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Meta-analysis of the prognostic significance of perinodal spread in head and neck squamous cell carcinomas (HNSCC) patients

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ABSTRACT

To assess the risk factor of capsular rupture for individual prognosis and potential therapeutic decision making, the present meta-analysis elaborated the prognostic significance of perinodal spread in a large group of patients suffering from head and neck squamous cell carcinomas (HNSCC). A review of the published literature was conducted, and fixed and random effects models were applied for estimation of the summarised odds ratio and 95% confidence intervals, including a test for homogeneity of the odds ratios. Study methodology allowed the enrollment of only nine studies of 115 published papers. Excluded studies lacked regarding primary tumour location, number and location of lymph node metastases, values on five-year survival, or adequate follow-up data. A summarised odds ratio of 2.7 leads to the conclusion that perinodal spread negatively impacts the five-year survival. The lower confidence limit of more than 2 also supports the concept that perinodal spread significantly reduces (doubled risk) the five-year-survival. These results support the conclusion that perinodal spread is a significant adverse risk factor for survival in patients with HNSCC.

1. Introduction

Ranking second after cardiovascular diseases, malignant neoplasms are one of the major diseases of today's society. Statistics specifically indicate an increase of head and neck squamous cell carcinomas (HNSCC). Lymph node metastasis significantly and negatively affects disease-specific survival in HNSCC. The literature reports five-year disease-specific survival for all sites around 59%. The overall disease-specific survival for patients with N0 disease is 67.9% compared with 39.9% for patients with N+ disease. N0 patients have significantly better disease-specific survival than patients with nodal disease, while patients with N1 disease had improved disease-specific survival compared with N2 or N3 patients, but there appears to be no survival difference between patients with N2 and N3 disease.[1]

Perinodal growth mostly occurs in advanced lymphogenic metastases (N+ neck). Small, peripherally located metastases may extend extracapsularly, e.g. when tumour cell emboli are deposited primarily in intra- or juxtacapsular lymph vessels.[2] Such extracapsular extension is termed perinodal spread.

The incidence of perinodal spread varies in studies between 21% and 85%.[3,4] In recent years, increasingly higher rates have been published; and these studies indicate inci-

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dences of 74–85% in cases of tumour-positive neck dissection specimens.[5–7] Around 20% of lymph node metastases with proven perinodal spread have a diameter of less than 1 cm.[8,9]

The identification or the exclusion of perinodal spread in HNSCC may directly influence treatment planning. In the case of histopathologically identified metastases with extracapsular tumour growth, adjuvant therapy in the form of concurrent radiation therapy and chemotherapy may be recommended.[10]

Great diversity in the terminology of capsular ruptures can be observed in the international literature, for example, extracapsular spread, capsular rupture, extra-nodal spread, and matting. There are many problems associated with this lack of a unique terminology. These terms do not provide a clear indication of the degree of capsular rupture. Transcapsular tumour spread generally describes microscopic capsular infiltration up to macroscopic invasion of the cervical soft parts. Thus, studies reporting on microscopic capsular infiltration may not be comparable to those referring to macroscopically visible metastatic spread into the cervical soft parts with regard to prognostic relevance. Such different criteria, however, may explain the different incidences of capsular ruptures in cases of N+ neck between 21%[11] and 85%.[6] Terminology of perinodal spread that differentiates the extended perinodal spread with regard to capsular infiltration versus capsular rupture with contact to perinodal tissue as well as microscopic versus macroscopic transcapsular spread is needed in order to elaborate any progressive worsening of the prognosis based on the extent of capsular infiltration.

The prognostic significance of extracapsular extrusion has been mainly described for macroscopic capsular ruptures, especially with regard to regional recurrence as well as distant metastases.[3,12] This meta-analysis was designed to examine the prognostic significance of perinodal spread in patients suffering from HNSCC with the hypothesis that perinodal spread negatively affects prognosis in patients with HNSCC.

2. Material and methods

A literature search was performed utilising the PubMed database (http://www.ncbi.nlm.nih.gov/PubMed) searching for ('extracapsular spread' or 'extra-nodal spread' or 'perinodal spread' or 'transcapsular spread') and 'HNSCC' and 'progn* significance'.

Selection criteria were as follows: (1) squamous cell carcinomas (SCC) of the oral cavity, oropharynx, larynx, hypopharynx; (2) histologic identification of a positive or negative lymph node status; (3) microscopic and macroscopic examination of the lymph node capsule in case of positive lymph node status; (4) data on the five-year survival rate in cases of cervical lymph node metastases.

Exclusion criteria were (1) Missing data on five-year survival rates; (2) non-specific definition of perinodal spread; (3) missing data on tumour status and lymph node findings; (4) missing data on numbers of patients; (5) distant metastasis present at first presentation.

The studies performed histological work-up with H&E as routinely done for neck specimen evaluation.[13]

2.1. Statistic analysis

The statistical procedures described by Whitehead and Whitehead[14] were applied in this meta-analysis. For each individual study the odds ratio with its 95% confidence interval was calculated. The test for deviations from homogenity between the studies according to Zelen[15] was used to check the odds ratios. The p-value was evaluated as a descriptive measure while a smaller p-value is accompanied by higher heterogeneity. Finally, for all publications a common odds ratio with 95% confidence interval was calculated according to Mehta et al.[16] In a 'fixed effects model' the only source of variability assumed is the coincidence variation within the study. Additionally, the calculation of the odds ratio was performed based on the 'random effects model'.[14] In cases of inhomogenous studies this procedure allows the calculation of a summarised odds ratio. Finally, Forrest-plots were created for visual comparison of the results and estimation of the heterogeneity. The statistical software StatXact 5 (Cytel Software Corporation, Cambridge, MA, USA) and SAS (SAS Institute Inc., Cary, NC, USA) were used to perform the analyses.

3. Results

One hundred and fifteen publications on the prognostic significance of perinodal spread were found. Nine of those studies corresponded to the inclusion and exclusion criteria set for the statistical evaluation of this meta-analysis (Table 1).

A total of 2573 patients were included in the meta-analysis. The primary tumour was located in the oral cavity in 1041 cases, in the oropharynx in 255 patients, in the larynx in 662 cases, and in the hypopharynx in 424 patients. The primary tumour site could not be exactly attributed either to the oral cavity or the oropharynx in 191 patients.

Cervical lymph node metastases were found histopathologically in 1620 patients and thus could be included in the statistical evaluation. In 997 of these 1620 patients (61.5%) perinodal spread was present, while 623 patients had intact lymph node capsules.

3.1. Study performed by Andersen et al.[17]

Andersen and co-workers investigated 106 patients with SCC of the hypopharynx (7), larynx (20), oral cavity (42), and oropharynx (37). The five-year survival rate was 55.8% in patients with perinodal spread and 75.3% in cases with an intact lymph node capsule. This observed difference in survival, however, failed to be statistically significant ($p = 0.2$).

3.2. Study performed by Brasilino de Carvalho[5]

Brasilino de Carvalho investigated 170 patients with SCC of the hypopharynx (77) as well as the larynx (25 supraglottic, 25 glottic, 43 transglottic tumours). Capsular rupture was found in 50% (5/10) of the N0 cases, in 56.3% (18/32) of the N1 cases; in 100% (14/14) of the N2a cases; in 88.9% (16/18) of the N2b cases; in 58.3% (7/12) of the N2c cases; and in 100% (14/14) of the N3 cases. The incidence of capsular rupture increased with the N stage of the TNM classification and the size of the lymph node diameter (>3 cm). The location

Table 1 – Studies enrolled in this meta-analysis

Study	Year	Number of patients	Location	Five-year survival (in %)		
				N0	R−	R+
Andersen et al.	2002	106	H, L, M, O	–	75.3	55.8
Brasilino d. C. et al.	1998	170 (100)	H, L	56.8	50	18
Hirabayashi et al.	1991	52 (30)	L	81	76	17
Mamelle et al.	1994	914 (567)	H, L, M, O	71.1	46.9	27.3
Myers et al.	2001	266 (120)	M	88	66	48
Pinsolle et al.	1997	337 (183)	H, L, M, O	62.4	44.6	35.5
Shingaki et al.	1999	61	M, O	–	72	40
Steinhart et al.	1994	522 (304)	H, L, M, O	77	54	28
Woolgar et al.	2003	173	M, O	–	70	33–36

N0, no ln metastasis; R−, metastasis without perinodal spread; R+, metastasis with perinodal spread; H, hypopharynx; L, larynx; M, oral cavity; O, oropharynx.
In parentheses: number of patients with metastasis.

of the primary tumour and the T stage had no statistically significant influence on the incidence of perinodal spread and adjustment of this potential risk factor did not alter the results. Capsular rupture was confirmed to be an independent prognostic factor in this study ($p = 0.0001$).

3.3. *Study performed by Hirabayashi et al.*[18]

The investigation of Hirabayashi analyzed a total of 52 patients who had primary laryngeal tumours. Perinodal spread was identified in 31% of the cases with N1 lymph node stage and in 72% of the cases staged N2/N3. The five-year survival of the patients who had no lymph node metastases was 81%. The five-year survival was 76% in cases of metastases limited to the lymph node. In cases of proven perinodal spread, however, it was only 17%. The T stage had no statistical significant influence on perinodal spread and adjustment of this potential risk factor did not alter the results. Strong correlation between perinodal spread and five-year survival rate could be identified in this study ($p = 0.001$).

3.4. *Study performed by Mamelle et al.*[19]

In this study, performed by Mamelle et al., 914 patients suffering from SCC of the upper aerodigestive tract were enrolled. Of these, 287 patients had carcinoma of the oral cavity, 249 had hypopharyngeal carcinoma, 247 patients had laryngeal carcinoma, and 131 had oropharyngeal carcinoma. Perinodal spread was detected in 397 of 567 (70%) patients with lymph node metastases. The lymph nodes (53%) smaller than 3 cm showed perinodal spread. The five-year survival rate of patients with perinodal growth was 27.3% and 46.9% in patients without perinodal spread. Of all patients, 47.2% survived the first five years. Using a multivariate Cox regression model, the prognostic significance of capsular rupture was not confirmed in this study ($p = 0.09$). Only the size, number, and location of the lymph nodes were noted to be significant prognostic factors ($p = 0.001$). The number of lymph node metastases correlated with the location of the primary tumour with decreasing risk for carcinomas of the hypopharynx (86%), the oropharynx (73%), the oral cavity (51%), and the larynx (45%).

3.5. *Study performed by Myers et al.*[20]

Myers et al. retrospectively evaluated 266 patients with SCC of the oral cavity who underwent complete resection of the primary tumour as well as neck dissection. Lymph node metastases were not found in 146 of 266 patients (55%). Patients (75/266 (28%)) had metastases limited to the lymph node. Perinodal spread was detected in 45 cases (17%). The five-year survival rate was 66% for patients without capsular rupture, and 48% for patients with rupture of the capsule ($p < .05$).

3.6. *Study performed by Pinsolle et al.*[21]

Pinsolle and co-workers evaluated 337 patients with SCC of the upper aerodigestive tract. The primary tumours were located in the oral cavity (246 patients), in the oropharynx (53 patients), in the hypopharynx (21 patients), and in the larynx (17 patients). Of the study group, 154 patients with node negative disease and 183 patients with positive lymph node disease were included. Of the node positive group, 54% (99/183) had extracapsular spread.

The five-year survival rate was 50.8% for all patients and 62.4% in patients with negative nodes. In patients with positive nodes and confirmed capsular rupture, the five-year survival rate was 35.5%, while patients with intact lymph node capsules had a five-year survival rate of 44.6%. With regard to distant metastatic frequency, this study revealed a prognostic relevance of perinodal spread ($p < .05$). However, this was not the case for survival ($p = .45$). Pinsolle et al. concluded that the low number of occult positive lymph nodes and perinodal growth was due to the high number of patients with primary tumours located in the oral cavity.

3.7. *Study performed by Shingaki et al.*[22]

In their investigation, Shingaki and co-workers analysed 61 patients with SCC located in the oropharynx (4) and the oral cavity (57), who had undergone radical neck dissection showing histologically proven lymph node metastases. Capsular rupture was detected in 28 (46%) of all patients and the incidence of capsular rupture increased with the N stage. The T

stage did not correlate with capsular rupture. The patients (72%) without capsular rupture survived for five years after diagnosis whereas only 40% of the patients with capsular rupture achieved this survival ($p = 0.008$).

3.8. Study performed by Steinhart et al.[23]

The investigation performed by Steinhart et al. enrolled a total of 522 patients with SCC of the head and neck who underwent unilateral or bilateral neck dissection and had a follow-up of at least five years. The primary tumours were located in the larynx (233 patients), in the hypopharynx (70 patients), in the oropharynx/oral cavity (191 patients), in the nose/paranasal sinuses (6 patients), in the salivary glands (9 patients), and in the nasopharynx (13 patients).

In 212 patients, one (99 patients) or more (113 patients) lymph node metastases were found with proven perinodal spread compared to 92 patients with nodes that had intact capsules. Depending on the location of the primary tumour, the incidence of capsular ruptures varied. Capsular rupture was present in 70% of hypopharyngeal cancers, in 37% of the oropharyngeal carcinomas, and in 33% of the laryngeal carcinomas ($p < .05$). Tumour related survival graphs were created for a total of 280 patients showing the five-year survival rates; however, they did not reveal how many patients quit the study during this time.

3.9. Study performed by Woolgar et al.[24]

Woolgar and co-workers analyzed 173 patients suffering from SCC of the oral cavity (143 patients) and the oropharynx (30 patients). Following neck dissection, all patients were histologically diagnosed to have lymph node metastases and those metastases were examined with regard to microscopic and macroscopic perinodal spread. Of the 102 patients who had nodes with capsular rupture, 54 had macroscopic rupture and 48 had microscopic rupture.

For patients with macroscopic perinodal spread, the five-year survival rate was 33%. Patients showing only microscopic perinodal spread had a five-year survival of 36% whereas the five-year survival of patients who had metastasis limited to the lymph nodes was 70%. The small difference between survival rates related to macro- and microscopic perinodal spread was not statistically significant ($p > .05$). There was no statistical significant correlation between the pathologic T stage and capsular rupture ($p = 0.35$). Perinodal spread showed significant correlation with regard to gender ($p = 0.047$), age ($p = 0.020$), status of the resection margins ($p = 0.036$), number of positive lymph nodes ($p < 0.001$) and the pathologic N stage ($p < 0.001$).

3.10. Evaluation of the odds ratio with regard to heterogeneity

The evaluated p-value amounts to 0.1132 and supports inhomogeneity, however, does not confirm it. Thus, the confidence interval was also evaluated using a 'random effects' (RE) model on the assumption of heterogeneity. The values correspond to those derived using the 'fixed effects' (FE) model, leading to the conclusion that the result is robust (Table 2).

3.11. Calculation of the summarised odds ratio

The odds ratios calculated by the FE and RE models are similar. Also, the confidence intervals differ only marginally (Table 3). It must be mentioned that the confidence interval is large due to somewhat unclear patient data provided in the studies. Because the five-year survival rates are frequently given as percentages and frequently lacked complete patient follow-up data, the numbers of patients had to be estimated. It is possible that more complete patient data would allow for narrower confidence intervals. This would affect the p-value when testing deviations from homogeneity.

The Forrest-plot of the nine studies including the values for the odds ratio calculated according to both models describes the significance of the published studies based on the location and width of the confidence intervals as well as the total values for the odds ratio (Fig. 1).

In conclusion, 668 of 1620 patients enrolled in this meta-analysis survived the first five years after diagnosis. This corresponds to an overall five-year survival of 41.23%. Of the 623 patients who had histologically intact lymph node capsules, 362 patients survived for five years, which corresponds to a five-year survival rate of 58.1%. In contrast, for the group of patients with perinodal spread, 306 of 997 patients survived for five years, which corresponds to a five-year survival rate of only 30.7%.

A summarised odds ratio of 2.7 leads to the assumption that perinodal spread negatively impacts the five-year sur-

Table 2 – Odds ratios and according 95% confidence intervals of the publications

Study	Number of patients, $n = 1620$	95%-CI: lower limit	Odds ratio	95%-CI: upper limit
Andersen et al.	106	0.97	2.494	6.38
Brasilino d.C. et al.	100	1.58	4.692	13.85
Hirabayashi et al.	30	1.94	15.00	132.5
Mamelle et al.	567	1.61	2.379	3.51
Myers et al.	120	0.92	2.091	4.77
Pinsolle et al.	183	0.76	1.440	2.73
Shingaki et al.	61	1.24	4.121	13.97
Steinhart et al.	280[a]	1.71	3.010	5.31
Woolgar et al.	173	2.26	4.558	9.26

Overview.
a Calculation from tumour survival graphs.

Table 3 – Results of the summarised odds ratios using FE and RE model

Test	95%-CI: lower limit	Odds ratio	95%-CI: upper limit
FE-model	2.162	2.696	3.365
RE-model	2.053	2.749	3.681

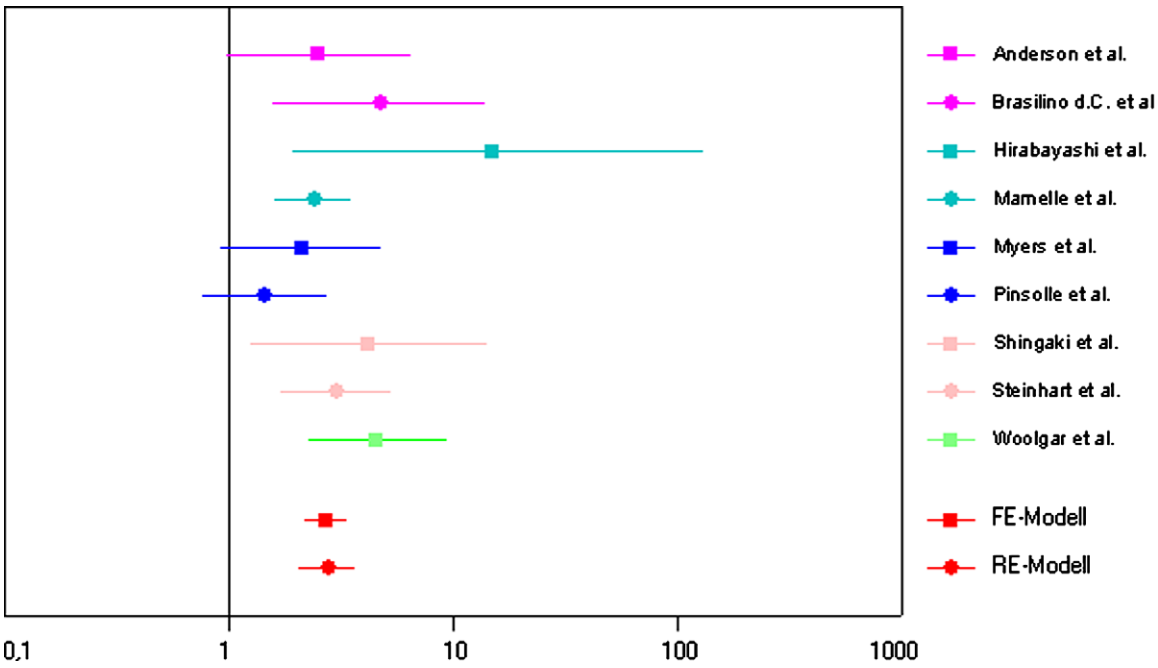

Fig. 1 – Forest-plot (odds ratio and 95% confidence interval) of the publications enrolled in the analysis including the values for the odds ratio calculated according to both models.

vival. A lower confidence limit of more than 2 (doubled risk) further supports the concept that perinodal spread relevantly impairs the five-year survival.

4. Discussion

In 1930, Willis[25] first described perinodal spread in lymph nodes. His investigations were based on a series of autopsies of patients with advanced carcinomas of the head and neck. In 1971, Bennett et al. reported that perinodal spread was an independent prognostic factor for patients with laryngeal and hypopharyngeal carcinomas.[26] Wenzel et al.[27] and Greenberg et al.[28] showed in their investigations that an increased number of ruptured capsules worsens the prognosis of HNSCC patients.

Generally, perinodal spread is identified by microscopic visualisation of tumour penetration of the lymph node capsule.[13] Because there is no standard definition of capsular rupture, varied incidences of capsular rupture (between 21%[11] and 85%[6]) are reported in the literature. Because of the proven prognostic relevance of capsular rupture in SCC nodal metastases, Snow et al.[8] urged pathologists to standardise the definition of perinodal spread as early as 1982.

The incidence of capsule rupture increases with the size of the metastatic lymph node. Snow et al.[8] detected an incidence of capsule rupture of 23% for lymph nodes less than 1 cm in size and in 74% of lymph nodes greater than 3 cm in size. About one third of metastatic lymph nodes less than 1 cm in size have perinodal spread.[4,11]

It has to be pointed out, that a potential source of inaccuracy or uncertainty lies in the term of lymph node 'size'. In pathological staging, size implies 'profile diameter of metastatic deposit' rather than size of positive node. Clinical staging uses the size of the entire node. Hence, the term 'size' without further specification or knowledge of the staging system is not specific enough. This statement also reveals the necessity for pathologists and clinicians to define a unique terminology in an interdisciplinary context. Knowledge of the terminology of all involved disciplines is a basic requirement for the formulation of international standards.

In their study, Jose et al.[4] criticised the fact that histological examinations often consider only macroscopic capsular ruptures because many studies describe microscopic perinodal spread as not a significant factor for survival.[3,5,23] Woolgar et al.[24] reported that although patients with macroscopic capsular ruptures succumb to their disease earlier compared to patients without perinodal spread, the outcome of patients with microscopic lesions is equally poor, even if postoperative radiation therapy is used.[24]

There are many investigations on the prognostic significance of perinodal spread; however, only very few studies provide complete data. Thus, the precision and quality of a meta-analysis of these studies has limitations and multivariate analyses are not possible. It should be noted, that Mamelle et al.[19] failed to determine prognostic significance in a multivariate analysis. Some of the more frequently missing data are the location of the primary tumour, the number and location of the lymph node metastases, five-year survival data and patient follow-up data. Because of this the present meta-analysis was not able to evaluate the prognostic significance of primary tumour location because adequate numbers of patients from studies with sufficiently complete stratification according to the above-mentioned criteria were not available.

This meta-analysis allowed the enrollment of only nine studies of more than 100 published papers. Despite this, the meta-analysis could confirm that the five-year survival rate is significantly reduced in cases of perinodal spread. From a

prognostic point of view, a summarised odds ratio of 2.7 leads to the assumption that perinodal spread negatively impacts the five-year survival. The lower confidence limit of more than 2 underlines that perinodal spread significantly reduces (doubled risk) the five-year-survival. In conclusion, perinodal spread is a doubling risk factor that reduces the five-year-survival by univariate analysis.

In order to perform a multivariate analysis that evaluates the risk of capsule rupture in the future, the compiled studies will need to contain detailed information on primary location, lymph node status, treatment, five-year survival data, and data that differentiate micro- and macroscopic perinodal spread. As the detection of perinodal spread may directly influence the treatment plan, we believe that the creation of international standards for assessment of micro- or macroscopic perinodal spread is important. In the future, this challenge should be approached by carefully designed multi-centre studies.

Conflict of interest statement

None declared.

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