# Incidence of Occult Cervical Metastasis in Head and Neck Carcinomas: Development Over Time


GEORGIOS PSYCHOGIOS, MD, PhD,* KONSTANTINOS MANTSOPOULOS, MD, PhD, CHRISTOPHER BOHR, MD, PhD, MICHAEL KOCH, MD, PhD, JOHANNES ZENK, MD, PhD, AND HEINRICH IRO, MD, PhD

*Department of Otorhinolaryngology, Head and Neck Surgery, Friedrich Alexander University of Erlangen-Nuremberg, Germany*



**Background:** With the development of imaging techniques in diagnostics of head and neck carcinomas, especially computed tomography and ultrasonogaphy, one might expect that the incidence of occult metastases would be reduced. The aim of this study was to determine the rate of occult metastases in a large population cohort and explore its changes with improvement of imaging techniques over the last 30 years.
**Methods:** All patients between 1980 and 2010 with head and neck carcinoma and cN0 neck status were retrospectively evaluated. Six hundred thirty-six patients with cN0 neck who received an elective neck dissection as part of a definitive surgical treatment were included.
**Results:** The overall rate of occult metastases was 24.8% (158/636). The rate was 26.5% (80/302) between 1980 and 1995 and 23.4% (78/334) between 1995 and 2010. Only pT1–2 glottic carcinomas had an occult metastases rate of less than 10%. All other pT1–2 carcinomas had an incidence of occult metastases between 19.1% and 42.5%. pT3–4 tumors showed an occult metastases rate of 24.5–53.3%.
**Conclusion:** The occult metastases rate showed only a marginal improvement over the last 30 years and is still above the 20% margin. All but pT1–2 glottic carcinomas should be considered for elective treatment of the neck.


## INTRODUCTION

Management of occult cervical metastases, which are defined as metastases that remain clinically undetected during diagnostic work-up before treatment, is a subject of ongoing debate in head and neck oncology [1–3]. Elective neck dissection is generally accepted if the probability of occult metastasis is 15–20% or more [4]. The advent of transoral laser resection in most early head and neck carcinomas further complicated the dilemma of optimal neck treatment [2,5,6]. The incidence of occult cervical metastases depends on many patient-related factors such as tumor size, location, differentiation, and perhaps biomarkers [7]. On the other hand, management-related parameters such as extent of neck dissection, details of the histopathological examination (e.g., step serial sectioning, immunohistochemistry) [8], and diagnostic method used can also have a major impact on detection of small cervical metastases [9].

With the development of imaging techniques in diagnostics of squamous cell carcinomas of the head and neck, especially computed tomography and ultrasonogaphy, one might expect that the incidence of occult metastases would be reduced. The aim of this study was to determine the rate of occult metastases in a large population cohort and explore its changes with improvement of imaging techniques over the last 30 years. To the best of our knowledge this is the first publication of this kind.

## METHODS

A retrospective study was conducted at an academic tertiary care center. The main inclusion criterion was previously untreated HNSCC (head and neck squamous cell carcinoma—i.e., oral, oropharyngeal, hypopharyngeal, and laryngeal carcinomas) with definitive surgical treatment between 1980 and 2010. Selected were all patients who had preoperative cN0 cervical status and had undergone an elective neck dissection as part of the primary surgical treatment. Patients previously treated for head and neck carcinomas or with histology other than squamous cell carcinoma (SCC) were excluded from the study. Also excluded were patients with neck dissection post radio(chemo)therapy or induction chemotherapy. Staging was re-evaluated after reviewing the surgical and pathology reports according to the 2010 American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) classifications. Approval was obtained from the institutional review board of the hospital.

Endpoints of the analysis were the calculation of the incidence of occult cervical metastases according to location, T-classification, and period of study. The compared periods were between 1980 until 1995 and 1995–2010. Statistical analysis was performed using binary logistic regression analysis and the chi-square test for independence. A $P$ value of $<0.05$ was considered significant. All statistical analyses were performed using SPSS Version 19 (SPSS, Inc., Chicago, IL).

Surgery of the neck was performed simultaneously with the primary site procedure or shortly thereafter, once the definitive histology results from the primary tumor were available. A modified radical

Abbreviations: HNSCC, head and neck squamous cell carcinoma; SCC, squamous cell carcinoma; AJCC, American Joint Committee on Cancer; UICC, Union Internationale Centre Contre Cancer; ND, neck dissection; MRI, magnetic resonance tomography; CT, computed tomography; SLNB, sentinel lymph node biopsy; PET, positron emission tomography.


*Correspondence to: Georgios Psychogios, MD, PhD, Department of Otorhinolaryngology, Head and Neck Surgery Friedrich Alexander University of Erlangen–Nuremberg Waldstrasse 1, 91054 Erlangen, Germany. Fax: 49-9131-8533833. E-mail: georgios.psychogios@uk-erlangen.de, gpsychogios@gmail.com

neck dissection (ND) levels Ib–V or a selective neck dissection levels II–IV was performed in most cases [10]. In cases with involvement of the anterior oral region, level Ia was included. Typical indications for a bilateral elective neck dissection were carcinomas near the midline such as anterior floor of mouth, tongue and uvula, supraglottic carcinomas, and carcinomas of the posterior pharyngeal wall. In cases where unilateral ND was performed, the contralateral neck was assumed to be free from tumor metastases.

Standard preoperative diagnostics included clinical examination, ultrasonograhy, and computed tomography. Fine needle aspiration was not performed in routine preoperative evaluation, and magnetic resonance tomography (MRI) was used only in a few cases. The use of ultrasound in the diagnostic approach to head and neck carcinomas has a long tradition in our department and is performed by the otorhinolaryngologist himself. Since 1995, we use high end sonography devices, and since 2007, we have an Acouson 2000 (Siemens, AG) with capabilities for Doppler sonography, elastography, tissue harmonic imaging and panorama imaging. Our radiology department is equipped with a 64-slice computed tomography scanner (Siemens, AG).

## RESULTS

The final study population included 636 patients who met the inclusion criteria. The median age at presentation was 58 years, ranging from 32 to 85 years (SD 10.5). Ninety-two (14.5%) of the patients were women, with a men to women ratio 5.9/1.

Of the 636 patients treated, 289 (45.4%) underwent a unilateral and 347 (54.6%) a bilateral neck dissection. Of the unilaterally treated patients, 167 underwent a modified radical ND, 110 a selective ND and 12 a radical ND. Of the bilaterally treated patients, 225 underwent a modified radical ND, 102 a selective ND and 20 a radical ND.

The overall rate of occult metastases was 24.8% (158/636). Table I shows the distribution of pN-classification according to pT-classification.

One hundred nine patients presented with oral, 165 with oropharyngeal carcinoma, 301 with laryngeal, and 61 with hypopharyngal carcinoma. Table II shows the incidence of occult metastasis according to primary tumor location and pT-classification. Only pT1–2 glottic carcinomas had an occult metastases rate of <10%. All other pT1–2 carcinomas had an incidence of occult metastases between 19.1% and 42.5%. pT3–4 tumors showed an occult metastases rate of 24.5–53.3%.

The overall rate of occult metastases was 26.5% (80/302) between 1980 and 1995 and 23.4% (78/334) between 1995 and 2010. Table III shows the development of incidence of occult metastases for each primary tumor site. In the whole study population, the study period had no significant influence on the incidence of occult metastasis, except for the hypopharyngeal site where further analysis with a binary logistic regression showed a statistically significant reduction.

For the whole period, we identified and statistically analyzed four possible prognostic factors that could play a role in the incidence of occult metastases. The logistic regression analysis showed a significant correlation for T-classification (T1–2 vs. T3–4) and tumor differentiation (well/moderate vs. poor/undifferentiated; Table IV). On the other hand, maximum tumor dimension and tumor depth did not show a correlation. Tumor depth was measured using an imaginary line reconstructing the basal membrane of the healthy mucosa to the deepest point of tumor invasion.

## DISCUSSION

The principle of ND in clinically N0 neck, defined as elective ND, was based on the observation that the ability of diagnostic techniques to assess cervical metastases is limited [11]. Currently, elective treatment of the neck is indicated if the probability of occult cervical metastases is at least 15–20% [12]. This percentage was mainly determined in a study by Weiss et al. [4] who performed a mathematical analysis and concluded that the benefits outweigh the costs of elective ND only when the risk for occult metastasis exceeds 20%. On the other hand, recent studies proposed various thresholds for performing elective ND, which lie between 17% and 44% [13].

Imaging techniques have seen impressive development in the last decade [14,15]. Computed tomography (CT) as well as ultrasonography are able to visualise lesions only a few millimeters (mm) in size. The spatial resolution of high frequency ultrasound is thought to be even better than CT or MRI [9]. Because of this improvement in head and neck imaging, one might expect that the occult metastases rate would decrease with time to below the 15–20% threshold, thus rendering elective treatment of the neck obsolete.

Unfortunately, this does not seem to be the case. This study shows that the incidence of occult metastases decreased only marginally in the last 30 years and is still above the 20% margin. Furthermore, this improvement was not statistically significant. Even for T1–2 carcinomas, the overall rate was 22% and only glottic tumors had an incidence of <10% (Table III). Perhaps the most important reason for this discrepancy are micrometastases, defined as a metastatic deposit >0.2 mm and not >2.0 mm in their greatest dimension, which cannot be detected with any imaging technique [9]. Micrometastases have been found in about one fourth of positive neck dissections from patients with cN0 neck [8,16]. The prognostic importance of micrometastases in head and neck carcinomas in still unclear, although a negative impact has been reported [17].

Other management related parameters influencing the incidence of occult metastases are the extent of performed neck dissection and the details of histopathological examination. In our study, most of the patients underwent a modified radical ND allowing for examination of all cervical levels. In recent years, we have increasingly performed selective ND for the treatment of clinically negative lymph nodes. According to the literature, there is only a negligible risk of missing lymph node metastases with this strategy [18]. At the same time, the improvement in morbidity and function is significant [19]. About half of our patients did not undergo a bilateral ND. Theoretically, this could have resulted to missing some occult metastases. But, we mainly performed unilateral ND in early carcinomas of the tonsillar region and the lateral floor of the mouth, which are known

**TABLE I. The Distribution of pN-Classification According to pT Classification**

| | pN0 | pN1 | pN2 | pN+ | All |
|---|---|---|---|---|---|
| pT1 | 151 | 21 | 18 | 39 (20.5%) | 190 |
| pT2 | 161 | 30 | 19 | 49 (23.3%) | 210 |
| pT3 | 70 | 11 | 15 | 26 (27.1%) | 96 |
| pT4 | 96 | 14 | 30 | 44 (31.4%) | 140 |
| All | 478 | 76 | 82 | 158 (24.8%) | 636 |

**TABLE II. Incidence of Occult Metastasis (%) According to Primary Tumor Location and pT-Classification**

| | pT1–2 | pT3–4 | All |
|---|---|---|---|
| Oral | 19.1% (18/94) | 53.3% (8/15) | 23.9% (26/109) |
| Oropharynx | 24.1% (33/137) | 32.1% (9/28) | 25.5% (42/165) |
| Hypopharynx | 42.5% (17/40) | 42.8% (9/21) | 42.6% (26/61) |
| Larynx | 15.5% (20/129) | 25.6% (44/172) | 21.3% (64/301) |
| Glottis | 8.6% (5/58) | 24.5% (23/94) | 18.4% (28/152) |
| Supraglottis | 21.1% (15/71) | 26.9% (21/78) | 24.2% (36/149) |
| All | 22.0% (88/400) | 29.7% (70/236) | 24.8% (158/636) |

**TABLE III. Development of Incidence of Occult Metastases for Each Primary Tumor Site**

| | 1980–1995 | 1995–2010 | All | Logistic regression |
|---|---|---|---|---|
| Oral-oropharynx | 26.3% (26/99) | 24.0% (42/175) | 24.8% (68/274) | No correlation ($P = 0.677$) |
| Hypopharynx | 60.9% (14/23) | 31.6% (12/38) | 42.6% (26/61) | $P = 0.028$; OR = 0.297; 95% CI = 0.101–0.875 |
| Larynx | 22.2% (40/180) | 19.8% (24/121) | 21.3% (64/301) | No correlation ($P = 0.668$) |
| All | 26.5% (80/302) | 23.4% (78/334) | 24.8% (158/636) | No correlation ($P = 0.361$) |

Oral and oropharyngeal carcinomas were merged to facilitate statistical analysis.

to have a very low incidence of bilateral lymph node metastases [20,21].

Histopathological examination has also undergone many improvements in the last 30 years (e.g., step serial sectioning, immunohistochemistry) [8,22]. Nevertheless in our institution, immunhistohemistry is used in only a minority of cases in addition to conventional light microscopy after hematoxylin eosin stain. Therefore, histopathological examination of neck specimens only changed marginally in the last 30 years and did not affect the incidence of occult metastases in our department. Furthermore, even patients without histological evidence of lymph node metastases may also develop regional treatment failure during the follow-up period—an indirect sign that the actual incidence of occult metastases could be even higher [23].

Our study shows that hypopharyngeal carcinomas have the highest rate of occult metastases among HNSSC with 42.6%. This is in agreement with other studies that show a high incidence of positive cervical lymph nodes even in T1–2 cancer of the hypopharynx [24]. On the other hand, oral, oropharyngeal, and supraglottic laryngeal carcinomas showed similar rates of occult metastases (Table II), which remained around 20% even for early stage tumors [25,26]. Glottic laryngeal carcinomas showed an incidence of occult metastases of 8.6% in pT1–2 cases, for which reason an elective ND is not typically performed in such cases. On the other hand, pT3–4 glottic cancers had a rate of 24.5%, very similar to the supraglottic carcinomas (26.9%) of the same pT category.

Logistic regression analysis of our cases could show that T-classification and tumor differentiation are independent prognostic factors for the development of occult metastases. This could be taken into account when deciding on elective treatment of the neck in borderline cases. On the other hand, tumor size and tumor depth did not show a correlation [27]. In several studies, tumor depth has been shown to be an independent predictor of increased incidence of regional metastasis and worse survival [28–31]. The main drawback of these studies is the small number of patients treated. On the other hand, our study includes a very heterogeneous group of patients with all tumor stages and localizations of the head and neck region. In addition, we only investigated the role of tumor depth in the incidence of occult metastasis, not the incidence of regional metastasis in general.

The main drawbacks of the study are its retrospective nature and the long period of study. During this period, changes have occurred not only in the imaging techniques but also in the extent of neck dissection and details of histopathological examination. On the other hand, this long study period allows an insight into development of occult metastases rate over time.

In order to improve the pretherapeutic diagnostics of cervical lymph node metastases, new innovations have been tried. The most promising and practical seems to be the combination of ultrasound with fine needle aspiration of lymph nodes likely to have subclinical metastases [9]. Another concept which has been tried with partial success, mostly in oral/oropharyngeal carcinomas in recent years, is sentinel lymph node biopsy (SLNB) [32]. SLNB in HNSCC is currently only employed in clinical trial settings and has not yet found acceptance in everyday clinical practice [33]. On the other hand, the use of positron emission tomography (PET) imaging to stage the N0 neck in early HNSCC has not produced the hoped-for results, perhaps due to the low resolution of PET [34]. The combination of PET with integrated CT has showed improved results in the detection of unknown primary [35]. Whether the same improvement can be also

**TABLE IV. Logistic Regression Analysis for the Correlation of T-Classification, Tumor Differentiation (Well/Moderate Vs. Poor/Undifferentiated), Maximum Tumor Dimension and Tumor Depth With the Rate of Occult Metastases in All Head and Neck Carcinomas**

| | Groups (patient numbers) | OR | $P$ (Wald-test) | CI |
|---|---|---|---|---|
| T-classification | T1–2 (400) vs. T3–4 (236) | 1.517 | 0.041 | 1.016–2.265 |
| Tumor differentiation | G1–2 (447) vs. G3–4 (158) | 1.503 | 0.031 | 1.037–2.179 |
| Max. tumor dimension | $\leq$25 mm (210) vs. $>$25 mm (138) | | No correlation ($P = 0.091$) | |
| Tumor depth | $\leq$8 mm (130) vs. $>$8 mm (101) | | No correlation ($P = 0.289$) | |

The numbers indicate the patients with available data.

achieved in detection of subclinical lymph node metastases has yet to be determined.

## CONCLUSION

In conclusion, the incidence of occult metastases decreased only marginally in the last 30 years and does not reflect the impressive development of imaging techniques in the same period. The rate is still over the 20% margin. Therefore, elective treatment of the neck should be considered in all but pT1–2 glottic carcinomas.

## ACKNOWLEDGMENTS

The authors would like to thank Philipp Grundtner for his valuable assistance during the statistical analysis of the data.

## REFERENCES

1. Fasunla AJ, Greene BH, Timmesfeld N, et al.: A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol 2011;47:320–324.
2. Rodrigo JP, Shah JP, Silver CE, et al.: Management of the clinically negative neck in early-stage head and neck cancers after transoral resection. Head Neck 2011;33:1210–1219.
3. Goudakos JK, Markou K, Nikolaou A, et al.: Management of the clinically negative neck (N0) of supraglottic laryngeal carcinoma: A systematic review. Eur J Surg Oncol 2009;35: 223–229.
4. Weiss MH, Harrison LB, Isaacs RS: Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994;120:699–702.
5. Iro H, Mantsopoulos K, Zenk J, et al.: Results of transoral laser resection in T1–2 oropharyngeal, hypopharyngeal and laryngeal carcinomas. Laryngorhinootologie 2011;90:481–485.
6. Psychogios G, Mantsopoulos K, Kuenzel J, et al.: Primary surgical treatment of T2 oropharyngeal carcinoma. J Surg Oncol 2012;105:719–723.
7. Takes RP, Rinaldo A, Rodrigo JP, et al.: Can biomarkers play a role in the decision about treatment of the clinically negative neck in patients with head and neck cancer? Head Neck 2008; 30:525–538.
8. Devaney KO, Rinaldo A, Ferlito A: Micrometastases in cervical lymph nodes from patients with squamous carcinoma of the head and neck: Should they be actively sought? Maybe. Am J Otolaryngol 2007;28:271–274.
9. Richards PS, Peacock TE: The role of ultrasound in the detection of cervical lymph node metastases in clinically N0 squamous cell carcinoma of the head and neck. Cancer Imaging 2007;7:167–178.
10. Ferlito A, Robbins KT, Shah JP, et al.: Proposal for a rational classification of neck dissections. Head Neck 2011;33:445–450.
11. Wei WI, Ferlito A, Rinaldo A, et al.: Management of the N0 neck–reference or preference. Oral Oncol 2006;42:115–122.
12. Pitman KT: Rationale for elective neck dissection. Am J Otolaryngol 2000;21:31–37.
13. Okura M, Aikawa T, Sawai NY, et al.: Decision analysis and treatment threshold in a management for the N0 neck of the oral cavity carcinoma. Oral Oncol 2009;45:908–911.
14. Rumboldt Z, Gordon L, Bonsall R, et al.: Imaging in head and neck cancer. Curr Treat Options Oncol 2006;7:23–34.
15. Lell M, Baum U, Greess H, et al.: Head and neck tumors: Imaging recurrent tumor and post-therapeutic changes with CT and MRI. Eur J Radiol 2000;33:239–247.
16. Ambrosch P, Kron M, Fischer G, et al.: Micrometastases in carcinoma of the upper aerodigestive tract: Detection, risk of metastasizing, and prognostic value of depth of invasion. Head Neck 1995;17:473–479.
17. Ferlito A, Rinaldo A, Devaney KO, et al.: Detection of lymph node micrometastases in patients with squamous carcinoma of the head and neck. Eur Arch Otorhinolaryngol 2008;265:1147–1153.
18. Ferlito A, Rinaldo A, Silver CE, et al.: Elective and therapeutic selective neck dissection. Oral Oncol 2006;42:14–25.
19. Teymoortash A, Hoch S, Eivazi B, et al.: Postoperative morbidity after different types of selective neck dissection. Laryngoscope 2010;120:924–929.
20. Olzowy B, Tsalemchuk Y, Schotten KJ, et al.: Frequency of bilateral cervical metastases in oropharyngeal squamous cell carcinoma: A retrospective analysis of 352 cases after bilateral neck dissection. Head Neck 2011;33:239–243.
21. Mantsopoulos K, Psychogios G, Waldfahrer F, et al.: Surgical treatment of locally limited tonsillar cancer. Surg Oncol 2012; 21:e13–e16.
22. Barrera JE, Miller ME, Said S, et al.: Detection of occult cervical micrometastases in patients with head and neck squamous cell cancer. Laryngoscope 2003;113:892–896.
23. Hoch S, Fasunla J, Eivazi B, et al.: Delayed lymph node metastases after elective neck dissection in patients with oral and oropharyngeal cancer and pN0 neck. Am J Otolaryngol 2012; DOI: 10.1016/j.amjoto.2011.11.005
24. Karatzanis AD, Psychogios G, Waldfahrer F, et al.: T1 and T2 hypopharyngeal cancer treatment with laser microsurgery. J Surg Oncol 2010;102:27–33.
25. El-Naaj IA, Leiser Y, Shveis M, et al.: Incidence of oral cancer occult metastasis and survival of T1-T2N0 oral cancer patients. J Oral Maxillofac Surg 2011;69:2674–2679.
26. Karatzanis AD, Psychogios G, Zenk J, et al.: Evaluation of available surgical management options for early supraglottic cancer. Head Neck 2010;32:1048–1055.
27. Markou K, Goudakos J, Triaridis S, et al.: The role of tumor size and patient's age as prognostic factors in laryngeal cancer. Hippokratia 2011;15:75–80.
28. Sparano A, Weinstein G, Chalian A, et al.: Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 2004;131:472–476.
29. Pentenero M, Gandolfo S, Carrozzo M: Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: A review of the literature. Head Neck 2005;27:1080–1091.
30. Karatzanis AD, Psychogios G, Mantsopoulos K, et al.: Management of advanced carcinoma of the base of tongue. J Surg Oncol 2012; DOI: 10.1002/jso.23135 [Epub ahead of print].
31. Tomifuji M, Imanishi Y, Araki K, et al.: Tumor depth as a predictor of lymph node metastasis of supraglottic and hypopharyngeal cancers. Ann Surg Oncol 2011;18:490–496.
32. Kovacs AF: Head and neck squamous cell carcinoma: Sentinel node or selective neck dissection. Surg Oncol Clin N Am 2007; 16:81–100.
33. Alkureishi LW, Ross GL, Shoaib T, et al.: Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a European multicenter trial. Ann Surg Oncol 2010;17:2459–2464.
34. Schroeder U, Dietlein M, Wittekindt C, et al.: Is there a need for positron emission tomography imaging to stage the N0 neck in T1-T2 squamous cell carcinoma of the oral cavity or oropharynx? Ann Otol Rhinol Laryngol 2008;117:854–863.
35. Keller F, Psychogios G, Linke R, et al.: Carcinoma of unknown primary in the head and neck: Comparison between positron emission tomography (PET) and PET/CT. Head Neck 2011;33: 1569–1575.