Combined ipsilateral treatment of cervical lymph nodes metastases from an unknown primary


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Introduction

Cervical lymph node metastases of squamous cell carcinoma from an occult primary are found in about 2-5.5% of all patients with carcinoma with an unknown primary site.1 Recent improvements in imaging procedures have reduced this incidence.2 However, the management of cervical lymph nodes metastases of squamous cell carcinoma from an unknown primary remains a therapeutic challenge. Since head and neck squamous carcinomas are characterised by mainly loco-regional progression and a relatively low risk of distant metastases, the priority is given to loco-regional control. Local modalities, including surgery and radiotherapy, therefore remain the cornerstones of treatment. The optimal treatment of head and neck carcinoma of unknown primary (CUP) has not yet been defined. Randomised studies are lacking. Published retrospective series include heterogeneous patient populations (with different histotypes) managed with various diagnostic and therapeutic procedures.1 We undertook a retrospective study of patients managed with the same diagnostic and therapeutic procedures for the same histotype of head and neck cancer.

Material and methods

Fourteen patients who had undergone a neck dissection followed by postoperative chemo-irradiation were included in this retrospective study. The median dose to the involved node(s) was 64 Gy, and 60 Gy to the rest of the neck. No mucosal irradiation was performed. The concomitant chemotherapy consisted of platinum-based (either cis- or carboplatinum) chemotherapy. The diagnostic work-up typically consisted of clinical examination and endoscopy of the aerodigestive tract, chest X-ray, and haematology and routine chemistry. Patients were staged according to the 1987 UICC classification. The distribution of involved lymph nodes was reviewed.

Results

A total of 14 patients with cervical lymph node metastases from an
unknown primary were identified. Their median age was 56 years. There were 9 men and 5 women. Metastatic cervical lymph nodes were most frequently localised at level II (8 cases) and level V (4 cases), followed by level I (2 cases). Squamous cell carcinoma was the only histopathological finding.

Treatment for cervical CUP was performed in all patients (Table 1). All patients underwent surgery, 10 patients underwent additional radiotherapy, 2 patients had concomitant chemoradiotherapy, one patient refused postoperative radiotherapy and one patient died before additional treatment. A unilateral modified neck dissection was performed in 12 cases and two patients had a radical neck dissection.

During follow-up, 3 patients developed recurrent metastasis in cervical lymph nodes after initial treatment, ipsilaterally in two cases and in the contralateral area of the cervical neck in one case.

The patient with the contralateral cervical recurrence was treated by surgery followed by radiotherapy. The first patient with an ipsilateral cervical recurrence was treated by surgery and chemotherapy. The second patient with an ipsilateral cervical recurrence associated with distant pulmonary metastases was treated with chemotherapy, but without success. A second patient presented a pulmonary generalisation without loco-regional recurrence at follow-up.

After a median follow-up of 46 months, 4/14 patients died: 2 patients with cervical recurrence (and pulmonary generalisation in one case); the last patient with cervical (contralateral) recurrence was successfully salvaged. The two other patients died from septic shock. One of these two patients presented distant pulmonary metastases without loco-regional recurrence 6 months after initial presentation. All the patients who died were N2 (3 cases) or N3 (one case). All the patients with a homolateral cervical recurrence or distant metastases died.

**Discussion**

The management of patients with an unknown primary tumour of the head and neck region and cervical adenopathy has become increasingly controversial.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Gender</th>
<th>Involved levels</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Chemoradiotherapy</th>
<th>Recurrence site</th>
<th>Follow-up</th>
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Legends
RND: radical neck dissection
MND: modified neck dissection.
The most frequently involved nodal area is level II, followed by level III. Levels I, IV and V are less frequent. In our series, the most frequently involved nodal area was level II. In our study, level V was more frequently involved than is usual in the literature.

Mean age at diagnosis varied from 55 to 65 years and the younger median age in some series may be explained partially by the inclusion of undifferentiated tumours. In our series, the mean age was 58 years.

As in other head and neck carcinoma populations, the majority of patients are male. In our series, 9/14 patients were male.

The reported median interval between the first symptoms and diagnosis and/or referral to the oncologic clinic was in the range of 3 months. The median time between the first recognition of the lymph node and the first medical consultation was 34.8 weeks.

Unilateral lymph node involvement is more common; bilateral adenopathy is present in about 10% of patients. In our series, all patients had unilateral cervical node involvement.

In large series, the median nodal size was 5 cm (range 2-14 cm) and there is an apparent prevalence of N2 cases. In our series, there was a prevalence of N2 cases (12/14 patients).

Various therapeutic approaches are being employed for CUP. Therapeutic approaches include radiotherapy alone, radiotherapy followed by surgery and surgery with or without postoperative radiotherapy. Some authors recommend the irradiation of the pharyngeal mucosa extending from the naso-pharynx to the upper oesophagus, whereas others think the resulting side-effects are too severe by comparison with the expected benefit. Grau et al. confirmed that patients with neck metastases from occult head and neck cancer treated with extensive irradiation to both sides of the neck and the mucosa in the entire pharyngeal axis and larynx have significantly fewer loco-regional failures compared with patients treated with ipsilateral techniques, but only a trend towards better survival. In a series of 136 patients treated at the MD Anderson Hospital, both sides of the neck and potential head and neck mucosal primary sites were irradiated. Recurrent disease in the neck developed in 12 patients (9%). The 5-year, cause-specific, survival rate was 74%. Reddy and Marks reported 52 patients treated for the neck alone and 36 patients in whom treatment focused on the neck and potential head and neck primary sites. Failure in the head and neck mucosa occurred in 44% of those who underwent treatment of the neck alone, compared with 8% in those who underwent irradiation of the head and neck mucosa (p = 0.0005). The 5-year survival rates were similar for the two treatment groups. However, Iganej et al. reported poor survival in patients treated by radiotherapy alone with advanced neck disease.

By contrast, Coster et al. found no survival benefit if irradiation of the mucosa was included.

However, treatment of the neck also depends on the extent of lymph node involvement. Patients with N1 and N2B neck disease located in the high-dose fields may be treated with irradiation alone if the nodes have resolved completely. Similarly, if the patient has undergone an excisional biopsy of a single positive node, the neck may be treated with radiation alone with a 95% likelihood of neck control. Patients with more advanced neck disease after an open neck biopsy undergo a planned neck dissection after radiation therapy. Patients who have a solitary positive neck node may be treated with a neck dissection alone if there has been no open biopsy before the procedure, and if there is no extracapsular extension. However, radiation therapy should be added if there are multiple positive nodes and/or extracapsular extension to reduce the likelihood of recurrent cancer in the neck.

Kirschner et al. reported that patients who were treated surgically according to the N status of the neck and who underwent postoperative radiation experienced complete remissions in 95% of cases. Local control was 76% after 5 years and the tumour-specific survival rate was 67%. In our series, local control was achieved in 12/14 patients treated with the same management protocol. Friesland et al. indicated that limited ipsilateral radiotherapy to mucosa and lymph nodes combined with surgery results in a 5-year survival rate of 41%. A further argument in favour of surgical treatment for the cervical lymph node might be the significantly increased local control on the ipsilateral neck side, independent of the type of radiation therapy.

Another issue meriting discussion is the question of the extent to which the type of neck dissection influences the survival rate of patients with a cervical CUP syndrome. Lefebvre et al. observed a higher rate of local recurrence after modified radical neck dissec-
Survival rate for lower cervical lymph node metastases is 9 +/- 6% with an overall survival rate of only 9.2 +/- 9%. This is mainly due to the high rate of distant metastases – 67% compared to 12% – if the lymph node metastases are located in the upper cervical region. Boscolo-Rizzo et al. also demonstrated that the survival rate for patients with metastatic nodes in the supraclavicular region was significantly poorer than for patients with involvement of the upper-middle jugular lymph nodes (p = 0.0003).

Fernandez et al. in their study of CUP syndrome, found no survival benefit for patients with a detected primary tumour.

However, the 34 patients treated by Kirschner et al. with primary tumours detected pretherapeutically showed a tendency towards better survival, with a 5-year survival rate of 21% compared to 10% in patients with undetected primaries.

Finally, Koivunen et al. analysed a series of prognostic factors for the disease. In a multivariate analysis, nodal stage N2C or N3, other metastases found at the time of treatment and age >65 years were significantly associated with a poor prognosis. In his series, median survival tended to be longer for patients treated with surgery combined with radiotherapy (39.9 months) compared with those treated with radiotherapy alone (16.8 months), but the difference was not statistically significant. Furthermore, Colletier et al. found that multiple nodes and extracapsular extension (p = 0.004) are prognostic factors, and that they are associated with worse regional control and disease-specific survival.

Conclusion
Modified radical neck dissection combined with postoperative radiation with or without chemotherapy is warranted in N1-N3 unknown head and neck primary site patients.

Careful follow-up is required for effective salvage treatment. Despite generally advanced disease at presentation, a reasonable survival rate is expected.

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