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REVIEW ARTICLE

Evolution of treatment and high-risk features in resectable locally advanced Head and Neck squamous cell carcinoma with special reference to extracapsular extension of nodal disease

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Summary

The employment of surgery as a single treatment modality for patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) has been associated with high rates of locoregional recurrences even after adequate resection. The addition of postoperative radiotherapy (RT) as adjuvant to surgical resection for advanced HNSCC was investigated in an effort to decrease locoregional failure rates and improve treatment outcome. The unsatisfactory results in terms of locoregional control (LRC) and survival rates achieved with postoperative RT in patients with high-risk features have led to the necessity of exploring the role of concurrent chemotherapy in the adjuvant treatment in resectable advanced HNSCC with confirmed presence of high-risk pathological features. Two prospective randomized independent trials designed and conducted by Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) demonstrated that the addition of cisplatin-based chemotherapy improved LRC and disease-free survival (DFS). Significant improvement in overall survival (OS) with the use of postoperative concurrent chemoradiotherapy (CCRT) was observed in the EORTC trial.

High-risk pathological features in patients with resected head and neck cancer representing adverse prognostic factors that are predictive for local and/or regional recurrence are related to the primary tumor and/or metastatic lymph nodes in the neck. Extracapsular extension (ECE) of nodal disease in the neck has been confirmed as a high-risk pathological feature negatively influencing LRC and survival in patients treated with either postoperative RT or postoperative CCRT.

This article reviews the historical progress in the management of resectable locally advanced HNSCC and the impact of ECE on clinical outcome in patients treated with adjuvant therapy following surgery. It can be concluded that strong evidence exists for an improved outcome for high-risk resected patients treated with adjuvant CCRT. Precise definition of the presence of ECE is highly recommended in order to provide proper selection of patients who would benefit from the postoperative CCRT.

Key words: *extracapsular extension, head and neck cancer, high-risk features, postoperative radiotherapy, postoperative concurrent chemoradiotherapy, surgery*

Introduction

Head and neck cancer is the fifth most common cancer worldwide representing a broad oncological problem with an annual incidence of 550,000 cases [1]. Squamous cell carcinoma is the most frequent histological type present in more than 90.0% of these tumors [2]. Locally advanced HNSCC (stages III, IVa, and IVb) makes up more than 50% of all cases [3]. According to the 7th American Joint Committee on Cancer (AJCC) staging criteria, locoregionally advanced disease

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is separated into either intermediately advanced (stage III), moderately advanced (stage IVa), and very advanced (stage IVb) tumors [4,5].

Evolution of treatment in resectable head and neck cancer

Surgery alone

The potential for surgical resection of the primary tumor and the metastatic lymph nodes in the neck creates a better prognosis than the presence of unresectable disease [6]. However, it has been repeatedly shown that definitive resection as a single treatment modality in patients with locally advanced disease has led to a high incidence of locoregional failures and distant metastases [7,8]. Predictors of local and/or regional recurrence following surgery included positive surgical margins, extranodal/extracapsular spread, perineural invasion, and the presence of two or more involved regional lymph nodes [7-9].

Radiotherapy as adjuvant treatment following surgery

Since locoregional failures remained a dominant problem, RT as an adjuvant locoregional treatment was added for stage III, IVa, and IVb disease. Although the effectiveness of RT after surgery was first reported by Martin et al. [10] in 1941, the confirmation that postoperative RT significantly reduced the risk of failure above the clavicles was shown in the early 1970s by Fletcher and Evers [11].

The results obtained in a number of retrospective studies comparing surgery alone with surgery and postoperative RT revealed significantly better locoregional tumor control for the entire group of patients treated with adjuvant irradiation [12-16]. This positive impact of postoperative RT on LRC was particularly evident in patients with positive margins of resection [14-16] and in those with ECE of the lymph node metastases [15,17].

In most of these studies, the improvement of the LRC rates was reflected in the increased rates of the OS [14-18].

Albeit the lack of randomized data regarding the role of postoperative RT in resectable HNSCC, RT has been traditionally delivered for more than 30 years as an adjuvant therapy to surgical resection.

According to Posner et al. [6], the rates of LRC reported in the literature for surgery combined with adjuvant RT ranges from 35.0 to 75.0% [12,19].

In the study of Cooper et al. [20], the locoregional relapse rate at 36 months of follow-up for high-risk patients presenting with margins of resection <5 mm and/or ECE of nodal disease who were treated by surgery and RT was 34.0%. The reported 3-year survival rate for high-risk patients was 50.0%.

In the large multi-institutional randomized clinical trial that tested the efficacy of adjuvant chemotherapy following surgery and postoperative RT for patients with locally advanced resectable HNSCCs, the reported results obtained in the group of patients treated with surgery and postoperative RT only, showed 4-year rates of locoregional recurrence, distant metastasis and OS of 29.0, 23.0, and 44.0%, respectively [21].

Postoperative concurrent chemoradiotherapy as adjuvant treatment following surgery

The unsatisfactory results in terms of LRC and survival rates achieved even with postoperative RT in patients with presence of high-risk features unveiled the necessity for introduction of postoperative CCRT in the adjuvant treatment. Based on the results of the trial by Bachaud et al. [22] published in 1996 which suggested better outcome of patients with locally advanced disease with high-risk features treated with postoperative CCRT compared with those who received postoperative RT alone, two similar, large-scale, prospective randomized trials were designed and conducted by the RTOG (RTOG trial 9501) [23] and the EORTC (EORTC trial 22931) [24] to evaluate the role of CCRT in the postoperative treatment, consisting of high-dose cisplatin (100 mg/m2 on days 1, 23, and 43 of RT) and radiation doses of 60-66 Gy, vs RT alone in high-risk head and neck cancers. In the RTOG trial 9501 [23], the 2-year LRC rates for the group treated with postoperative RT alone and for the group treated with postoperative CCRT were 72.0 and 82.0%, respectively ($p=0.01$). There was also a significantly longer DFS observed in the postoperative CCRT group ($p=0.04$). In the EORTC trial 22931 [24], a significantly lower incidence of locoregional relapses was found in the group given postoperative CCRT ($p=0.007$). This group of patients had significantly higher 5-year progression-free survival and OS rates compared with the group treated with postoperative RT alone ($p=0.04$ and $p=0.02$, respectively). In 2004, the National Cancer Institute (NCI) level I evidence for recommendation was established because both trials demonstrated that postoperative CCRT was more efficacious compared to RT alone in terms of LRC and DFS [25]. Currently, postoperative CCRT is considered a gold standard for resected patients at high-risk of failure.

Both, RTOG trial 9501 [23] and EORTC trial 22931 [24], and their comparative analysis [26] confirmed that the most impressive benefit of postoperative CCRT was achieved in patients with ECE and positive margins of resection. ECE and positive margins of resection as pathological factors associated with the highest risk of recurrence were also confirmed in the long-term follow-up of the RTOG 9501 trial [27]. The results of this long-term follow-up analysis showed that the significant improvements in LRC and DFS from postoperative CCRT persisted in the subgroup that had ECE and/or involved surgical margins of resection [27].

High-risk pathological features in patients with resected head and neck cancer

The identification of high-risk pathological features affecting patient prognosis through the increased risk of locoregional failure and distant metastasis development, could allow for a better choice of postoperative treatment [25,28]. According to Mendenhall et al. [29], the adverse prognostic factors after surgery alone that are predictive for local and/or regional recurrence may be related to the primary tumor and/or metastatic lymph nodes in the neck. Important parameters include close (<5 mm) or positive margins of resection [30-33], ECE [19,34,35], two or more positive lymph nodes [36], and perineural invasion [37].

The prospective randomized study conducted in 1990s at the University of Texas M. D. Anderson Cancer Center has a very important role in the analysis of risk assessment with its specific aim to evaluate the clinical and pathological criteria defining subsets of patients at higher or lower risk of recurrence after treatment by surgery and postoperative RT alone [38]. The univariate analysis of factors predictive for recurrence above the clavicles including oral cavity primary, close or positive margins of resection, perineural invasion, number of positive nodes ≥2, largest node >3 cm, extracapsular nodal disease present, Zubrod score ≥2, and delay in starting RT >6 weeks, showed that extracapsular nodal extension in the neck was the only factor with independent significance in predicting treatment failure. In the analysis of the crude recurrence rates by ECE status and the number of other adverse factors, ECE was shown as a dominant prognostic factor compared to other prognostic indicators. However, increasing combinations of two or more risk factors were also found to be associated with a progressively higher risk of local failure [38].

The results of the study of Cooper et al. [20] conducted for precise definition of high-risk resectable head and neck tumors based on the results provided by RTOG #85-03 and RTOG #88-24 trials [21,39], confirmed and expanded the conclusions drawn from the M. D. Anderson Cancer Center data. It has been shown that patients with metastases in two regional lymph nodes or ECE of involved lymph node had elevated risk of locoregional recurrence. Greater risk of locoregional recurrence was confirmed for tumors that microscopically extended to the surgical margin.

In 2005, Langendijk et al. [28] reported three different risk groups among patients treated with surgery and postoperative RT alone that could be identified by recursive partitioning analysis (RPA). In this classification, very high risk class consisted of patients who had a pN3 neck, >2 positive lymph nodes with ECE, or a pT3 tumor with close or positive surgical margins.

According to the European Head & Neck Society (EHNS), the European Society for Medical Oncology (ESMO), and the European Society for Therapeutic Radiology and Oncology (ESTRO), high-risk features that lead to unsatisfactory local and distant control in patients with resectable head and neck cancer include node-positive status (N2 or N3), ECE of nodal disease, close or positive margins of surgical resection, bone invasion, and perineural or lymphovascular invasion [40].

In the conclusion of the comparative analysis of the RTOG 9501 [23] and EORTC 22931 [24] trials realized in order to define the risk levels in locally advanced head and neck cancers, Bernier et al. [26] clearly stated that ECE from neck nodes and microscopically involved margins of resection are the most significant prognostic factors for poor outcome as assessed either by locoregional recurrence or survival.

Taking into consideration that ECE has been repeatedly confirmed as a high-risk pathological feature with its presence negatively influencing LRC and survival in patients treated with adjuvant therapy following surgery either with postoperative RT alone or postoperative CCRT, the data in the literature regarding this prognostic factor would further be outlined.

Extracapsular extension as a high-risk pathological feature

The presence of lymph node metastasis in the neck in patients with HNSCC represents a single most important factor negatively affecting patient outcome [41], reducing the 5-year actuarial survival rate by approximately 50.0% [42,43]. In a review by Strong [44], in patients with metastatic lymph nodes discovered in the surgical specimen after neck dissection, the rate of subsequent regional relapses was 54.0%. According to Layland et al. [45], patients with positive neck lymph nodes have significantly worse disease-specific survival than patients without nodal disease. The overall disease-specific survival for patients with positive neck is 39.9% compared with 67.9% for patients with negative neck.

ECE of neck lymph node metastasis was first described in 1930 by Willis [46] who based his observations on a series of autopsies of patients with advanced head and neck cancer. Further elaboration upon this earliest observation led to the finding that among the factors related to the pathological characteristics of lymph node metastases, the presence of ECE has been shown to have the most important prognostic influence [7,47-49].

It should be pointed out that there is an evident lack of unique terminology of capsular ruptures in the international literature. The presence of tumor outside the confines of metastatic neck lymph node is reported as extracapsular spread (ECS), capsular rupture, extranodal spread (ENS), or ECE. Taking into account the possible difference of prognostic relevance between microscopic capsular infiltration and macroscopically visible metastatic spread into the soft parts of the neck, the 7th edition of AJCC Staging System gives recommendations regarding the pathological classification of ECS [4]. According to this system, ECS should be classified as either gross (Eg), characterized by tumor apparent to the naked eye beyond the confines of the lymph node capsule, or microscopic (Em), defined as metastatic tumor beyond the lymph node capsule with an associated desmoplastic stromal reaction [4]. There is also a possibility for soft tissue disease in the neck that might represent a lymph node which has been completely replaced by metastatic carcinoma or a true extranodal metastasis [50].

In this review the term ECE has been adopted according to the reports of the RTOG 9501 trial [23] and the EORTC 22931 trial [24]. However, in the remaining text, the terms originally used by the authors of different studies will be used as such.

Studies evaluating the prognostic significance of extracapsular extension in patients treated with surgery alone

In 1971, Bennet et al. [51] reported the results of their study which included histological examination for the presence of metastases confined to the regional lymph nodes or extranodal spread in patients with laryngeal or hypopharyngeal cancer. The authors first described ECE as an adverse prognostic factor for this patient category, showing decrease of the 5-year survival rate from 26.0 to 15.0%, in association with extranodal spread of the metastatic disease. The role of ECE of lymph node metastases as an indicator of poor prognosis was tested by Johnson et al. [19] in a retrospective review of 177 radical neck dissections. The negative impact of ECE on patient outcome was confirmed through the statistically significant reduced number of survivors among patients with lymph node metastases demonstrating extracapsular spread. In a retrospective clinico-pathological study of 405 patients with head and neck cancer treated with radical neck dissections, histological extranodal spread was found to be the most important single prognostic factor [7]. The retrospective examination of surgical specimen from 349 patients with HNSCC also confirmed that ECE was associated with a statistically significant reduction in survival when compared to patients without ECE [47]. In the study of Carter et al. [34], histopathological examination of radical neck dissection was performed in 203 patients with HNSCC and an association was found between macroscopic transcapsular spread and local tumor recurrence. Macroscopic transcapsular spread demonstrated in a previous radical neck dissection was associated with a high risk (44.0%) of development of recurrent tumor in the ipsilateral neck [34].

In the prospective study by Richard et al. [48] with 1,713 HNSCC patients who were submitted to neck dissection, the prognostic significance of the histological analysis of the nodal metastasis was confirmed and showed that capsular rupture was the most important prognostic factor irrespective of the primary site and the size of the tumor.

Retrospectively analyzing several histopathological variables that may predict neck recurrence after neck dissection in 284 patients with pathologically confirmed metastatic squamous cell carcinoma who underwent neck dissection and received no adjuvant therapy, Olsen et al. [35] found that invasion of soft tissue in the neck adversely affected regional recurrence. In the study of Violaris et al. [49], the histological data of 497 patients with HNSCC who had radical neck dissection were reviewed. Nodal disease was present in 359 patients of which 165 had extracapsular rupture. The 5-year tumor-specific survival of patients with extracapsular rupture was 33.0% and 50.0% for patients with no extracapsular rupture. The presence of extracapsular rupture (p<0.0001) along with the number of nodes (p<0.0001), and the presence of soft tissue free metastases (p<0.001) was found to be highly significant for patients survival. Alvi and Johnson [52] analyzed 109 patients with clinically negative neck who underwent neck dissection. Extracapsular spread was present in 49.0% of the patients with revealed occult metastasis in the neck predicting statistically significant worse outcome.

In the series of 110 patients treated for carcinoma of the supraglottic larynx reviewed by Myers and Alvi [53], the 2-year survival rate in patients with observed extracapsular spread was 31.0%, whereas 72.0% of the patients with nodal metastasis without extracapsular spread survived 2 years. The authors also noted that extracapsular spread was associated with a distant metastatic rate of 71.0%. Alvi and Johnson [54] evaluated risk factors for the development of distant metastasis in a retrospective study of 130 patients with surgically treated advanced stages of hypopharyngeal, tongue, and supraglottic cancer. Greater risk for distant metastasis was observed in patients with histological evidence of nodal metastases, involvement of multiple nodes, and the presence of extracapsular spread. Extracapsular spread was present in 88.0% of the patients in the distant metastasis group and in only 60.0% of the patients in the group without distant metastasis (p<0.05).

De Diego et al. [55] retrospectively analyzed 119 surgically treated patients with laryngeal and hypopharyngeal cancer with histologically confirmed lymph node metastasis to evaluate the impact of the presence of extracapsular spread and desmoplastic pattern on treatment outcome. Extracapsular spread was shown to have statistically significant influence on the development of tumor recurrence (p<0.03). Jose et al. [56] analyzed 215 prospectively collected neck dissections from 155 patients with squamous cell carcinoma of the upper aerodigestive tract in order to assess the prevalence of extracapsular spread and soft tissue deposits and to determine their impact on survival. The results of the study confirmed that the presence of extracapsular spread and/or soft tissue deposits had a significant adverse effect on actuarial and recurrence-free survival compared with patients without neck metastasis (p<0.001) and also compared to patients with lymph node metastasis but without extracapsular spread or soft tissue deposits (p<0.0025).

Studies evaluating the prognostic significance of extracapsular extension in patients treated with surgery followed by adjuvant therapy

Lefebvre et al. [57] retrospectively reviewed 884 clinical records of previously untreated patients with hypopharyngeal and laryngeal cancer, but only 231 patients who were treated with surgery followed by RT alone were studied for the evaluation of pathologic prognosis factors. Extracapsular spread together with multiple positive nodes, or lower-neck positive nodes were found to significantly decrease survival and neck control and significantly increase the risk of distant metastases (Table 1). The results of the preliminary report of the prospective randomized trial by Bachaud et al. [58] evaluating the efficacy of postoperative concurrent cisplatin-based chemoradiotherapy in patients with advanced head and neck cancer and histological evidence of extracapsular spread of the tumor in lymph node metastases, revealed that in the one-variable analysis, extracapsular spread was one of the three factors being significantly predictive of survival and locoregional failure (Table 1). In the study performed at the Medical College of Virginia exploring the role of postoperative RT alone in head and neck carcinoma with histologically proven ECE and/or positive resection margins, ECE was confirmed as an important negative prognostic factor for LRC (p<0.0001) and survival (p<0.001) in the group treated with surgery alone as well as in the group that received surgery and postoperative RT alone [15] (Table 1). Vaidya et al. [59], in their study with 128 patients who underwent primary tumor resection and postoperative RT alone and/or postoperative chemoradiotherapy for HNSCC retrospectively reviewed the data to examine the pattern of spread and the site of recurrent disease. ECE was found as the only significant predictor for the development of distant metastasis (p=0.002). No relation was found between local recurrence and the presence of nodal metastasis and ECE (Table 1). A retrospective review of medical records of 266 patients with oral tongue cancer treated with surgery that included a neck dissection at the University of Texas M. D. Anderson Cancer Center was performed by Greenberg et al. [60]. Postoperative RT alone as part of their treatment was

Table 1. Results of the prognostic significance of extracapsular extension in studies on patients treated with surgery and postoperative radiotherapy or surgery and postoperative concurrent chemoradiotherapy

First author [Ref]	*Year*	*Patients N*	*Primary site*	*Description of prognostic significance of ECE*
Lefebvre et al. [57]	1987	231	L,H	Significantly decreases survival and neck control; significantly increases the risk of DM.
Bachaud et al. [58]	1991	44	OC, Or, H, L	Significant predictive factor for survival and locoregional failure.
Huang et al. [15]	1992	Total=125 S in 71 S+RT in 54	OC, Or, L, H, PS, other	Independent negative prognostic factor for LRC (p<0.0001) and survival (p<0.001).
Vaidya et al. [59]	2001	128	NR	Significant predictor for DM development (p=0.002). Not predictive for local recurrence.
Greenberg et al. [60]	2003	Total=226 S in 121 S + RT in 105	OT	Not predictive for disease-free interval, survival rates, and DM development.

ECE: extracapsular extension, L: larynx, H: hypopharynx, DM: distant metastasis, OC: oral cavity, Or: oropharynx, S: surgery, RT: radiotherapy, PS: paranasal sinuses, LRC: locoregional control, OT: oral tongue, NR: not reported

realized in 105 patients. The extent of ECE along with the number of lymph nodes involved with tumor with or without ECS were variables evaluated in relation to disease-free interval, survival rates, and distant metastases. The results of this study showed that extracapsular spread outside of the lymph node capsule did not predict patient outcomes (Table 1).

In the prospective randomized clinical study of Smid et al. [61] testing postoperative CCRT with mitomycin C and bleomycin for resectable head and neck cancer, all patients were stratified according to stage and the site of the primary tumor and the presence or absence of high-risk prognostic features (extracapsular tumor spread, perineural, lymphatic, and/or venous invasion, and micro and/or macroscopic residual disease). These high-risk factors were confirmed as independent prognostic factors for LRC for the total number of patients, while in patients in the chemoradiotherapy group, the presence of high-risk factors had no significant impact on LRC. The presence of high-risk factors in the group treated with postoperative RT only resulted in significantly lower LRC and DFS rates. These results clearly suggested that patients who actually benefited from chemotherapy were those with extracapsular tumor spread, perineural, lymphatic, and/or venous invasion, micro and/or macroscopic residual disease.

It has to be stressed that all the studies designed to evaluate postoperative CCRT included patients with advanced stage HNSCC with high-risk features represented by ECE of nodal disease and positive or close mucosal margins of resection (<5 mm) [23,24,62]. Some studies included advance-stage head and neck cancer with positive margins of resection, extracapsular spread of lymph node metastasis, or multiple positive nodes [63-65]. The study of Lee et al. [66] involved patients with advanced stage head and neck cancer with extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism, and patients with oral cavity or oropharyngeal tumors with involved lymph nodes at level IV or V.

Interestingly, the inclusion high-risk criteria varied between the two largest prospective randomized trials RTOG 9501 [23] and EORTC 22931 [24]. The inclusion criteria common to both trials were the presence of ECE of nodal disease and/or microscopic involvement of the mucosal margins of resection [25]. Other inclusion criteria in the EORTC 22931 trial were stage III-IV disease, level IV or V metastatic lymph nodes in patients with oral cavity or oropharynx carcinomas, vascular, and/or perineural invasion [24]. Histological evidence of invasion of two or more regional lymph nodes was selected as additional high-risk characteristic in the RTOG 9501 trial [23]. The results of RTOG and EORTC trials [23,24] have shown that the impact of postoperative CCRT on patient outcome was influenced by the type of high-risk factors included. Namely, there were significantly poorer OS rates in both trials (p=0.002 in RTOG 9501 trial, and p=0.002 in the EORTC 22931 trial) in patients with ECE and/or positive surgical margin than in those without the presence of these risk factors [26]. There was also an evident impact of postoperative CCRT on OS rates (p=0.063 in the RTOG 9501 trial, and p=0.0019 in the EORTC

Table 2. Studies included in the meta-analysis

First author [Ref]	*Number of patients*	*Number of patients with lymph node metastasis (% of patients with perinodal spread)*
Hirabayashi et al. [69]	52	30 (60.0)
Mamelle et al. [70]	914	567 (70.0)
Steinhart et al. [71]	522	304 (69.7)
Pinsolle et al. [72]	337	183 (54.0)
Brasilino de Carvalho [73]	170	108 (74.0)
Shingaki et al. [74]	61	61 (46.0)
Myers et al. [75]	266	120 (37.5)
Andersen et al. [76]	106	106 (34.0)
Woolgar et al. [77]	173	173 (59.0)

22931 trial) for patients who had ECE and/or positive surgical margins [26].

A retrospective review of the data from University of Pittsburgh Medical Center Head and Neck Oncology Registry carried out to assess neck lymph node histological characteristics and to detect their prognostic value differences, included 1510 patients with high-risk HNSCC who were initially treated with resection of the primary tumor and dissection of the lymph nodes in the neck [67]. The results of multivariate analysis showed that extracapsular spread in patients with nodal disease had a significant negative impact on OS (p<0.001). The presence of extracapsular spread was also associated with reduced disease-specific survival (p=0.001). There was no association found between the extracapsular spread and neck disease recurrence. Benefit from the introduction of adjuvant therapy, especially adjuvant CCRT, was obtained in patients with positive lymph nodes in the neck regardless of the status of extracapsular spread.

Meta analysis of the prognostic significance of perinodal spread in patients with squamous cell carcinoma of the head and neck

The meta-analysis conducted by Dunne et al. [68] was designed to examine the prognostic significance of perinodal spread in patients with HNSCC with the hypothesis that perinodal spread negatively affects prognosis in this patients category. According to the study methodology of the meta-analysis, enrollment of only 9 studies out of 115 reviewed published papers was allowed (Table 2).

In the study of Hirabayashi et al. [69] published in 1991, the 5-year overall survival rate of patients with primary laryngeal cancer without pathological evidence of metastasis in the neck lymph nodes was 81.0%. There was statistically significant difference in the 5-year survival rates between patients who had neck node metastasis without extracapsular spread and those with presence of extracapsular spread (76.0 vs 17.0%, p=0.001).

In the retrospective study of Mamelle et al. [70] published in 1994, patients with cancers of oral cavity, hypopharynx, larynx, and oropharynx who underwent lymph node dissection were included. Postoperative RT was used only for patients with positive nodes. The 5-year survival rates of the whole group of patients, of patients without extracapsular spread, and of those with extracapsular spread were 47.2, 46.7, and 27.3%, respectively. Multivariate analysis showed a non-significant value for extracapsular spread (p=0.09).

In 1994, Steinhart et al. [71] reported the results of their retrospective study on the prognostic significance of extracapsular invasion in neck lymph node metastases of head and neck cancer. Patients with tumors of the larynx, hypoharynx, oropharynx, oral cavity, nose and paranasal sinuses, salivary glands, and nasopharynx who were treated with unilateral or bilateral neck dissection were investigated. The highest rate of extranodal spread was seen in patients with hypopharyngeal cancer (70.0%). The authors reported a great difference in 5-year survival rates between patients without neck metastases and patients with extranodal spread (77.0 and 28.0%, respectively).

The prognostic value of extracapsular spread was also evaluated by Pinsolle et al. [72]. The results of their study conducted on patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx treated with neck dissection were reported in 1997. The 5-year survival rate in patients with metastatic lymph nodes in the neck and confirmed extracapsular spread was 35.5%. The 5-year survival rate in patients with nodal disease without ECE was 44.6%. Analysis of prognostic factors showed no significant difference for extracapsular spread (p=0.45).

In a prospective study from Brazil published in 1997, Brasilino de Carvalho [73] investigated the influence of the extension of capsular lymph node involvement on the recurrence and survival rates in patients with squamous cell carcinoma of the larynx or the hypopharynx. There was an increased incidence of capsular rupture found with increased N stage and the size of the lymph node diameter (>3 cm). For patients without lymph node metastasis, the reported 5-year rates of global and DFS were 52.0 and 56.8%, respectively. The presence of macroscopic transcapsular spread significantly worsened the 5-year global and DFS rates (5.8 and 10.2%, respectively). Capsular rupture was confirmed as an independent pathological prognostic factor (p<0.001).

The retrospective study of Shingaki et al. [74] was undertaken to evaluate the prognostic significance of extranodal spread of metastases on treatment failure and survival in patients with oroharyngeal and oral cavity cancer with histologically confirmed lymph node metastases following radical neck dissection. The study was published in 1999 showing that extranodal spread was associated with increased risk of distant metastases. Statistically significant difference was found in the 5-year disease-specific survival rates between patients with extracapsular spread and those without (72.0 and 40.0%, respectively, p=0.008).

Myers et al. [75], retrospectively studied patients with squamous cell carcinoma of the oral tongue treated with surgical resection of the primary tumor and neck dissection at the Department of Head and Neck Surgery of the University of Texas. In 2001, the authors reported that the rate of regional recurrence (28.9%, p<0.05) and the incidence of distant metastasis (24.4%, p<0.01) was highest in the group of patients with presence of extracapsular spread of the nodal metastases. Comparing the patient survival data with extracapsular spread and those without, the authors revealed that the 5-year OS rate was significantly lower in the first group of patients compared to that obtained in the second group (29.0 vs 51.0%, p<0.014). The 5-year disease-specific survival rates were 48.0% for patients with extracapsular spread and 66.0% for those without (p<0.02).

Andersen et al. [76] in 2002 reported the results of their retrospective study determining the oncologic efficacy of selective node dissection in patients with node positive squamous carcinoma of the hypopharynx, oropharynx, oral cavity, and larynx. Although there was a difference in the 5-year survival rates between patients with ECE (55.8%) and patients with intact lymph node capsule (75.3%), this was not statistically significant (p=0.2).

In the study of Woolgar et al. [77] published in 2003, patients with oral cavity and oropharyngeal cancer treated with neck dissection and found to have neck lymph node metastasis on the histological assessment of the resection specimen, were analyzed with regard to microscopic and macroscopic extracapsular spread. The 5-year survival rates of patients with metastasis confined to lymph node, of patients with microscopic extracapasular spread, and of patients with macroscopic extracapsular spread were 70.0, 36.0, and 33.0%, respectively. Multivariate analysis revealed extracapsular spread as the most predictive factor for patient survival.

The results of the meta-analysis showed 5-year survival rate of 58.1% in patients with histologically intact lymph node capsules, and 30.7% in the group of patients who had perinodal spread of the lymph node metastatic disease. Analysis of these data (summarized odds ratio of 2.7), led to the assumption that perinodal spread negatively impacts the 5-year survival. The concept that perinodal spread relevantly impairs the 5-year survival was further supported by the revealed lower confidence limit of more than 2 (doubled risk) [68].

Conclusion

In the vast majority of studies presented in this particular review, ECE has been shown as the most important prognostic factor in patients with neck lymph node metastases. ECE has been revealed to have negative influence on LRC, DFS, and OS. Its impact on the increased risk of distant metastasis development has also been observed. Consequently, the presence of ECE clearly predicts poor patient prognosis.

Therefore, the precise definition of the presence of ECE in the pathology reports is highly recommended in order to enable proper selection of patients in the therapeutic decision-making process. The detection of ECE should be an indicator for a multimodality treatment plan, taking into account that CCRT as an adjuvant to surgery is established as a gold standard treatment approach for head and neck cancers with high-risk pathological features with its highest benefit achieved in patients with ECE and/or positive mucosal margins of resection.

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