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REVIEW ARTICLE

Role of Extracapsular Nodal Spread and Surgical Margin Status in defining High-risk Head and Neck Squamous Cell Carcinoma and its Treatment Intensity

Volkert B Wreesmann

ABSTRACT

High-risk head and neck squamous cell carcinoma (HNSCC) includes an ill-defined collection of tumors that share an extremely poor outcome after seemingly appropriate multimodality treatment. Accumulating evidence suggests that extracapsular nodal spread and suboptimal surgical margins may be markers of high-risk HNSCC, but their utility is limited by ambiguous pathological criteria and unsatisfactory establishment of independent prognostic value. Inaccurate definition of high-risk HNSCC continues to obscure the scientific basis of treatment intensification protocols that have been proposed for high-risk HNSCC. Recent studies propose a more objective definition of clinically relevant extracapsular nodal spread (ECS) and surgical margins, which may contribute to improved staging and treatment selection.

Keywords: Extracapsular nodal spread, Head and neck squamous cell carcinoma, Margins, Outcome, Treatment.

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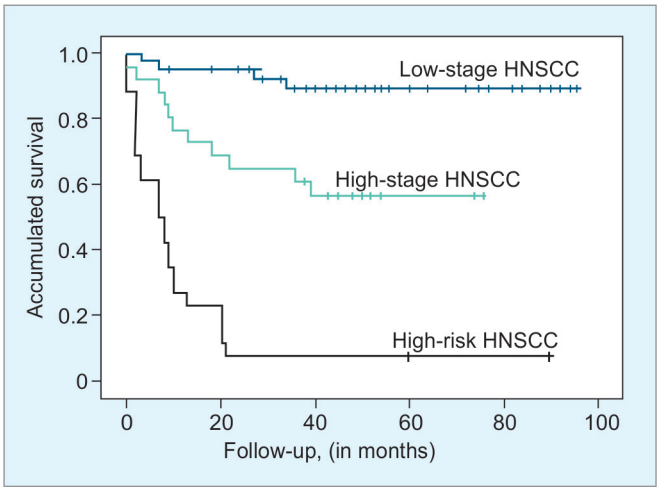
INTRODUCTION

Although they originate from a common upper aerodigestive tract mucosal source, head and neck squamous cell carcinomas (HNSCCs) are causally rooted in a highly diverse profile of extrinsic (tobacco, alcohol, viruses) and intrinsic susceptibility factors.[1] The resultant clinical behavior of HNSCC is extremely variable and quite unpredictable, which complicates selection of appropriate treatment significantly. This is critical given the tenuous therapeutic index of HNSCC treatment, influenced by the grave consequences of treatment failure on the one hand, and the impact of HNSCC treatment on both the functionally important head and neck anatomy and the suboptimal medical condition of most HNSCC patients on the other.

Conception of the Tumor node metastasis (TNM) staging system in the 1970s contributed significantly to optimization of the therapeutic index of HNSCC treatment.[2] Although its original editions were primarily based on anatomical factors, continuous development has allowed for reduction of predictive uncertainty by inclusion of histopathologic and molecular factors [human papilloma virus (HPV)].[3] Tumor node metastasis-based risk stratification helped develop the classic treatment paradigm for HNSCC patients including viability of single-modality treatment in case of low-stage HNSCC, but requirement of multimodality treatment in case of high-stage HNSCC. Although resultant survival curves confirm excellent outcome in low-stage patients, while acceptable curves for high-stage HNSCC, significant debate has surrounded identification of a third group of patients, characterized by extremely poor survival despite seemingly appropriate multimodality treatment (Graph 1). Since its designation as high-risk HNSCC, significant debate has surrounded determination of factors that help to identify affected patients early, and guide exploration of treatment intensification viability.[4]

The current review is focused on the role of extracapsular nodal spread (ECS) and positive surgical margins



Graph 1: Differences in survival curves between low-stage HNSCC, high-stage HNSCC, and high-risk HNSCC

Surgeon

Department of Otolaryngology–Head and Neck Surgery Portsmouth Teaching Hospitals, Portsmouth, UK

Corresponding Author: Volkert B Wreesmann, Surgeon Department of Otolaryngology–Head and Neck Surgery Portsmouth Teaching Hospitals, Portsmouth, UK, e-mail: vwreesmann@yahoo.com

as identifiers of high-risk HNSCC, and determinants of its required treatment intensity.

EXTRACAPSULAR NODAL SPREAD

Extracapsular nodal spread involves spread from a tumor deposit that has nested itself within a lymph node outside of the capsule of the lymph node. The presence of ECS in metastatic lymph nodes derived from patients with HNSCC was first documented by Willis.[5] However, it was not until 1971 that Bennett et al[6] reported its unfavorable prognostic features in patients with squamous cell carcinoma (SCC) of the hypopharynx. However, the histopathologic criteria of ECS remain ill-defined and subject of significant debate. Although diagnostic debate is obviously minimal in cases where the invasive front of the metastatic deposit is located away from the lymph node capsule (either overtly confined to the lymph node or extending overtly outside of the lymph node), a worrisome degree of intra- and interobserver variability obscures the diagnostic assessment of ECS in many other instances.[7] This is most pronounced when the invasive tumor front of the metastatic deposit is located in close approximation to the capsule of the metastatic lymph node, in cases in which the invasive tumor front is located in or near the nodal hilum area (which lacks a capsule), in cases where the capsule is discontinuous, in cases where a desmoplastic immune response surrounds and mimics the capsule, or in cases where capsular breach is incomplete. In these cases, uncertainty regarding the presence or absence of ECS may induce a degree of overdiagnosis fuelled by the possibility of adverse prognostic implications derived from a missed ECS diagnosis.[8]

Since the first description of adverse prognostic implications of ECS, multiple retrospective studies have focused on confirmation of this finding.[9,10] The presence of ECS is confirmed in approximately 50% of pathologically positive neck dissection specimens from patients with HNSCC. In most retrospective studies, univariate analysis confirms ECS is associated with dismal outcome. Unfortunately, most early studies failed to report multivariate analysis, thereby insufficiently ruling out the possibility for confounding. Data by Woolgar et al[11] exposed possibly sources for confounding by showing that the presence of ECS is linearly related to the volume of metastatic disease in affected lymph nodes. For example, ECS is more common in patients with an increasing number and size of metastatic lymph nodes. It also relates to contralaterality of metastatic lymph nodes and presence of metastatic lymph nodes in more caudally located anatomic neck levels, and all of these factors should be corrected for in statistical analysis. Although several retrospective studies published since have aimed to correct for confounders, few of these consistently included all conceivable nodal prognostic factors into their multivariable models. Several studies that do adhere to this principle do not support an unequivocal prognostic utility of ECS. For example, a study by Mamelle et al[12] reported ECS in 640 of 914 HNSCC patients (70%) and demonstrated ECS, nodal size, number of involved nodes, T-stage, and involved nodal neck level as significant determinants of outcome in univariate analysis. In multivariate analysis, involved nodal level and nodal size were independent predictors of outcome, but not ECS. Four other studies aimed to assess the prognostic role of ECS in the absence of nodal volume factors, by focusing exclusively on oral cavity SCC with clinically negative but pathologically positive lymph node metastasis.[13-16] Although ECS was identified in 24 to 49% of patients, ECS was not a predictor of outcome in any of these studies. A well-performed study by Brasilino de Carvalho[17] performed histologic slide review of 170 neck dissection specimens of patients with HNSCC and reported that nodal stage, nodal size, microscopic ECS, and macroscopic ECS were outcome predictors; however, only macroscopic ECS remained an independent predictor of outcome in multivariate analysis. A prognostic difference between microscopic ECS and macroscopic ECS has been observed in multiple studies, although an exact quantification of prognostically relevant electric convulsive therapy (ECT) extent remained obscure, complicating the analysis of ECS further.[9]

Overall, the lack of clearly defined ECS diagnostic criteria and convincing establishment of its independent prognostic value continues to fuel debate. This has generated the question whether ECS is merely an epiphenomenon of advanced nodal disease, rather than a truly intrinsic hallmark of aggressive tumor biology. Before an objective and widely accepted definition of clinically relevant ECS will be established, this debate is anticipated to continue.

MARGINS

Surgery continues to represent a prominent treatment avenue in HNSCC, and persistence of cancer cells within the surgical field is one of the most important risk factors for local recurrence and decreased survival in HNSCC patients.[18] Local recurrence is not only a result of the mere persistence of cancer cells in the surgical field, but also results from their increased survival chances in a postsurgical environment marked by abundant growth factors and increased delivery of oxygen and nutrients.[19] Postsurgical persistence of cancer cells may also be an indirect reflection of aggressive tumor biology, as it is frequently associated with high-stage tumors, perineural invasion, infiltrative tumor margins, and other high-risk factors that decrease chances for successful surgical

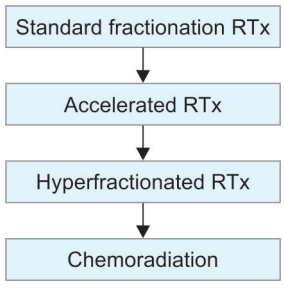
resection.[19] Finally, survival decrease associated with persistence of cancer cells in the wound bed may result from increased chances of distant metastasis due to inflammatory vasodilatation. For these reasons, postoperative histopathological assessment of surgical tumor margins provides a paramount piece of information to improve risk stratification and determination of adjuvant treatment requirement. Several factors influence our ability to accurately assess the status of surgical margins, including meticulous and thoughtful surgical technique, careful handling of the surgical specimen, consensus-based orientation of the specimen through effective communication between the pathologist and surgeon, and application of ink to the margins of the resection specimen before it is processed for subsequent microscopic analysis.[20] It is clear that mistakes during this delicate handling process can have significant impact upon our ability to gauge the surgical margins status accurately. Although the subsequent steps leading up to the microscopic assessment of the surgical margins, including the fabrication and processing of paraffin embedded tissue blocks, are a fairly standardized and automated process, the actual microscopic assessment of surgical margins is associated with significant intra-and interobserver variability.[19] In cases where microscopic analysis clearly shows that a tumor extends into the ink-colored specimen margin, it is obvious that a positive surgical margin is present, and the chances for persistence of cancer cells within the surgical wound are increased sharply. In these cases, little discussion typically exists, unless the surgeon has provided clearly defined additional resection margins which correspond to the exact anatomical location at which the positive surgical margin was identified. In contrast, cases where the invasive tumor front approaches the resection margin but does not extent directly into it may generate significant observer variability. Subjectivity is related not only to interindividual observation discrepancies, but also to a variety of different tools that are available to measure the margin distance. Shrinking of the resection specimen and its margins during specimen processing is a well-known factor that may influence margin assessment as well.[19] Finally, sampling bias may influence margin assessment, as the selection of two-dimensional tissue slides from a three-dimensional tumor specimen is arbitrary. Per universal convention, a tumor margin is deemed to be negative when the distance between invasive tumor front and the resection specimen margin is ≥5 mm, while a distance less than 5 mm indicates a close margin. It is clear that this binary approximation of an in reality continuous phenomenon has greatly facilitated categorization of patients into risk groups, but loss of information in this translation also contributes to decreased accuracy of risk prediction.

Although the conventional definition of margins as negative, close, and positive has not been supported by convincing scientific evidence, the prognostic consequences of positive and close surgical margins have been described in many retrospective studies.[18,19,21] Not surprisingly, local recurrence is sharply increased in the setting of positive margins, but also in patients with close surgical margins the rate of local recurrence is increased, albeit to a lesser degree. As a reflection of adverse tumor biology, several studies also confirm disease-specific survival (DSS) and overall survival to be influenced by close and positive surgical margins. Although independent prognostic significance of positive margins is quite universally accepted in the scientific community, the prognostic implications of close surgical margins are subject of significant debate. This not only results from the limited scientific basis of the arbitrarily selected 5 mm threshold, but also stems from inadequate correction for risk factors that are associated with close margins, such as infiltrative tumor borders, perineural invasion, lymphovascular invasion, tumor size, and local invasion among others in multivariate analysis.

HIGH-RISK HNSCC AND ITS TREATMENT INTENSITY

Management of high-risk HNSCC has been accelerated significantly by a combination of retrospective identification of risk factors (such as ECS and suboptimal margins), combined with simultaneous improvements in adjuvant radiation treatment intensification protocols provided by alteration of radiation fractionation and addition of chemotherapy (Flow Chart 1). Several trials explored the interplay between these characteristics in a randomized fashion (Figs 1 and 2, Table 1). Peters et al[4] from the MD Anderson Cancer Center included low-risk and high-risk HNSCC based on assignment of relative risk factor-based weight scores, and randomized these groups to different adjuvant radiation dose intensities. The study revealed that ECS was a significant predictor of 2-year actuarial locoregional control ($p = 0.04$), and determinant of high-risk HNSCC. The presence of multiple metastatic lymph nodes

Flow Chart 1: Developments in radiation treatment intensification; addition of chemotherapy to radiation therapy is superior regardless of fractionation mode



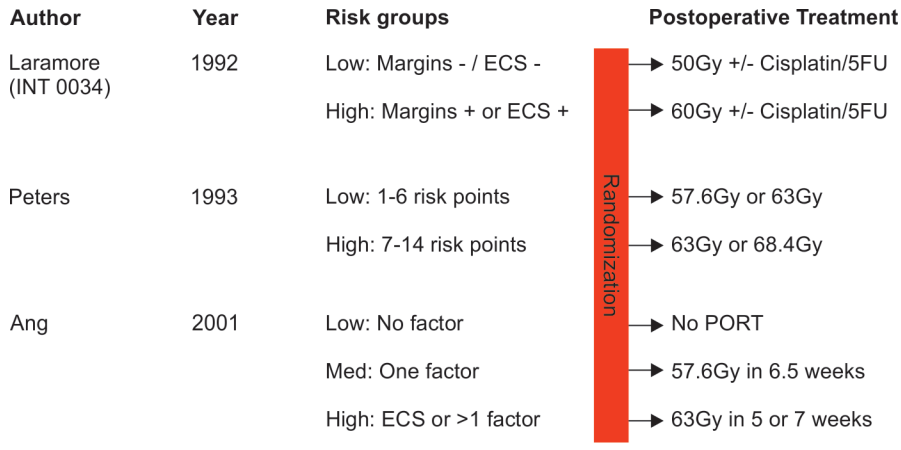
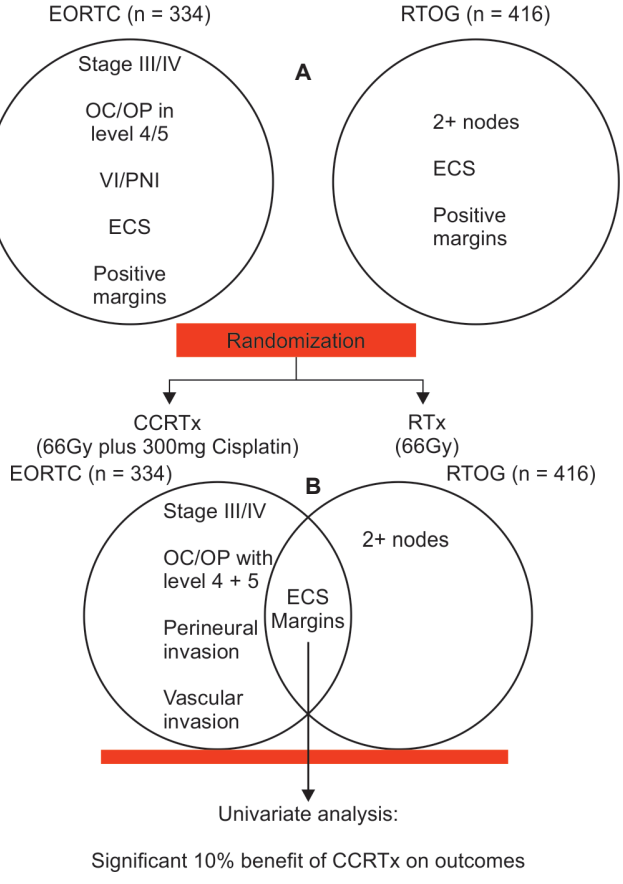


Fig. 1: Global outline of available randomized controlled trials aimed to study relationship between risk factors and treatment intensity in HNSCC

bordered on significance in univariate analysis, but no satisfactory multivariate analysis of the data was performed. The study further identified 63 Gy as the optimal dose for adjuvant radiation in high-risk HNSCC. Ang et al[22] from the same institution capitalized upon Peters' data by comparing high-risk HNSCC defined by presence of ECS or more than two other risk factors, to medium (one non-ECS risk factor) and low-risk HNSCC (no risk factors)



Figs 2A and B: A. Global outline of the RTOG 9501[24] and EORTC 22931,[25] trials and B. the combined data analysis,[26] Adjuvant chemoradiation benefit was statistically significant only in patients eligible for both studies but not in patients eligible for one study only. RTOG: Radiation oncology therapy group; EORTC: European organization for research and treatment of cancer

Table 1: Key inclusion and outcome parameters of the RTOG 9501 and EORTC 22931 trials. Heterogeneity in inclusion criteria affects data generalizability and creates potential for confounding.

Parameters	*RTOG 9501*	*EORTC 22931*
N	416	334
Site	4 sites	4 sites
Oropharyngeal origin	42%	30%
Hypopharyngeal origin	10%	20%
N2-3	94%	57%
ECS	53%	57%
LRC	NS	0.007
DMFS	NS	NS
DFS	NS	0.04
OS	NS	0.02
Grade 3 Comp	<0.001	<0.001

RTOG: Radiation oncology therapy group; EORTC: European organization for research and treatment of cancer

to randomized adjuvant treatment paradigms. This study revealed again that ECS was an excellent marker of high-risk HNSCC, although no multivariate analysis was presented, and that accelerated radiation therapy and a treatment package time less than median of 11 weeks were both associated with improved survival in these patients.

Laramore et al[23] defined low-risk HNSCC by absence of close (<5 mm) margins (positive margins excluded) or ECS, while defining high-risk SCC by the presence of positive margins or ECS. The low-risk group was randomized to 50 Gy of radiation therapy with or without induction cisplatin-based chemotherapy, while the high-risk group was randomized to 60 Gy of radiation therapy with or without the same chemotherapy regimen. Outcome in the high-risk group was significantly worse relative to the low-risk group (despite 10 Gy more radiation therapy). Disease-free survival and overall survival were improved in the proportion of patients that received chemoradiation ($p = 0.06$) in the high-risk group, but not in the low-risk group. Although margins were clear in all cases, margin status was a significant predictor of failure as well, but no prognostic impact of ECS was revealed and no multivariate analysis performed.

Inspired by these findings, the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Oncology Therapy Group (RTOG) conceived two landmark trials to assess the degree of adjuvant treatment intensity required for postsurgical high-risk patients with identified by characteristics such as ECS and/or suboptimal margins.[24,25] Each of these studies included high-risk HNSCC only, and aimed to explore the value of adjuvant treatment intensification. The results of both trials continue to influence the definition and management of high-risk HNSCC today. The EORTC trial included 334 patients with high-risk HNSCC defined by the presence of stage 3/4, oropharyngeal/oral cavity SCC with metastatic nodes in lower neck levels (levels 4 or 5), vascular invasion/perineural invasion, ECS, and/or positive/close margins. The RTOG trial included high-risk HNSCC patients defined by slightly different criteria including the presence of two or more metastatic nodes, ECS, or positive margins. Both of these trials randomized patients after inclusion and stratification to similar treatment arms including approximately 60 to 66 Gy of adjuvant radiation therapy with or without cisplatin-based concurrent chemotherapy. Primary clinical endpoints of the trials differed significantly, and included locoregional control in the RTOG trial and progression-free survival in the EORTC trial. Median follow-up of both trials was approximately 4 to 5 years. The original publication revealed that outcome per most primary and secondary endpoints was improved by an absolute risk reduction of approximately 5 to 10% in patients receiving chemoradiation treatment. In a subsequent publication in 2005, the lead authors of both trials combined their datasets to explore the relationship between adjuvant treatment intensity and risk factors in more detail.[26] These data showed that 70% of EORTC patients featured ECS and/or suboptimal margins, while 59% of the RTOG patients exhibited these characteristics. The study revealed that patients with ECS or positive margins had significantly reduced survival compared with patients without these two risk factors in univariate analysis ($p = 0.02$), when data from each trial were analyzed separately. This analysis also showed that patients with ECS or positive margins experienced significant outcome improvement when receiving chemoradiation compared with receiving radiation alone, while this was not observed in patients without any of these two risk factors. When the data of both trials were pooled, analysis showed that chemoradiation therapy reduced locoregional recurrence with 42% overall. Altogether, when analyzing patients eligible for both trials (ECS and margin-positive patients), chemoradiation benefit was significant. This was not the case when patients eligible for one study (ECS/margins negative) were analyzed separately. Based on univariate analysis, the authors concluded that ECS and positive surgical margins were indicators of chemoradiation and adjuvant chemoradiation benefit. Multivariate analysis was not performed.

EVIDENCE LIMITATIONS

Since its original publication, the validity and generalizability of the EORTC and RTOG trials have been subject of increasing criticism. Concerns regarding generalizability have focused on the inclusion profile of HNSCC subtypes of both studies, which does not seem to reflect the typical profile of surgically managed HNSCC (Table 1). For example, a minority of included patients were affected by SCCs originating in the oral cavity (27%), which represent a majority of surgically managed HNSCC nowadays. Instead, the majority of included cases featured HNSCC originating in the larynx, oropharynx, and hypopharynx (72%), a large proportion of which is nowadays treated by nonsurgical treatments. Of the included oropharyngeal carcinomas, the proportion of cases exhibiting the favorable HPV-association profile remained unclear. This represented a potential confounder, since HPV-associated oropharyngeal carcinomas are highly chemoradiation sensitive, in a notoriously ECS-independent manner.[10] Additional criticism has surrounded the different inclusion criteria for high-risk HNSCC between the studies. Apart from ECS and positive margins, which were shared inclusion criteria for high-risk HNSCC patients, the remainder of risk factors were differentially present in both trials. The significant heterogeneity in risk factors further contributed to the possibility for confounding, due to the omission of multivariate analysis. For example, inclusion of close margins in the positive margins group in the EORTC trial but not in the RTOG trial, potentially influenced the identification of margin status as an outcome predictor. In addition, the identification of ECS as a predictor of chemoradiation response in univariate analysis insufficiently ruled out confounding by the significant abundance of nodal volume factors, such as N2/3 neck disease in the EORTC (57%) and RTOG (94%) trials. As a high percentage of patients featured ECS and positive margins combined, while only 6 and 13% of included cases were characterized by positive margins alone in the RTOG and EORTC trials, the lack of multivariate analysis provided insufficient proof that patients with positive margins and absence of ECS would truly benefit from chemotherapy addition. In recent years, the validity of ECS and positive margins as predictors of chemoradiation treatment has been scrutinized even more by publication of the 10-year follow-up data of the RTOG trial, which revealed that the improved outcome in the chemoradiation arm was no longer significant after 10 years of follow-up.[27] As long as the 10-year follow-up analysis of the EORTC dataset remains unpublished, this effectively

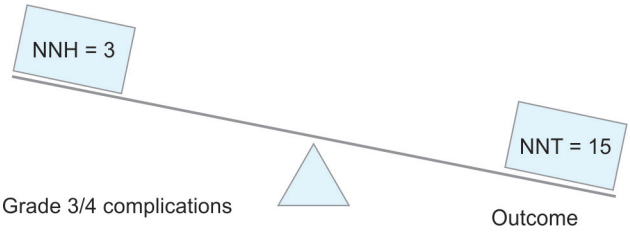


Fig. 3: Global outline of the observed imbalance between the NNT and NNH for HNSCC patients treated with adjuvant chemoradiation. Compared with adjuvant radiation alone, the NNH indicates that an average of 1 out of every 3 patients treated will develop grade III/IV complications, while only 1 out of 15 treated patients will experience survival benefit after adjuvant chemoradiation treatment. NNH: Number needed to harm, NNT: Number needed to treat

reduced support for the ECS/margin-dependent chemoradiation benefit to a single randomized controlled trial. This diminished the credibility of the combined analysis further as well, which represented a *post hoc* retrospective analysis of low evidence quality (level 2b-4) to begin with.[26] A recent study by Trifiletti et al[28] further casts doubt about the exclusivity of chemotherapy benefit for patients with ECS or positive margins, describing significant benefits in ECS/margins-negative HNSCC patients, especially those with multiple metastatic nodes.

The increasing uncertainty in evidence quality for adjuvant chemotherapy benefit has fuelled concerns about the risk/benefit ratio of this treatment, as it is associated with significant treatment sequelae. For example, the RTOG trial reported that treatment complications graded III or higher were observed in 34% of patients receiving radiotherapy alone, compared with a staggering 77% of patients receiving chemoradiation, which was highly significant ($p < 0.001$). In the EORTC trial, a similar difference between radiation therapy (21%) and chemotherapy (41%) with regard to grade III/IV complications was noted. With the 5 to 8% benefit associated with chemotherapy addition in mind, these data suggest that the relationship between the number needed to treat and the number needed to harm is gravely out of balance in adjuvant treatment of high-risk HNSCC (Fig. 3).

RECENT PROGRESS

Overall, the validity of ECS and surgical margins as determinants of high-risk HNSCC and its treatment has been hampered by unsatisfactory pathologic definitions and unconvincing prognostic assessments. This may contribute to a degree of undertreatment of patients at risk, or inadvertent exposure of patients to the severe side effects and toxicities of chemoradiation treatment in the absence of a well-defined benefit. Essentially, the current debate is sustained by unavailability of an objective and widely accepted definition of clinically relevant ECS and surgical margin status.

Two recent studies aimed to objectify the prognostic pathologic definitions of both parameters.[8,29] These studies empirically quantified ECS extent and margin status by two-dimensional metric measurements, before subjecting it to rigorous statistical analysis. Time-dependent receiver operator characteristic (ROC) analysis was chosen to identify a prognostic cut-off at which sensitivity and false-positive rate were balanced optimally for both individual parameters. A large and well-defined sequential cohort of uniformly treated oral cavity SCC patients formed the subject of this analysis. An important strength of these studies includes their joint basis upon meticulous rereview of original histologic slides by dedicated head and neck pathologists.

Using this approach, Wreesmann et al[8] identified an ECS extent risk threshold of 1.7 mm, which stratified patients into minor ECS (<1.7 mm) and major ECS (>1.7 mm) groups. Patients were then subjected to prognostic analysis together with ECS-negative patients. Univariate analysis reveals that both minor and major ECS were prognostic factors of outcome, but after correction for nodal volume factors in multivariate analysis only major ECS remained an independent prognostic factor. Although multiple previous studies had shown that the prognostic utility of macroscopic ECS was better than that of microscopic ECS, this study was the first to empirically define an exact prognostic cut-off between these entities in the context of well-defined prognostic factors.

Zanoni et al[29] used the same approach to identify a cut-off of 2.2 mm margin distance that optimally balanced the sensitivity and false-positive rate in the same oral cavity cancer cohort. Prognostic analysis revealed that patients with a margin of 2.2 mm or greater experienced virtually identical outcome as patients with the classical 5 mm margin [90% 2-year local recurrence-free survival (LRFS)]. In sharp contrast, patients with a less than 2.2 mm surgical margin distance experience a significantly lower 2-year LRFS of approximately 76%. Subsequent correction for confounding prognostic factors revealed that both positive margins and margins below the threshold of 2.2 mm were independent prognostic factors of adverse 2-year LRFS.

Strengths of both studies include inclusion of a well-defined, large, and uniformly treated cohort of oral cavity SCC patients, review of histopathological slides by dedicated head and neck pathologists, empiric and objective definition of the identified cut-offs, application of sophisticated statistical analysis, and correction for all conceivable prognostic confounders (including treatment effects) with the use of multivariate analysis. Greenberg et al[30] were previously unable to detect a difference between patients with greater than 2 mm ECS extent and patients with less than 2 mm ECS extent in a univariate

analysis based on information derived from pathologic reports. A previous study by Wong et al[31] applied ROC analysis to identify an optimal margin distance cut-off in patients of oral cavity SCC based on review of pathology reports rather than histologic slides. These authors identified an optimal cut-off at 1.6 mm of margin distance that optimally stratified patients with regard to DSS, but no cut-off was identified for local recurrence. Few other studies have provided data for comparison.

Limitations affecting the Wreesmann and Zanoni studies include the choice for a two-dimensional marker of an in reality three-dimensional phenomenon, the choice to dichotomize an in reality most likely continuous variable, the choice for gauging the maximal extent of ECS and margin distance based on analysis of a sample of microscopic slides rather than surveying the entire tumor, the possibility for selection bias based on exclusion of cases that did not have any available histologic slides, and the choice for ROC analysis among an array of other viable statistical analytic tools. Although the latter may be viewed as arbitrary, we felt that the choice for adjuvant chemoradiation should be based on a balanced assessment of its risks and benefits. The advantage of time-dependent ROC analysis lies in its optimal appreciation of both sensitivity (decreasing the risk of undertreatment) and false-positive rate (potential for overtreatment) simultaneously. Recent inclusion of the ECS extent marker into the TNM staging system may help to validate this marker for future trial inclusion.

CONCLUSION

Evidence supporting application of adjuvant chemoradiation over radiation alone in the setting of HNSCC is insufficient. This is due to several factors including our inability to accurately define high-risk HNSCC. Two well-known trials suggested that ECS and margin status were primary determinants of high-risk HNSCC and its chemotherapy-based adjuvant treatment intensification. However, these studies were associated with severe limitations, including ambiguous pathologic and prognostic definitions. Two recent studies provided a more objective definition of ECS and margin status, in order to improve identification of high-risk HNSCC.[8,29] Recent inclusion of one of the parameters into the TNM staging system may help to guide the intensification of treatment for high-risk HNSCC.[3]

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