

Original article

Squamous cell carcinoma metastatic to cervical lymph nodes from unknown primary origin: the impact of chemoradiotherapy

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Abstract

The management of cervical lymph node metastases of squamous cell carcinoma from an unknown primary site is still a therapeutic challenge. We report here our experience in treating these patients with chemoradiotherapy as a curative approach. Data from 40 patients were reviewed. In total, 20 (50%) patients underwent excisional biopsy. All patients underwent radiotherapy, which was delivered to both sides of the neck and pharyngeal mucosa (extensive field), and concurrent chemotherapy consisting of weekly cisplatin at a dose of 40 mg/m². The clinical stage of the cervical nodes at presentation was N1 in 25%, N2 in 60%, and N3 in 15%. Most patients (75%) developed at least grade 3 mucositis. Eight patients (20%) had grade 3 xerostomia and 18 patients (45%) required esophageal dilation for stricture. The 5-year overall survival (OS) rate of all patients was 67.5%. The 5-year OS rates of patients with N1, N2, and N3 lesions were 100%, 67%, and 41%, respectively ($P = 0.046$). The 5-year progression-free survival rate was 62.5%. In multivariate analysis, only N stage significantly affected OS ($P = 0.022$). Emergence of the occult primary was very limited (1 patient only). Our results suggest that extensive irradiation of both sides of the neck and pharyngeal mucosa with concurrent chemotherapy results in a lower emergence of primary tumor. Because the survival of patients with unknown primary is comparable to that of patients with known primary, an attempt at cure should always be made.

Key words Squamous cell carcinoma, cervical lymph node metastases, unknown primary origin, chemoradiotherapy

Cervical lymph node metastases from unknown primary origin constitute about 5% (range, 2%–9%) of all head and neck cancers [1]. Squamous cell carcinoma (SCC) is the most common histotype, followed by adenocarcinoma, undifferentiated carcinoma, and other types [2]. Metastases of SCC from unknown primary origin to cervical lymph nodes represent 2% to 7% of head and neck cancers [3]. The management of these metastases remains a major challenge in oncology. Multiple therapeutic approaches have been used in this scenario, including neck dissection followed by adjuvant radiotherapy or chemoradiotherapy and radiotherapy-based management alone [4]. The radiation fields have classically covered all potential mucosal disease sites [5]. Although phase III trials have demonstrated the

superiority of concurrent chemoradiotherapy in both the definitive and the postoperative setting for selected patients with head and neck cancer, it must be recognized that patients with head and neck cancer of unknown primary origin were specifically excluded from these studies [6,7]. As a result, the value of adding concurrent chemotherapy is uncertain for this subset of patients, and there are no randomized prospective studies to support this approach.

Here, we report a retrospective study of managing patients with SCC metastatic to cervical lymph nodes from unknown primary origin. To obtain more information on the optimal treatment of these patients and especially on the impact of chemoradiotherapy, we reviewed the clinical data of 40 patients and analyzed their prognosis.

Materials and Methods

Patients

The records of 40 patients with histologically proven SCC metastatic to cervical lymph nodes from unknown

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primary origin were reviewed. Patients were treated at Northamptonshire Cancer Center and Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital. Data were collected from 2000 to 2010.

Diagnostic workup

A patient was classified as having SCC metastatic to cervical lymph nodes from unknown primary origin if diagnostic workup confirmed metastatic cervical SCC and failed to identify a primary head and neck cancer site. In general, patients had cervical SCC proven by fine-needle aspirate or excision biopsy. A search for a head and neck primary site included physical examination, fiberoptic nasopharyngoscopy, computed tomography and/or magnetic resonance imaging from the skull base to clavicles, a meticulous examination under anaesthesia with panendoscopy (direct laryngoscopy, oesophagoscopy, nasopharyngoscopy, and bronchoscopy), and targeted biopsies of the most likely primary sites. Other sites were biopsied only if the mucosa was macroscopically abnormal. If these investigations failed to reveal the primary tumor, cervical node metastases from unknown primary origin was diagnosed. Chest computed tomography and bone scan were used to identify distant metastasis.

Treatment schedule

Surgery Thirty patients (75%) underwent surgery consisting of neck dissection (10 patients) and excisional biopsies (20 patients) as the initial treatment. The median number of removed lymph nodes was 10 (range, 1–22). Among the patients who underwent surgery, pathologic N categories were as follows: N1, 25%; N2, 60%; and N3, 15%. Twelve patients (30%) had extracapsular nodal extension. Three (7.5%) had microscopically positive margins documented on pathologic examination.

Radiotherapy All patients received continuous-course, external-beam, conventional fractionation radiotherapy delivered daily. At simulation, the head, neck, and shoulders were immobilized in a hyperextended position using a perforated thermoplastic head mask with the neck supported. The target volumes covered the bilateral nodal regions and mucosal axis, including the nasopharynx, oropharynx, larynx, and hypopharynx. A shrinking field technique was used with initial opposed lateral fields to treat the primary involved cervical lymph nodes. In general, the anterior border included the posterior third of the nasal cavities and the anterior tonsillar pillars; the posterior border was placed behind the spinous process; the superior border was placed at the midsphenoid sinus or bottom of the pituitary fossa to

encompass the nasopharynx and skull base; and the inferior border was placed just above the shoulders. Any surgical scar was wired to ensure 2 cm of coverage in all directions. The lower cervical nodes were treated with a matched low anterior cervical field using an isocentric technique to eliminate divergence into treatment fields. The spinal cord was limited to 45–50 Gy. Electrons were used to boost areas overlying or posterior to the spinal cord after field reductions. The total doses of radiation ranged from 60 to 66 Gy (median, 60 Gy) to the involved tumor bed, 54 to 60 Gy (median, 56 Gy) to the pharyngeal axis, and 50 to 54 Gy (median, 50 Gy) to prophylactically treated nodal areas. Irradiation was delivered by a linear accelerator (6 MV X-rays) or cobalt. In some cases, additional boost beams were delivered by electrons (8–10 MeV).

Chemotherapy Concurrent chemotherapy consisted of cisplatin, which was typically administered weekly with a dose of 40 mg/m² for a median of 4 cycles (range, 3–6 cycles). No additional or maintenance chemotherapy was administered after patients completed radiotherapy.

Evaluation of toxicity

Acute and late normal tissue effects were graded according to the radiation toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for the Treatment of Cancer^[8]. Acute toxicity was defined as that occurring within 90 days of treatment completion. A complication that occurred during treatment that persisted after 90 days was also considered late toxicity.

Follow-up

Patients were asked to return for follow-up visits 4–6 weeks after the completion of radiotherapy and then every 2 months for the first year, every 4 months for the second year, and less frequently in subsequent years. Regional failure was recorded if there was evidence of a cervical or supraclavicular mass. Patients who had persistent or recurrent nodal disease were referred for salvage neck dissection. Failure was counted only if the patient had pathologic evidence of residual disease. Salvage of recurrences was not taken into account in the evaluation of locoregional control.

Statistical analysis

Overall survival (OS) and progression-free survival (PFS) were calculated according to the Kaplan-Meier method. OS was defined as the time from the date of initial diagnosis to last follow-up or death from any cause. PFS was defined as time to progression or death

from any cause. The events that contributed to the endpoint of PFS included locoregional recurrence/progression and distant metastasis, and all events were measured from the last day of radiotherapy. Multivariate analysis was performed using the Cox proportional hazards model. *P* value was considered significant if less than 0.05. Statistical analysis was performed using a commercially available software package (SPSS for Windows 15; SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

The patient characteristics are listed in Table 1. The median age at first diagnosis was 55 years (range, 24–77 years). Of the 40 patients, 29 were men and 11 were women. The Eastern Cooperative Oncology Group performance status at presentation was 0 in 28 patients and 1 in 12 patients. Ten patients were never smokers. All patients had SCC, 24 with poor differentiation and 11

with moderate differentiation. Of the 40 patients, 24 had N2 lesions and 10 had N1 lesions. The most inferior, grossly involved nodal station was level II in 24 patients, level III in 14 patients, and level IV in 9 patients.

Treatment characteristics

Before radiotherapy, 10 patients underwent neck dissection and 20 underwent excisional biopsy as the initial treatment. All patients underwent continuous-course external-beam radiotherapy. The total doses of radiation to the involved tumor bed ranged from 54 to 66 Gy (median, 60 Gy). Doses to the pharyngeal axis ranged from 54 to 60 Gy (median, 56 Gy). Doses to prophylactically treated nodal areas ranged from 50 to 54 Gy (median, 50 Gy). All patients underwent concurrent chemotherapy consisting of weekly cisplatin at a dose of 40 mg/m². Six patients underwent post-chemoradiotherapy neck dissection, 5 of whom showed residual disease; at the end of follow-up, 4 patients died and 1 was still alive. One of the 6 patients underwent dissection due to suspicion of residual cancer on

Table 1. Baseline characteristics of 40 patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site

Characteristic	No. of patients (%)
Gender	
Male	29 (72.5)
Female	11 (27.5)
ECOG performance status	
0	28 (70.0)
1	12 (30.0)
Smoking history	
Non-smoker	10 (25.0)
Smoker	30 (75.0)
Tumor differentiation	
Well	5 (12.5)
Moderate	11 (27.5)
Poor	24 (60.0)
Level of nodal involvement	
I	4 (10.0)
II	24 (60.0)
III	14 (35.0)
IV	9 (22.5)
V	2 (5.0)
Classification of neck disease ^a	
N1	10 (25.0)
N2	24 (60.0)
N3	6 (15.0)

^a According to UICC/AJCC staging system.

post-treatment imaging, but postoperative pathologic examination showed negative results.

Acute and late toxicities of treatment

The acute locoregional toxicities of treatment are listed in Table 2. Most patients (75%) developed at least grade 3 mucositis, whereas only 11 patients (27.5%) experienced grade 3 or 4 dermatitis. Thirty patients had grade 3 esophagitis. Of the 40 patients, 36 underwent prophylactic gastrostomy tube placement before treatment. The late toxicities are listed in Table 2. Of the 36 patients who had a gastrostomy tube placed, 34 had it removed at a median of 6 months after treatment completion. Eighteen patients developed esophageal stenosis requiring dilation, and 3 developed a stenosis not requiring dilation. Twenty patients developed grade 2 and 8 developed grade 3 xerostomia. Only 1 patient had grade 1 trismus and another had grade 2 fibrosis.

Clinical prognosis for all patients

The median follow-up for the whole series was 60

months (20–120 months). Thirteen patients died of local and/or distant failure or emergence of the primary cancer, and 1 died of another disease (Table 3). The 5-year OS rate was 67.5% for all patients (Figure 1A), and was 100%, 67%, and 41% for patients with N1, N2, and N3 lesions, respectively ($P = 0.046$). The 5-year PFS rate was 62.5% (Figure 1B). Of 15 patients who had progression, 2 were alive: 1 had local failure and underwent neck dissection, and 1 had distant bone metastasis and underwent palliative radiotherapy. In the Cox proportional hazard model, gender, age, N stage, and initial surgery were included. The results showed that only N stage was independent predictor for OS ($P = 0.022$) (Table 4).

Discussion

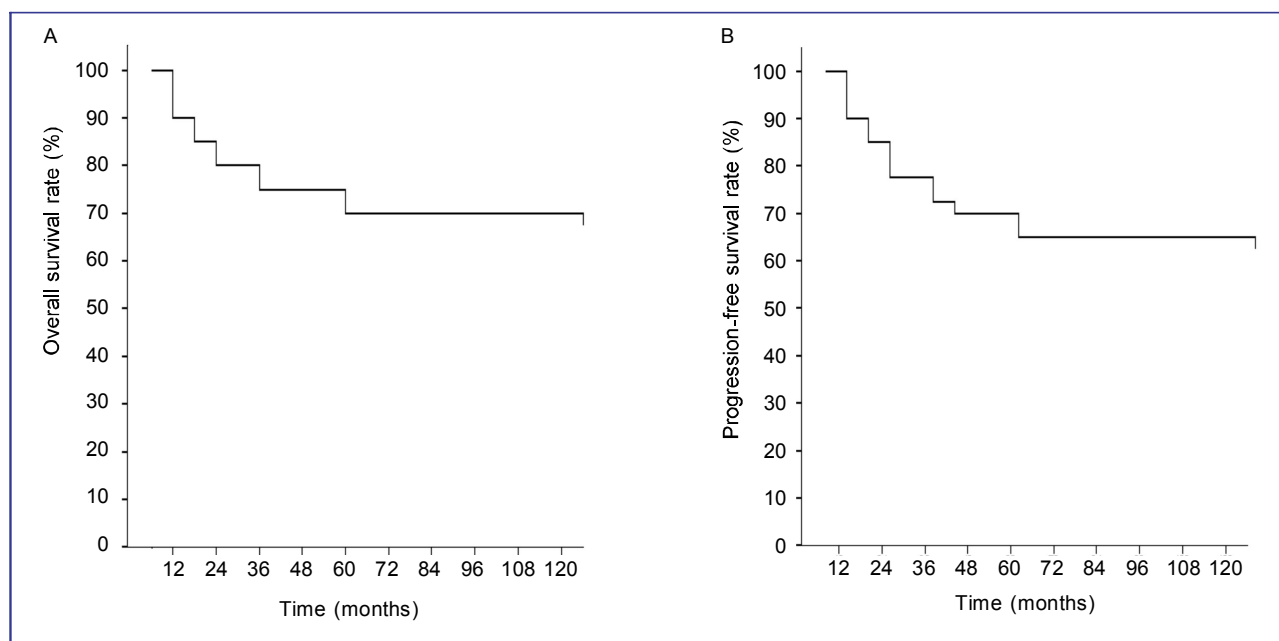
The management of patients with cervical lymph node metastases of SCC from unknown primary origin is still a therapeutic challenge. In this trial of extensive radiation to the bilateral neck and pharyngeal mucosa

Table 2. Acute and late toxicities of patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site treated with weekly cisplatin concurrent with radiation

Toxicity	No. of patients (%)
Mucositis	
Grade 2	10 (25.0)
Grade 3	28 (70.0)
Grade 4	2 (5.0)
Dermatitis	
Grade 2	29 (72.5)
Grade 3	10 (25.0)
Grade 4	1 (2.5)
Esophagitis	
Grade 2	10 (25.0)
Grade 3	30 (75.0)
Grade 4	0
Esophageal stenosis	
Grade 2	3 (7.5)
Grade 3	18 (45.0)
Grade 4	0
Trismus	
Grade 1	1 (2.5)
Grade 2	0
Grade 3	0
Xerostomia	
Grade 1	12 (30.0)
Grade 2	20 (50.0)
Grade 3	8 (20.0)
Fibrosis	
Grade 1	3 (7.5)
Grade 2	1 (2.5)

Table 3. Causes of death in 13 patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site treated with weekly cisplatin concurrent with radiation

Cause of death	No. of patients (%)
Distant metastases	7 (53.8)
Bone	3 (23.1)
Lung	3 (23.1)
Liver	1 (7.7)
Cervical lymph node metastases	4 (30.8)
Primary tumor	1 (7.7)
Pneumonia	1 (7.7)
Total	13 (100)

**Figure 1.** Kaplan-Meier survival curves of 40 patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site treated with weekly cisplatin concurrent with radiation. A, overall survival curve; B, progression-free survival curve.**Table 4.** Multivariate Cox regression analysis of survival for 40 patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site treated with weekly cisplatin concurrent with radiation

Variate	Partial regression coefficient	Wald χ^2	P value	Hazard ratio	95% Confidence Interval
Sex (male)	-0.37	1.77	0.232	0.69	0.41-1.18
Age (>55 years)	0.54	3.01	0.084	1.72	1.20-3.77
N category (N2, N3)	0.64	5.65	0.022	1.89	1.12-3.19
Initial surgery (biopsy)	-0.40	3.54	0.067	0.67	0.44-1.01

with concurrent chemo therapy, we made several observations about these patients.

N2 was the commonest nodal stage followed by N1 and N3, and Grade III mucositis was the commonest side effect followed by xerostomia. The 5-year OS rate of all patients was 67.5%, and the 5-year PFS rate was 62.5%. In multivariate analysis, only N category significantly affected OS ($P = 0.022$).

Cervical node metastases from unknown primary origin are diagnosed after thorough assessment fails to reveal the presence of tumor in the upper aerodigestive tract. Although recent developments in imaging and pathology have increased our diagnostic spectrum, the diagnosis and workup of cervical node metastases from unknown primary origin remains a challenge. The quality of diagnosis over the years has simply reflected the emerging technologies available to the clinician, including computed tomography (CT), magnetic resonance imaging (MRI), and fiberoptic imaging [9]. Hence, we believe that imaging of the neck, if performed, should be to define the extent of nodal disease and its resectability rather than search for a primary. However, Sinnathamby *et al.* [10] have recommended routine imaging to avoid missing an occult primary and unnecessary radiation to mucosal areas.

Recently, using functional imaging modalities, such as positron-emission tomography (PET), to detect primary tumor has become a very attractive option. PET can detect primary tumors in 5%–43% of patients with negative results from routine clinical examination, CT, and MRI [2,11,12]. Miller *et al.* [9] found that PET was able to detect occult primary tumors in 9 (29%) of 31 patients in whom a comprehensive head and neck examination (including flexible endoscopy) and CT and/or MRI failed to identify primary tumors. However, occult primary tumors were detected by panendoscopy in 5 (16%) of 31 patients despite negative PET results. The results showed that the true value of PET imaging was in the small subset of patients who had a careful head and neck examination by an experienced surgeon and negative results from imaging studies, including CT and/or MRI [9]. In this select situation, PET may guide the surgeon at panendoscopy and/or biopsy. No patient in our study underwent PET scan, and we cannot give more data on the value of PET imaging in cervical node metastases from unknown primary origin.

The management of cervical metastases from unknown primary origin evokes considerable controversy and has not been standardized. Nieder *et al.* [13] suggested surgery alone for selected patients with N1 lesions without extracapsular extension and without history of incisional or excisional biopsy. This was based on their finding of a 25% detection rate of primary tumors. In our study, the detection rate of primary on

subsequent follow-up was very limited (1 patient only). This may be due to extensive radiotherapy, covering both sides of the neck and nasopharyngeal, oropharyngeal, and hypopharyngeal mucosa, with concurrent chemotherapy. Other studies showed that ipsilateral neck radiotherapy was correlated with the detection rate of primary tumors, with the latter similar to that observed after extensive radiotherapy [14,15]. Although ipsilateral radiotherapy was associated with a high risk of neck relapse and/or a high detection rate of primary tumors in some series, OS was not affected [16]. Nevertheless, considering the lack of comparative studies, the optimal radiotherapy strategy remains to be delineated.

Similarly, the role of chemotherapy in the management of cervical metastases from unknown primary origin is also indistinct. In fact, in the review by Nieder *et al.* [13], substantial data supporting the use of chemotherapy was deficient.

In the present study, we found that the 5-year OS rate of all patients was 67.5% and 5-year PFS rate was 62.5%. The treatment outcome was comparable with those observed in most reports [14,16,17]. For comparable N category, patients with occult primary have a better prognosis than patients with known primary. Similar results were confirmed by Mistry *et al.* [18]. This observation should be interpreted with caution, as the comparison is with historical data. Jones *et al.* [19] did not find any difference in the survival between the two groups in a similar comparison. The most frequent site of relapse in our study was distant metastases followed by cervical nodes and primary site. Our study also confirmed N category as the most important prognostic factor for OS. Some studies also reported the same finding [17,18,20].

Our study is potentially limited by several factors. One is the relatively small number of patients. Another factor is that it is a retrospective study. However, all patients had similar histology, and treatment was uniform in all patients. Based on this, it appears that routine blind biopsies from the upper aerodigestive tract may not be necessary. N category at presentation affects the outcome of these patients.

In conclusion, the optimal diagnostic and therapeutic approach of cervical lymph node metastases of SCC from an unknown primary site still eludes us. Extensive radiation to both sides of the neck and pharyngeal mucosa with concurrent chemotherapy results in a lower detection rate of primary tumor. The survival of patients with unknown primary is comparable to that of patients with known primary.

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