CARCINOMA METASTATIC TO CERVICAL LYMPH NODES FROM AN OCCULT PRIMARY TUMOR: THE OUTCOME AFTER COMBINED-MODALITY THERAPY

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Head and Neck

Carcinoma Metastatic to Cervical Lymph Nodes From an Occult Primary Tumor: The Outcome After Combined-Modality Therapy

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Background: The aim of this retrospective analysis was to analyze the results of treatment of patients with cervical node metastases from carcinoma of occult primary with a policy including neck dissection and postoperative comprehensive radiotherapy.

Methods: Ninety patients were treated with curative intent from 1990 to 2002.

Results: The actuarial rate of neck disease control was 68.8% at 5 years (95% confidence interval [CI], 58.9%–78.7%). On multivariate analysis, the rate of neck disease control was significantly related to lymph nodal metastatic level ($P = .006$). The actuarial rate of developing head and neck primary tumors at 5 years was 8.9% (95% CI, 2.6%–15.2%). The 5-year actuarial rate of distant metastases was 19.1% (95% CI, 9.4%–28.9%). In multivariate analysis, a statistically significant difference in the rate of distant metastasis was obtained when patients were stratified according to the level of nodal involvement ($P = .01$) and the presence of extracapsular extension ($P = .013$). At the time of analysis, 50 of the 90 patients were alive. A total of 32 (35.6%) had died from causes related to their primary disease. Actuarial disease-specific survival at 2 and 5 years was 73.6% (95% CI, 64.3%–82.9%) and 62.8% (95% CI, 51.9%–73.7%), respectively. In multivariate analysis, a statistically significant difference in disease-specific survival was obtained when patients were stratified according to the level of nodal involvement and the presence of extracapsular extension.

Conclusions: Our study seems to support the use of combined-modality therapy in patients with neck metastases from carcinoma of occult primary. However, in the absence of randomized trials, comprehensive irradiation cannot be routinely advised.

Key Words: Occult primary—unknown primary—head and neck cancer—treatment—radiotherapy—neck dissection.

Carcinoma of occult primary (COP) is an intriguing heterogeneous clinical phenomenon that remains a major therapeutic challenge in oncology and accounts for 2% to 5% of cancer patients.[1,2] The three main aspects of this clinical entity are still a matter of controversy: the biology of the unknown primary tumor, the optimal diagnostic algorithm, and the best treatment.

Neck nodes are preferential sites of COP. Cervical lymph node metastases from COP constitute approximately 2% to 9% of all head and neck cancers.[3,4] Histologically, it is most often squamous cell carcinoma (65%–76%), followed by undifferentiated carcinoma (22%) and adenocarcinoma (13%).[5]

The treatment of patients with cervical lymph node metastases from COP is still controversial as a result of the lack of randomized clinical trials comparing

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treatment options. Consequently, the treatment is based on nonrandomized data and institutional policies. Because head and neck squamous cell carcinoma is characterized by its ability to spread mainly locally and regionally, surgery and radiotherapy are also accepted as the hallmarks of treatment in cases of COP, whereas no data seem to support the benefit of chemotherapy.[6] However, the optimal extents of surgery and radiotherapy, as well as combined-modality treatment, have to be cleared.

Since 1990, our policy has been to treat cervical lymph node metastases from COP with neck dissection followed by comprehensive irradiation (bilateral neck plus upper aerodigestive tract irradiation). In this study, we retrospectively evaluated the clinical records of all patients treated for cervical lymph node metastases from COP at the ENT Department, University of Padua, Treviso Regional Hospital, and at the Department of Radiation Oncology, Treviso Regional Hospital, Treviso, Italy, between 1990 and 2002. We analyze and discuss the effect of combined-modality therapy on nodal control, recurrence, and survival.

MATERIALS AND METHODS

Criteria for Inclusion in Study

The criteria for inclusion were (1) cervical lymph node metastasis; (2) no primary site detected by clinical, instrumental, or surgical investigation; and (3) curative treatment intent.

Diagnostics

All patients underwent accurate evaluation of head and neck mucosa with fiberoptic and/or rigid pharyngoscopy and laryngoscopy under general anesthesia; chest radiography; esophagogastroduodenoscopy; bronchoscopy; B-mode ultrasonography of the neck; and computed tomography and/or magnetic resonance imaging of the neck. Blind biopsies from macroscopically normal-appearing mucosa of the upper aerodigestive tract (tonsil, piriform sinus, base of the tongue, and nasopharynx) were routinely performed. Systematic ipsilateral tonsillectomy was performed in 22 patients. If all investigations were still consistent with cervical node metastasis from COP, the search for an occult primary tumor was completed by computed tomographic scans of chest and abdomen, dermatological and urogenital/gynecological examinations, and, in few cases, by ^{18}F-fluorodeoxyglucose positron emission tomography.

Finally, after completion of the diagnostic work-up, the diagnosis of ''real'' cervical lymph node metastasis from COP was confirmed in 114 patients. We report on 90 patients who were treated with combined surgery and postoperative comprehensive radiotherapy.

Patient Characteristics

The 90 patients in the study consisted of 77 men (85.6%) and 13 women (14.4%) ranging in age from 27 to 90 years (median, 62.5 years). The levels of origin of cervical metastasis were as follows: level I, 17 patients (18.9%); level II, 26 patients (28.9%); level III, 24 patients (26.7%); level IV, 17 patients (19.9%); and level V, 6 patients (6.7%).

All cervical metastases were restaged according to the 2002 tumor-node-metastasis system7. The distribution of patients according to N stage was as follows: N1, 12 patients (13.3%); N2a, 19 patients (21.1%); N2b, 21 patients (23.3%); N2c, 7 patients (7.8%); and N3, 31 patients (34.4%).

Macroscopic extracapsular extension (ECE) of node metastasis was evident in 48 patients (46.7%). The distribution of tumors according to histological differentiation was as follows: well differentiated, 7 patients (7.8%); moderately differentiated, 21 patients (23.3%); poorly differentiated, 50 patients (55.6%); and undifferentiated, 12 patients (13.3%).

Treatment

The surgical treatment consisted of radical neck dissection and, in seven cases, in type III modified radical neck dissection. All patients underwent comprehensive neck dissection (levels I to V) that was bilateral in seven cases. The time interval between the operation and the beginning of radiotherapy was 27 to 43 days (median, 34 days). Patients were irradiated in the supine position; for immobilization, a custom-made thermoplastic mask was used.

A comprehensive irradiation, in which both sides of the neck—including the oropharynx, larynx, and hypopharynx—were irradiated, was delivered through parallel opposed fields. A half-beam blocked low anterior neck field was placed to treat lower cervical and supraclavicular nodes. The nasopharynx was included in the radiation field in 13 patients with metastases from undifferentiated nasopharyngeal-type carcinoma and/or with level IIb/V involvement. The oral cavity was irradiated in 17 patients with submandibular adenopathy.

The planning target volume was irradiated with a dose of 30 to 52 Gy (median, 50 Gy) of 4- to 6-MV photons of a linear accelerator administered in 2-Gy daily fractions applied five times weekly. The spinal cord was limited to a maximum of 46 Gy. In 86 patients, an electron beam boost (8–10 MeV) was given to the involved neck region up to cumulative dose of 64 to 72 Gy (median, 66 Gy) in the presence of ECE and 50 to 64 Gy (median, 60 Gy) in the absence of ECE. A total irradiation dose of < 50 Gy was delivered in four patients as a consequence of severe acute side effects.

Follow-Up

The routine follow-up program consisted of locoregional examination at 2-month intervals during the first year, 3-month intervals in the second year, 4-month intervals between the third and fifth years, and every 6 months thereafter. All patients underwent annual chest radiography. The median follow-up for surviving patients was 72 months (range, 15–149 months).

End Points and Statistical Analysis

Actuarial curves for overall survival, disease-specific survival (DSS), regional control, and mucosal and distant failure were analyzed by using the standard Kaplan-Meier method. Tests of significance were based on the log-rank statistic. DSS was calculated by censoring deaths from diseases of unrelated causes; in calculating overall survival, all deaths were considered events. Multivariate regression analysis was performed by using the Cox proportional hazards model. Variables with $P > .1$ in univariate analysis were not entered into the multivariate analysis. Variables tested for an association with nodal control, mucosal failure, distant failure, and DSS included age, sex, pN stage, N level, the presence of ECE, and grading. The effect of irradiation dose on end points was evaluated after adjusting it for ECE. P values $< .05$ were considered statistically significant. In all analyses, time 0 was the date of the end of treatment. This study protocol was approved by the Institutional Review Board of Treviso Regional Hospital.

RESULTS

Nodal Control

Nodal control was achieved in 72 patients (80.0%). The actuarial rate of neck disease control was 68.8% at 5 years (95% confidence interval [CI], 58.9%–78.7%). As shown in Table 1, univariate analysis revealed that age, nodal level involvement (Fig. 1), the presence of ECE, and N stage significantly affected the rate of nodal control; in multivariate analysis, the nodal control rate was negatively associated with the involvement of levels IV and V ($P = .006$). Irradiation dose was not significantly related with local outcome ($P = .547$).

TABLE 1. *Nodal control*

Variable	5-y Rate (%)	*P* value (univariate)	*P* value (multivariate)
Age (y)			
< 65	76	.026	.254
> 64	59		
Sex			
Male	68	.888	NT
Female	69		
N stage			
N1	83	.003	.673
N2	80		
N3	43		
N level			
I, II, III	80	< .001	.006
IV, V	37		
ECE			
Negative	88	< .001	.129
Positive	51		
Grade			
1, 2	59	.485	NT
3, 4	73		

ECE, extracapsular extension; NT, not tested.

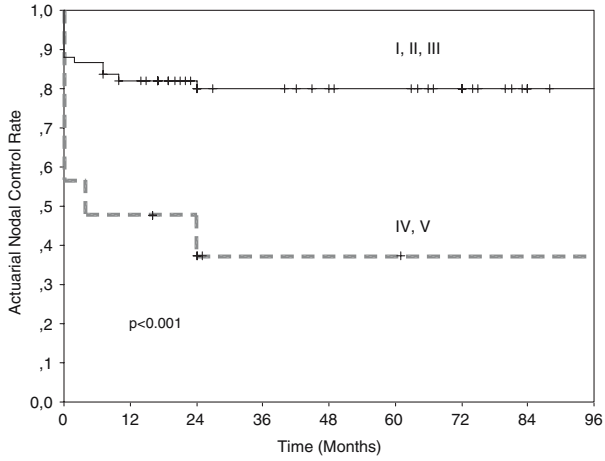

FIG. 1. Actuarial nodal control rate according to the level of nodal involvement.

Primary Tumors

Primary tumors were subsequently detected in 13 patients (14.4%) between 3 and 75 months (median,

TABLE 2. *Mucosal failure*

Site of primary tumor	N° (%)	Subsite	N°
UADT	8 (61.5%)		
		Piriform sinus	3
		Tonsil	2
		Base of the tongue	2
		Floor of the mouth	1
Lung	4 (30.8%)		
Esophagus	1 (7.7%)		

UADT: upper aerodigestive tract.

16 months) after neck treatment. The distribution of primary tumors is shown in Table 2. The actuarial rate of developing primary tumors at 5 years was 17.4% (95% CI, 7.6%–27.2%). The actuarial rate of developing head and neck primary tumors at 5 years was 8.9% (95% CI, 2.6%–15.2%). None of the considered variables was predictive of mucosal failure.

Distant Metastases

Thirteen patients (14.4%) developed distant metastases 9 to 38 months after neck treatment. The 5-year actuarial rate of distant metastases was 19.1% (95% CI, 9.4%–28.9%). Univariate analysis showed that involvement of levels IV and V (Fig. 2A; $P < .001$), the presence of ECE (Fig. 2B; $P = .007$), and grades 3 and 4 ($P = .002$) significantly affected the rate of distant metastases.

In multivariate analysis, distant failure was positively associated with involvement of levels IV and V ($P = .010$) and ECE ($P = .013$). Irradiation dose was not significantly related to distant failure ($P = .858$).

Causes of Death

At the time of analysis, 50 of the 90 patients were alive. A total of 32 (35.6%) had died from cause related to their primary disease: nodal disease, 14 patients (43.7%); distant metastases, 12 patients (37.5%); and primary tumor, 6 patients (18.8%). Eight patients had died from unrelated causes.

Survival

Actuarial overall survival at 2 and 5 years was 71.7% (95% CI, 62.2%–81.1%) and 59.9% (95% CI, 49.1%–70.5%), respectively; the 2- and 5-year actuarial DSS (Fig. 3) was 73.6% (95% CI, 64.3%–82.9%) and 62.8% (95% CI, 51.9%–73.7%), respectively. As shown in Table 3, univariate analysis revealed that nodal level involvement (Fig. 4A), presence of ECE (Fig. 4B), and N stage significantly affected the rate

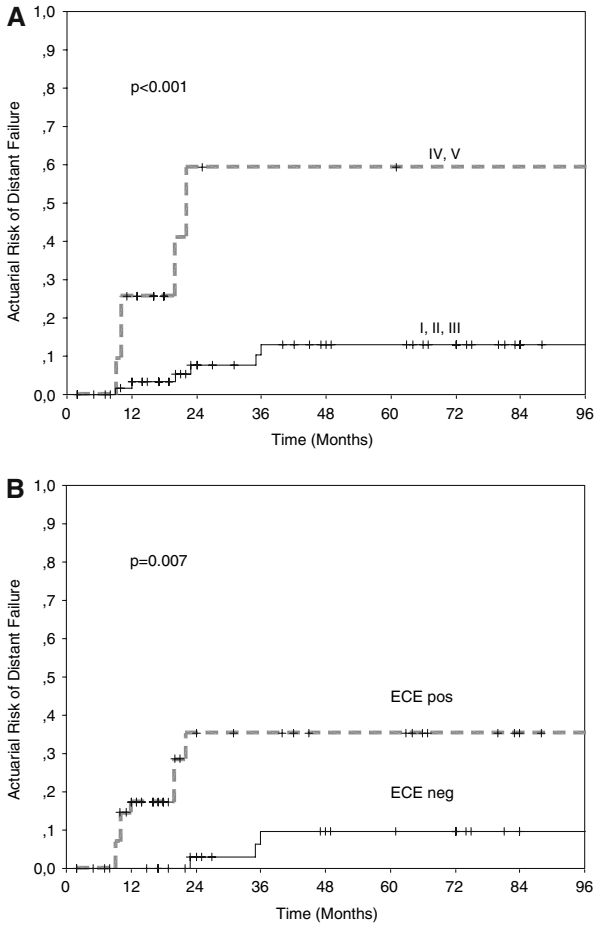

FIG. 2. Actuarial risk of distant failure according to (**A**) the level of nodal involvement and (**B**) extracapsular extension (ECE).

of DSS. Multivariate analysis revealed that the involvement of levels IV and V ($P = .001$) and the presence of ECE ($P = .001$) were negatively associated with actuarial DSS. Irradiation dose was not significantly related to DSS ($P = .884$).

Treatment Morbidity

Surgery-related morbidity was limited to painful sensation and reduced mobility of the neck and shoulder in 46 patients (51.1%) who underwent radical neck dissection. No patient had severe postoperative complications.

According to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score, grade 3 mucositis and dermatitis were seen in five (5.5%) and four (4.4%) patients, respectively. A grade 4 mucositis was seen in one patient. The main late side effects were grade ≥2 xerostomia in 47 (52.2%) patients and subcutaneous

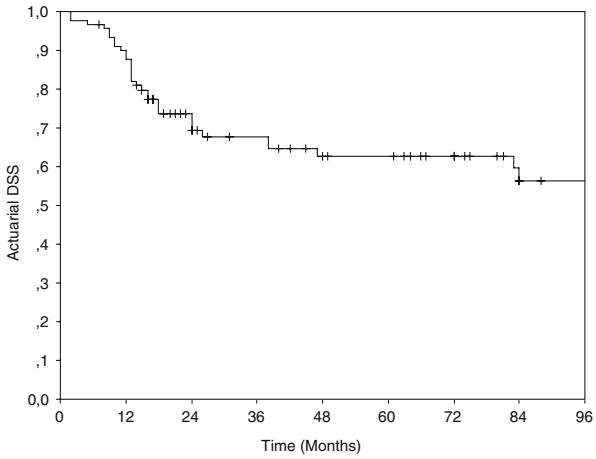

FIG. 3. Actuarial disease-specific survival (DSS).

TABLE 3. *Disease-specific survival*

Variable	5-y Rate (%)	*P* value (univariate)	*P* value (multivariate)
Age (y)			
< 65	69	.160	NT
> 64	53		
Sex			
Male	62	.843	NT
Female	69		
N stage			
N1	83	.002	.868
N2	66		
N3	48		
N level			
I, II, III	76	< .001	.001
IV, V	26		
ECE			
Negative	85	< .001	.001
Positive	42		
Grade			
1, 2	60	.634	NT
3, 4	64		

ECE, extracapsular extension; NT, not tested.

fibrosis in 39 (43.3%) cases. No patients had osteonecrosis.

DISCUSSION

Patients with cancer of unknown primary present with metastatic disease and no identifiable site of origin at presentation. Generally, the overall prognosis is poor, with a mean survival of 5 to 10 months.[2] An exception to this occurs with unknown primary carcinomas of the cervical lymph nodes, with which a more favorable prognosis and sometimes long-term survival are achievable.[1,5] Indeed, in these cases, cervical lymph node metastasis can represent a

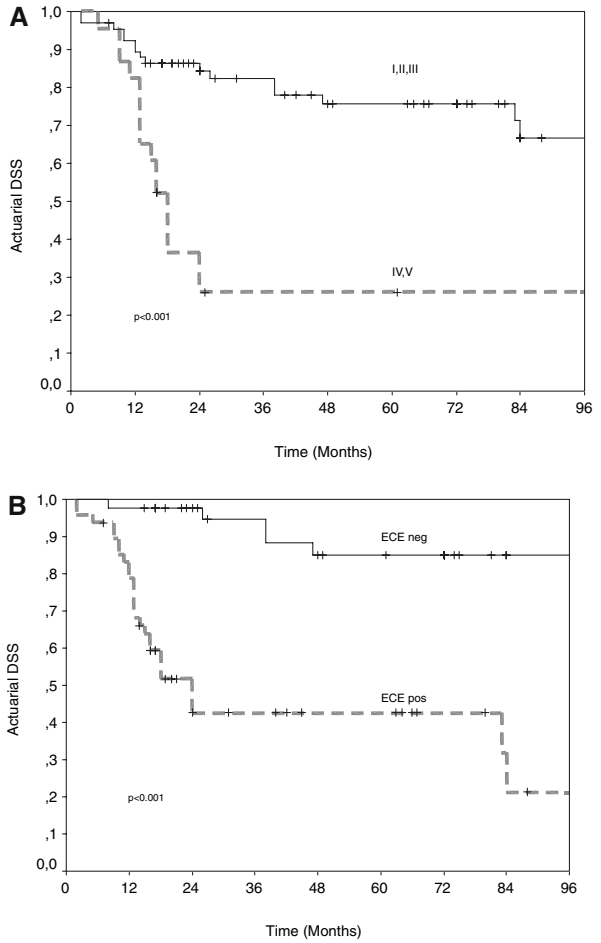

FIG. 4. Actuarial disease-specific survival (DSS) according to (**A**) the level of nodal involvement and (**B**) extracapsular extension (ECE).

regional and still controllable spread of undetectable upper aerodigestive tract cancer. Therefore, it is not surprising that the prognosis is similar to that of patients with known primary head and neck carcinoma and an identical N category, with up to 50% of these patients being long-term survivors.[1,5] This reasonable prognosis is crucial in determining justification for an aggressive management. However, in the absence of randomized trials, the most favorable treatment approach has not, until now, been defined.

Furthermore, the optimal diagnostic algorithm has not yet been established. In our experience, bronchoscopy and dermatological, gynecological, and urogenital examinations were not cost-effective because they did not reveal any primary tumor. In the last 3 years, we routinely performed a multislice helical computed tomography scan of the neck, chest, and superior abdomen. In our opinion, the role of esophagogastroduodenoscopy is not different from

that in staging patients with known primary tumors of the head and neck.

From 1990, our policy has been to treat all patients with cervical metastases from COP with neck dissection followed by comprehensive irradiation whenever feasible. A review of the literature suggests the most promising results with this approach.[4,6] The advantages of combined therapy are an improved control of neck disease, the possibility of reducing the total irradiation dose to obtain more tolerable treatment-related morbidity, and the possibility to obtain additional information about the disease from histopathologic examination of resected specimen.[8]

The proposed treatment options for neck metastases include neck dissection alone, radiotherapy alone, or neck dissection with postoperative radiotherapy. Some authors advocate single-modality therapy for patients with N1 and N2a disease.[9] Many authors suggest surgery alone in selected patients with N1 disease without ECE.[9–15] Radiotherapy alone is used in some centers to treat most patients.[10,11,16] Although a selection bias cannot be excluded, neck dissection performed after radiotherapy showed evidence of nodal disease in up to 44% of patients.[9,17–19]

Mendenhall et al.[20] reported node control rates when radiotherapy was used for positive neck nodes in patients with squamous cell carcinoma of the head and neck: the control rate was 92% in cases with N1 metastatic disease, and for patients with a solitary node measuring >3 cm or with multiple nodes, the control rates ranged from 45% to 75%. Furthermore, the control rate in patients with fixed nodes was 55%.

Conversely, only a neck dissection provides additional information about the extent and aggressiveness of disease (pN, histopathologic grade, and extracapsular spread). Clinical neck staging and pathologic staging can differ considerably. Reflecting the findings in patients with known head and neck tumors, 45% of patients with clinical N1 neck metastases from an unknown primary tumor have multiple nodes, and 35% have evidence of extracapsular spread.[22]

In this series, DSS was strongly associated with the presence of ECE. This correlation is consistent with other reports.[8,23,24] A recent review showed that the prognosis in individuals with ECE of the tumor in cervical lymph nodes is quite poor; moreover, ECE seems to be the most important prognostic factor in patients with cervical metastasis, in relation to both local recurrence and distant metastasis.[25] Because extracapsular spread was evaluated by the naked eye at the time of nodal dissection, our rate could be underestimated. According to other authors, an involvement of levels IV and V was associated with a worse prognosis in multivariate analysis. This may be due to a higher rate of distant metastases observed in these patients.[16,26–28] Compared with other reports,[8,9,22] the rate of level IV and V involvement was higher in this series. We have no proper explanation for this, nor for the high rate of bilateral metastases.

The emergence of a subsequent primary tumor is a main topic in neck metastases from an unknown primary tumor. Several studies showed that the subsequent detection of a primary tumor is associated with a poorer prognosis.[29–31] Prophylactic mucosal irradiation is performed to treat the putative site of the primary tumor. In our series, the actuarial rate of developing head and neck primary tumors at 5 years was 8.9%. This rate is comparable to those recorded in other series in which comprehensive irradiation was performed[4] and is similar to the rate of second primary tumors in patients with evident head and neck cancer. Particularly, this last observation seems to support the usefulness of mucosal irradiation in patients with unknown primary tumors.[16] Conversely, this strategy is associated with side effects due to the increased irradiated volume.[31] For that reason, other authors suggest a limited-field radiotherapy treating the ipsilateral neck only. Some authors reported that ipsilateral radiotherapy considerably reduced the risk of having an emerging mucosal primary tumor when compared with patients treated with surgery alone.[16] This ''mucosal effectiveness'' may be due to incidental irradiation of potential lateral tumors in the oropharynx.

An acceptable tolerance was observed. In accordance with other reports, the main complication was grade ≥2 xerostomia, observed in 52.2% of cases.[8,9] To reduce toxicity, according to other authors,[22] we advise irradiation of the nasopharynx only in cases of posterior metastases (level IIb and level V) or undifferentiated histotypes; likewise, the oral cavity was irradiated only in patients with submandibular metastases. Furthermore, some authors suggest excluding patients from radiation treatment of the hypopharynx when there is a strong suggestion that the nasopharynx is the primary site.[8]

In this series, the 5-year actuarial rate of distant failure was 19.1%. According to other authors, an involvement of levels IV and V ($P = .010$) and the presence of ECE ($P = .013$) was positively associated with distant metastases in multivariate analysis.[8,9] The European Society of Medical Oncology suggests neoadjuvant platinum-based chemotherapy for N3 disease.[4] Conversely, a recent review does not sup-

port the utility of chemotherapy in patients with neck metastases from an unknown primary tumor.[6] However, the role of chemotherapy should be investigated in patients with a high risk of distant metastases, such as those with supraclavicular node metastases or undifferentiated tumors.

The 5-year DSS of 62.8% (95% CI, 51.9%–73.7%) calculated in our series is similar to the results reported in other series in which the same management strategy was used.[4] This rate resembles that for patients with upper aerodigestive tract cancer and regional disease.[32]

CONCLUSION

Patients presenting with cervical metastasis from an unknown primary tumor have a reasonable prognosis resembling that of patients with a known primary tumor and the same N stage. In this sense, management is a discussion of the treatment of advanced head and neck carcinoma. Some patients with N1 disease (stage III) may be carefully selected for a single-modality treatment. Patients with N2 or N3 disease (stage IV) should undergo combined-modality therapy. The surgical treatment for neck metastases from COP should be a comprehensive neck dissection (levels I to V). Some authors suggest a supraomohyoid neck dissection in patients with N1 disease in the upper neck.[21] The extent of irradiation remains debatable. Most patients receive a comprehensive irradiation in which both sides of the neck and the upper aerodigestive tract are irradiated. Bilateral neck plus mucosal irradiation seems to give the most promising results. However, in the absence of randomized trials, comprehensive irradiation cannot be routinely advised.

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