cases of recurrent pharyngeal and laryngeal carcinoma after primary RT [34]. In another study reviewing 540 patients with advanced HNSCC treated with CRT, 61 patients had suspected regional residual or recurrent disease and underwent 68 salvage neck dissections. Neck dissection specimens contained viable tumor in 26 (43 %) patients. Of these, 13 had a SND and 13 a MRND. All but one patient had residual or recurrent metastases in levels II–IV. Only one (2 %) patient had a lymph node metastasis in level V. Of note, in 23 of the 26 patients (88 %), the metastases were found at the same levels as before treatment. A non-significant trend towards better regional control after MRND was observed (5-year regional control rate MRND 90 %, SND 77 %, p = .70), but the OS was better for patients with a SND, probably due to patient selection [35]. In another recent study, 32 patients with advanced primary HNSCC that received treatment with CRT and presented an isolated nodal persistence (without evidence of residual disease at primary site) were treated with a salvage neck dissection. A SND was performed in 15 patients without clinical o radiological evidence of extra-nodal extension, and none of these patients experienced a new isolated recurrence in the neck, suggesting that SND could be effective in these patients [36].

3.2. Super-selective neck dissection in the management of rN + necks

As a further step, several studies have examined the application of super-selective neck dissection (SSND) for surgical salvage in cases of recurrence/persistence of tumor in the neck after organ preservation treatment. One of them was a retrospective case series that included patients who underwent CRT for HNSCC at different sites [37]. Although SSND was not performed for salvage (only SND, MRND, and RND were performed), the operation would have removed 90 % of the nodes involved in patients with a partial response to CRT [37]. Two studies, both conducted by Robbins et al., included patients with stage III and IV HNSCC treated with intra-arterial cisplatin and RT [38,39]. In one of the studies [38], 95 patients required salvage neck dissection or residual neck disease after intra-arterial cisplatin and RT. Fifty-four patients had radiographic evidence of residual disease confined to one neck level, and 52 of these had pathologic findings confined to one level, suggesting that imaging could guide the use of SSND for salvage. In the second study, Robbins et al. [39] investigated the use of SSND as a therapeutic option in a similar group of patients. Among the 84 patients who underwent planned neck dissection for advanced N stage (N2 and N3): 12 underwent a MRND, 65 a SND, and 7 a SSND (levels II-III only). Over a median follow-up period of 58 months, the regional control rate reached 100 % in the SSND group, 91 % in the SND group, and 82 % in the MRND group. These results suggest that SND and SSND represent viable treatment options for patients with residual disease limited to a single level following intra-arterial CRT, and most probably in the context of other CRT protocols [39]. A third study by Robbins et al. [40] combined a cohort from one of the previous studies with a group of patients who received various CRT protocols. In this study 35 SSND's were performed on 30 patients following CRT as either a planned or early salvage intervention and none of the patients developed isolated recurrences in the neck. This suggests again that SSND is an effective intervention for patients with advanced head and neck cancer treated with CRT whose risk for residual nodal disease is confined to one level [39].

4. Conclusions

The evidence reviewed in this paper suggests that END should not be routinely performed in patients undergoing surgery for residual/recurrent rN0 laryngeal carcinoma following CRT. The available data shows a low incidence of occult nodal metastasis (especially when a PET/CT was used for diagnosis/staging), and a lack of survival benefit.

However, performing an END in patients with recurrent disease at the primary site who had locally advanced (T3-T4) cancer or T2-4 supraglottic cancer may be justified based on the propensity for the high incidence of associated occult nodal disease. While consideration for an END should be entertained, patient involvement in the decision-making process, and their performance status should be thoroughly considered in determining the extension of surgical procedures.

Improved personalized treatment of the clinically negative neck may become possible by the application of sentinel node biopsy, radiomics and artificial intelligence in the near future.

In patients with rN + residual/recurrent laryngeal cancer after CRT, the literature review provides evidence that SND can be an effective and oncologically safe surgical procedure for patients with rN1 and rN2 necks when the lymph node disease is confined to two or less of the primary echelon levels. Furthermore, SSND could be an effective option if recurrent/persistent lymph nodes are limited to one primary echelon neck level. It is essential to employ preoperative imaging studies to accurately assess the presence and extent of lymph node metastasis in order to identify suitable candidates for SND/SSND among cN + cases.

CRediT authorship contribution statement

Juan P. Rodrigo: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing-original draft, Project administration. **Fernando López-Álvarez:** Methodology, Formal analysis, Writing-review & editing. **Jesus E Medina:** Formal analysis, Writing-review & editing. **Carl E. Silver:** Formal analysis, Writing-review & editing. **K Thomas Robbins:** Formal analysis, Writing-review & editing. **M Hamoir:** Formal analysis, Writing-review & editing. **Antti Mäkitie:** Formal analysis, Writing-review & editing. **Remco de Bree:** Formal analysis, Writing-review & editing. **Robert P. Takes:** Formal analysis, Writing-review & editing. **Pawel Golusisnki:** Formal analysis, Writing-review & editing. **Luiz P. Kowalski:** Formal analysis, Writing-review & editing. **Arlene A. Forastiere:** Formal analysis, Writing-review & editing. **Akihiro Homma:** Formal analysis, Writing-review & editing. **Ehab Y. Hanna:** Formal analysis, Writing-review & editing. **Alessandra Rinaldo:** Formal analysis, Writing-review & editing. **Alfio Ferlito:** Conceptualization, Formal analysis, Writing-review & editing, Project administration.

Declaration of competing interest

In relation to the manuscript “Treatment of the neck in residual/recurrent advanced primary laryngeal cancer after chemoradiotherapy” submitted for publication to the European Journal of Surgical Oncology, the authors state that they have not conflicts of interest to disclose.

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