



Comparison of Clinical Versus Pathological Staging in Patients with Carcinoma of Unknown Primary Treated by Comprehensive Neck Dissection

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Abstract

Introduction: Treatment of Carcinoma of Unknown Primary (CUP) that represent 3-7 % of all head and neck cancer is controversial and dependant on stage. Radiotherapy or chemoradiotherapy as primary modality of treatment followed by neck dissection for the patient's persistent disease is employed. However, a combined modality approach, with surgery followed by postoperative (chemo) radiotherapy depending on the pathology findings is also widely recommended.

The aim of the paper in CUP patients who underwent neck dissection is to compare the preoperative clinical staging and postoperative histological staging and determine the extent of neck dissection without compromising the oncological outcome

Methods: A cohort of patients with clinically T0N+ of the neck managed surgically was reviewed. Demographical and tumour factors were recorded for all the patients. Preoperative clinical staging, details of adjuvant therapy and histological features were recorded. Outcomes data on recurrence and details of mode of death were extracted from hospital records.

Results: A total of 23 patients were identified of whom 3 (13 %) were female. The median age was 66 years (range 37- 83 years). The clinical N stage was cN1 in 8 patients, cN2 in 9 patients and cN3 in 6 patients. 8 patients were postoperatively treated by surgery and radiotherapy, and 15 patients had post-operative chemoradiotherapy. Radiotherapy fields included all levels of the ipsilateral neck and mucosal surfaces. The median time for surgery to completion of radiotherapy was 89 days (range 46-113 days). All the patients had comprehensive neck dissection (including levels I-V). Following histopathological analysis of surgical specimens, the pN stage was N1 in 5 cases, N2 in 12 and N3 for the remaining 6 patients. 9/23 (39 %) patients had evidence of extracapsular extension on histological analysis.

The mean follow-up was 49 months (range 2- 72 months). There were 10 deaths. No patient developed evidence of local recurrence within the upper aerodigestive tract during follow-up. Three patients developed regional recurrence, two of which were ipsilateral, all of them ultimately died of disease. Three patients developed metastatic disease. Four patients died from primary lung cancer.

The 5 year overall survival, and regional recurrence free survival were 56,5 and 86 % respectively. From a total of 666 excised nodes, 211 (32 %) were found to contain metastatic SCC. Nodes from multiples levels were found to be involved in 16 cases (70 %). In the remaining 7 cases (30 %), involvement was limited to a single level. Of the 23 patients who had all levels of the neck treated surgically, level I was clinically involved in three cases (13 %), level II in 16 (69,5 %), level III in 9 (39 %), level IV in 6 (26 %) and level V in one case (4 %).

Postoperative histopathological assessment identified disease in level I in three cases (13 %), level II in 20 cases (87 %), level III in 11 (49 %), level IV in 7 (30 %) and level V in 6 cases (26 %). Comparison of clinical versus pathological staging in the patients with comprehensive neck dissection revealed that 22 % of nodal basins preoperatively considered free of disease were later shown to harbor microscopic pathological evidence of occult metastasis.

Conclusions: Our results suggest that in patients with carcinoma of unknown primary, the probability of occult disease may be high enough to consider level V when performing neck dissection.

Keywords: Unknown Primary; Head and Neck Cancer; Pathological Staging; Neck Dissection

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Introduction

Carcinoma of unknown primary of the neck (CUP) accounts for 3-7 % of all head and neck cancers. Treatment of CUP is controversial and dependant on stage. Radiotherapy or chemoradiotherapy as primary modality of treatment followed by staged neck dissection for those with clinical or radiological evidence of persistent disease is widely employed. However, a combined modality approach, with surgery followed by postoperative (chemo) radiotherapy depending on the pathology findings is also widely recommended.

The aim of the paper is to compare the preoperative clinical staging and postoperative histological staging in patients who underwent surgical management of CUP in order to determine the extent of neck dissection and minimize, without compromising the oncological outcome, the post treatment morbidity.

Methods

All the patients with clinically T0N+ of the neck were investigated. Patient factors collected include age at procedure and gender. Tumour factors including TNM stage and level specific details on clinical examination were recorded for all the patients. Details of adjuvant therapy were recorded. Histological features such as pTNM stage (including level specific data), degree of differentiation and the presence of extracapsular spread were collected from histopathological examination reports of the surgical specimens.

All the patients in this cohort were systematically irradiated or received chemoradiotherapy depending on the pathology findings. Outcomes data on local, regional and distant recurrence were reported. Details of mode of death were extracted from hospital records.

Results

A total of 23 patients were identified of whom 3 (13 %) were female. The median age was 66 years (range 37- 83 years). The cN stage was cN1 in 8patients, cN2 in 9patients and cN3 in 6 patients (Table 1). 8 patients had combined surgery and radiotherapy, and 15 patients had post-operative chemoradiotherapy. Radiotherapy fields included all levels of the ipsilateral neck and mucosal surfaces. The median time for surgery to completion of radiotherapy was 89 days (range 46-113 days). All the patients had comprehensive neck dissection (including levels I-V). Following histopathological analysis of surgical specimens, the pN stage was N1 in 5 cases, N2 in 12 and N3 for the remaining 6 patients. 9 patients had evidence of extracapsular extension on histological analysis.

The mean follow-up was 49 months (range 2- 72 months). There were 10 deaths. No patient developed evidence of local recurrence within the upper aerodigestive tract during follow-up. Three patients developed regional recurrence, two of which were ipsilateral, all of them ultimately died of disease. Three patients developed metastatic disease. Four patients died from primary lung cancer.

The 5 year overall survival and regional recurrence free survival were 56.5 % and 86 % respectively. From a total of 666 excised nodes, 211 (32 %) were found to contain metastatic SCC. Nodes from multiples levels were found to be involved in 16 cases (70 %). In the remaining 7 cases, involvement was limited to a single level. Of the 23 patients who had all levels of the neck treated surgically, level I was clinically involved in three cases (13 %), levelIII in 16 cases (69,5 %), level III in 9 (39 %), level IV in 6 cases(26 %) and level V in one case

Table 1: Demographics, staging, treatments and outcomes of treated patients.

| Variable | N= number of patients (%) |
|--------------------------------|---------------------------|
| Gender | |
| Male | 20 (87) |
| Female | 3 (13) |
| cN stage | |
| cN1 | 8 (35) |
| cN2 | 9 (39) |
| cN3 | 6 (26) |
| pN stage | |
| pN1 | 5 (22) |
| pN2 | 12 (52) |
| pN3 | 6 (26) |
| Differentiation | |
| Well | 4 (17) |
| Moderately | 2 (9) |
| Poorly | 17 (74) |
| Extracapsular extension | |
| No | 14 (61) |
| Yes | 9 (39) |
| Adjuvant therapy | |
| RT | 8 (35) |
| CRT | 15 (65) |
| Recurrence | |
| Local | 0 (0) |
| Regional | 3 (13) |
| Distant | 3 (13) |
| Survival | |
| Death second primary | 4 (17) |
| Cause specific death | 6 (26) |

Table 2: Rate of occult disease (from the comprehensive neck dissections).

| Neck levels | Clinically uninvolved | Pathologically involved | Rate of occult disease (%) |
|-------------|-----------------------|-------------------------|----------------------------|
| I | 20 | 0 | 0 |
| II | 7 | 4 | 57 |
| III | 13 | 2 | 15 |
| IV | 17 | 1 | 6 |
| V | 22 | 5 | 22 |
| Overall | | | 20 |

(4 %).Postoperative histopathological assessment identified disease in level I in three cases (13 %), level II in 20 cases (87 %), level III in 11 cases (49 %), level IV in 7(30 %) and level V in 6 cases (26 %). Comparison of clinical versus pathological staging in the patients with comprehensive neck dissection revealed that 22 % of nodal basins preoperatively considered free of disease were late shown to harbor microscopic pathological evidence of occult metastasis (Table 2).

Discussion

The management of CUP in the head and neck remains controversial. In our study a combined modality approach, with

surgery followed by postoperative (chemo) radiotherapy depending on the pathology was adopted as therapeutic option. We identified 23 patients of whom 3 (13 %) were female. The median age was 66 years (range 37- 83 years). In their study, Dragan et al (1) identified 25 consecutive CUP patients over an 11-year period. The median age was 55 years (range 42-87 years). The demographic description of their cohort was similar to that reported by other authors (2;3;4). In our series, we identified a rate of 73 % of poorly differentiated disease (68 % in Dragan's series). In contrast, Wallace et al [2] identified poorly differentiated squamous cell carcinoma in 85 of the 179 reported patients with squamous cell carcinoma from unknown head and neck primary site (47 %). Moreover, we found a rate of extracapsular spread of 39 %. Colletie et al [5] studied one hundred thirty six patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary source. They reported a 65 % rate of extracapsular extension (a 56 % rate is reported by Drangan et al [1]. In contrast, Chen et al [4] reported a 35 % rate of extracapsular spread. In our study, the cN stage was cN1 in 8 patients (35 %), cN2 in 9 patients and cN3 in 6 patients. Our rate of N1 disease was higher in comparison to other groups (26 % in Aslani's study (6), 8 % in Dragan's study and 7 % in the study reported by Patel [8] but inferior to the rate of 41 % reported in Miller's study [7]. In our study, 8 patients had combined surgery and radiotherapy, and 15 patients had post-operative chemoradiotherapy, all of these patients presented with bulky N2b or N3 disease.

Previous studies have shown poor rates of disease control of T0N3 neck. Miller et al in 2007 described four cases of N3 CUP, out of which one developed a regional recurrence in the neck at 9 months, another one developed lung metastasis and a third patient developed a second primary in the lung, only one being free of disease at 22 months. In our study, we reported six cases of N3 carcinoma of unknown primary. 5 patients died of disease after a mean follow-up of 49 months. At the end of the follow-up, no patients developed mucosal disease in our series. In their series, Dragan and all reported that, after a median follow-up of 32 months, no patients developed mucosal disease. Moreover, they reported a 5 year regional recurrence free survival of 100 % in pN1, 79 % in pN2 and 75 % in pN3 ($p=0.759$). In addition, no patients who underwent selective neck dissection developed recurrent disease in the undissected levels of the neck.

In order to determine which type of neck dissection is more appropriate to treat patients with CUP, we recorded both the preoperative clinical staging and postoperative histological staging to analyse the patterns of occult metastasis of our cohort. The most frequently involved level of the neck was level II (in 87 %) on histological examination of the specimens excised through comprehensive neck dissection. In their study, Dragan and all found that the most frequently involved level of the neck was II with a rate of 84 %. Overall, postoperative histopathological assessment identified disease in level I in 3 cases, level II in 20 cases, level III in 11 cases, level IV in 7 and more surprisingly level V in 6 cases (26 %).

We calculated the rates of occult disease on a level by level basis. We found a rate of occult disease of 57 % in level II, 15 % in level III, 6 % in level IV but a high rate of 22 % in level V. No occult metastasis was diagnosed in level I (0 %).

In their series, Dragan and all found the same rate of occult metastasis (0 %) in level I. They found a rate of occult disease of 40 % in level II, 6 % in level III but only a rate of 6 % in level V.

Naiboglu and all (8) found that, because level V was not involved in any patient when the other levels were not involved, it might be reasonable to preserve level V especially in clinically and intraoperatively N0 patients.

Lim and all [9] performed a retrospective analysis of 93 head and neck patients who underwent surgical treatment of the primary lesion along with a simultaneous comprehensive neck dissection. Of these, only one patient had a clinically positive neck node at level V but the majority of patients had an oral and oropharyngeal squamous cell carcinoma. The prevalence of metastases in the level V lymph nodes was 5 % (5/93). Occult metastasis rate of ipsilateral level V was 4 % (4/92). In their studies, there was a statistically significant association between level V metastases and a positive N stage above N2b ($p=0.01$). They recommend that level V lymph node pads may be preserved in modified neck dissections on OOSCC patients with clinically N+ neck below the nodal stage N2a.

However, our results, after comparison between clinical and anatomopathological staging in patients with CUP suggest that the probability of occult disease may be high enough to consider level V when performing neck dissection.

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