

## Unknown primary of the head and neck

YOAV P. TALMI, M.D.\*, GREGORY T. WOLF, M.D., F.A.C.S.†, MARK HAZUKA, M.D.‡,  
CHARLES J. KRAUSE, M.D., F.A.C.S.†

### Abstract

The occurrence of metastases to the cervical lymph nodes from an unknown primary tumour is seen in approximately three to six per cent of patients with cervical adenopathy and the primary tumour commonly remains elusive. Single modality treatment is occasionally advocated but combined treatment seems to obtain the best results.

A retrospective analysis of patients' charts with unknown primary of the head and neck in the University of Michigan Medical Center was undertaken for the years 1978–1992. Forty-eight records met study criteria and were reviewed.

Our series' size and heterogeneity prevents drawing conclusions regarding treatment effectiveness. The majority (67.5 per cent) of our patients were treated by surgery followed by irradiation. Our overall survival rates compare favourably with the general statistics although it should be noted that longer follow-up in our first group of patients may alter our results. Extracapsular spread did not adversely affect survival in our small series of five cases. We discovered six primary sites within one year and three additional cases within four years. The primary site was included in the radiation fields in all instances of squamous cell tumours that were eventually found. It has been suggested that eventual manifestation of the primary site adversely affects prognosis, which is in agreement with our results.

**Key words:** Neoplasm metastasis; Neoplasms, unknown primary; Head and neck neoplasms

### Introduction

The occurrence of metastases to the cervical lymph nodes from an unknown primary tumour comprises approximately three to six per cent of patients with cervical adenopathy (Spiro *et al.*, 1983; de Braud *et al.*, 1989; Maulard *et al.*, 1992). An extensive search for the primary tumour is essential in all cases and should include a complete upper aerodigestive tract examination with appropriate imaging studies. Panendoscopy and directed biopsies (blind biopsies) of suspicious sites should be undertaken.

Optimal treatment of the unknown primary in the neck is still unclear. Some reports favour single modality treatment such as radiation only (Barrie *et al.*, 1970; Spiro *et al.*, 1983), or surgery (Bataini *et al.*, 1987; Harper *et al.*, 1990); however, combined treatment seems to be the most effective in these cases (Leipzig *et al.*, 1981; Silverman *et al.*, 1983; Wang *et al.*, 1990; Coster *et al.*, 1992). Chemotherapy may also play a therapeutic, and not just a palliative role, (de Braud *et al.*, 1989).

Five-year patient survival rates are in the range of 50 per cent, but may vary greatly depending on N staging, nodal fixation and extracapsular spread

(Coster *et al.*, 1992; Maulard *et al.*, 1992). The discovery of the primary tumour may indicate worse prognosis. We have undertaken a retrospective study of patients with cervical lymph node metastasis from occult primaries in order to evaluate our experience in diagnosis, management and survival of these patients.

### Methods

Patients' charts were retrieved through the University of Michigan medical records and tumour registry and were cross-indexed with the records of the department of Radiation Oncology. Cross-referencing was also carried out with patients listed as undergoing neck dissections with the primary site unknown. Charts were reviewed for the 15-year period from 1978 to 1992. Patients with melanoma, lymphoma and those with supraclavicular metastasis were excluded.

Fifty-six patients' records met study criteria and were reviewed. Follow-up was found to be adequate in 48 of them. A detailed review of each of these patients was then performed and forms the basis of this report. Patient age, sex, presenting symptom

From the Department of Otolaryngology, Head and Neck Surgery\*, the Chaim Sheba Medical Centre, Tel Hashomer, Israel and the Department of Otolaryngology, Head and Neck Surgery† and Radiation Oncology‡, the University of Michigan Medical Center, Ann Arbor, Michigan, USA.

Accepted for publication: 31 December 1995.

(including duration), staging according to the recent AJCC classification (American Joint Committee on Cancer. Manual for staging of Cancer 1988), location according to neck node levels, and histology were determined. Diagnostic procedures, including directed biopsies, were reviewed. Treatment modalities, eventual discovery of the primary site, follow-up and survival were determined.

## Results

Thirty-four patients were males and 14 were females. Patients' ages ranged from 39 to 80 years with a mean of 60 and a median of 59 years. Duration of symptoms ranged from two weeks to 24 months with a mean of 5.5 months and a median of 3.5 months. The presenting symptom was usually a single neck mass. Neck masses presented on the left side in 24 patients, on the right side in 22 patients and were bilateral in two cases. Neck mass size was clearly described in 30 cases (Table I), and exact site in the neck could be ascertained in 27 patients. Reference to smoking was found in 25 charts with 21 patients being smokers. Eight patients of the 25 were defined as consuming alcohol on a regular basis.

A complete history and physical examination was performed on each patient. This included indirect and in many cases, fibre optic laryngoscopy and nasopharyngoscopy. Examination under anaesthesia was performed with directed biopsies of the nasopharynx, tongue base and pyriform sinuses in all cases. Ipsilateral or bilateral diagnostic tonsillectomy was performed in eight patients and eight others also had biopsies from the larynx or oropharynx. Laboratory examination including complete blood count, chemistry and urinalysis was performed and each patient had a chest X-ray. CT scan of the head and neck was done in 39 patients, all after 1983. MRI was performed in only three cases. Forty-two patients (75 per cent) had squamous cell carcinoma, three (five per cent) had adenocarcinoma and three undifferentiated carcinoma. Findings of extracapsular spread were recorded in only five patients. Squamous cell differentiation was well-differentiated in six per cent of patients, moderately well-differentiated in 41 per cent and poorly differentiated in 53 per cent.

The patients were treated with chemotherapy, surgery, radiation or a combination of two or three modalities. Surgery was the initial treatment in 40 cases followed by radiation in 27 patients. Radiation was the only treatment in seven cases, including one patient with severe chronic lung disease, and two patients with disease deemed unresectable. Radiation dosage ranged from 5800 to 7560 cGy. Chemotherapy was given as a third treatment

TABLE I  
NECK MASS SIZE (N = 30)

$N_1 < 3$ cm	10
$N_2 > 3 < 6$ cm	12
$N_3 > 6$ cm	8

TABLE II  
PRIMARY TUMOUR LOCATION

Duration (months)	Site
9	Oropharynx
6	Base of epiglottis
6	Nasopharynx
6	Pancreas
20	Base of tongue
24	Larynx
48	Larynx
6	Parotid
12	Nasopharynx

modality in two cases and as the initial treatment followed by radiation in one additional patient.

The primary tumour was found in nine cases with six discovered within a year and the other three within four years. Primary tumour location is shown in Table II. The primary tumour was discovered in the pancreas in one of the three cases with undifferentiated carcinoma and in the parotid gland in one case of adenocarcinoma. The other seven cases in which a primary was found were all squamous cell cancer.

Patients were followed for a minimum of two years. Follow-up ranged from two to 21 years with a mean of five years. Fourteen patients were followed from two to four years and 29 patients for over four years. Five patients were lost to follow-up. Nine (64 per cent) of the patients followed for under four years were alive without disease, two (14 per cent) were alive with disease and three (21 per cent) were dead of their disease. Fourteen (48 per cent) patients, comprising half of the group followed over four years, were seen alive without disease and one was alive with disease five years after definitive treatment. Ten (34 per cent) were dead of their disease and four (14 per cent) of other causes. Overall survival was 60 per cent with 53 per cent determinant disease-free survival.

Of the nine patients with the primary eventually found, six were dead of their disease, two alive and well and one alive with disease. All of these cases had radical neck dissection followed by radiation. In one case the primary was found in the pancreas and another in the parotid with neither site included in the treatment fields. In the other seven cases the primary was discovered in a previously irradiated area.

No correlation was seen between lymph node size, tumour recurrence rate or survival. Of the five cases with documented extracapsular spread, one has died of disease, one is alive with disease and three are alive without disease. No correlation was found between squamous cell tumour differentiation and survival.

## Discussion

Survival rates are usually reported after a five-year period although several reports describe three-year follow-up results. Survival in a recent major series is depicted in Table III. A significant number of our patients were followed for less than four years. Our

TABLE III  
UNKNOWN PRIMARY SERIES—PUBLISHED 1980–present

No.	Senior author	Year of publication	Years patients followed	No. of patients	Median age	M/F ratio	Treatment			Histology		f/u period (years)	Five-year survival	Primary found (%)	Primary found after (%)	Most common site	
							Cx	XRT	Sx	SCC	Undiff	Adeno					
1	Leipzig	1981	69–77	48	51	2:1				32		16	3	28% (adeno-all DOD)	40%		NP
2	Silverman	1983	64–79	83	>40	58:25		80%	25%	58	24		5–10	38%	22	<2 yr	
3	Spiro	1983	65–76	132	56–61	76:45		39%	78%	60%	10%	22%	>5	50%	15%	14–67 months	hypo-pharynx
4	Bataini	1987	60–80	138	57.5	117:21		65%	35%	100%			>3	33%	43%	<5 months	np
5	de Braud	1989	76–87	41	58	28:13	16%	16%	9%	85%	7%		>35 m	–	10%	10–57 months	lx
6	Harper	1990	64–86	69	61.4	58:11		93%	26%	100%			5	48%	12%		oc
7	Wang	1990	53–88	157	60.5	4:1		62%	64%	100%			47 months	55%	18%	<12 years	skin
8	Maulard	1992	72–86	113	59	96:17		100%	100%	100%			4–18 months	38%	9.7%	3–46 months	lung
9	Coster	1992	65–87	24	63	3:1				100	100%		8.5	67%	12.5%	>5	lx
10	Present study	1996	78–91	48	59	34:14	3	27	37	42	3	3	14>2 yrs.	53%	19%	1 yr	lx
													34>4 yrs.				

current absolute disease-free survival rates are 64 per cent for the two to four year follow-up period and 48 per cent for the four to 15 year group.

A heterogeneous group of patient data and treatment modalities are seen even in large series. Harper *et al.* (1990) however, describe a rather large and homogeneous group of patients treated with highly effective radiation. De Braud *et al.* (1989) advocate aggressive treatment including chemotherapy in N<sub>3</sub> cases, demonstrating higher complete response and longer survival time as compared with patients treated with surgery only or surgery and radiation. Maulard *et al.* (1992) consistently treated 113 patients with surgery and large-field post-operative radiation. Their five-year overall survival rates were lower than the former series but such a comparison is difficult to evaluate. Others (Leipzig *et al.*, 1981; Silverman *et al.*, 1983; Wang *et al.*, 1990; Coster *et al.*, 1992), also recommend combined treatment, usually surgery followed by radiation or primary radiation for non-resectable tumours followed by surgery, in those which regressed or have become resectable.

Our series' size and heterogeneity prevents drawing conclusions regarding treatment effectiveness. The majority (67.5 per cent) of our patients were treated by surgery followed by irradiation. Our overall survival rates compare favourably with the general statistics although it should be noted that longer follow-up in our first group of patients may alter our results.

Extracapsular spread was found to adversely affect survival (Barrie *et al.*, 1970; Silverman *et al.*, 1983; Maulard *et al.*, 1992) but this was not the case in our small series of five cases.

It has been reported that primary lesions are eventually identified in 4.3 to 40 per cent of patients. This compares to our discovery rate of 19 per cent. In most cases, primary tumours were found within a period of up to five years although discovery was reported even up to 12 years following definitive

treatment (Barrie *et al.*, 1970). We discovered six primary sites within one year and an additional three cases within four years. It has been suggested that eventual manifestation of the primary site adversely affects prognosis (Barrie *et al.*, 1970), which is in agreement with our results.

Jesse *et al.* (1973) reported a series of 184 patients with different treatment modalities. Twenty per cent of the patients treated with neck dissection alone developed a mucosal primary lesion compared with nine per cent of those treated with radiotherapy alone. The treatment groups differed as stated by the authors in that the patients treated with neck dissection alone had, for the most part, earlier and well-differentiated neck disease. It is to be noted that the primary site was included in the radiation fields in all instances of squamous cell tumours that were eventually found.

In patients with squamous cell neck metastases, the nasopharynx and base of the tongue are reported as the most frequent primary sites. Other anatomical areas such as the hypopharynx and Waldeyer's ring are also implicated. In our series the larynx was the most common area afflicted followed by the nasopharynx. The primary site was found to originate most commonly in the skin in one series (Leipzig *et al.*, 1981). The diversity of the primary site of origin indicates the need for a meticulous search in all areas of the head and neck. As we excluded patients with supraclavicular metastasis, only one site of origin was found below the clavicles.

## References

- American Joint Committee on Cancer. Manual for Staging of Cancer (1988) 3rd Edition. J. B. Lippincott Company, Philadelphia.
- Barrie, J. R., Knapper, W. H., Strong, E. W. (1970) Cervical nodal metastases of unknown origin. *American Journal of Surgery* **120**: 466–470.
- Bataini, J. P., Rodriguez, J., Jaulerry, C., Brugere, J., Ghossein, N. A. (1987) Treatment of metastatic neck

- nodes secondary to an occult epidermoid carcinoma of the head and neck. *Laryngoscope* **97**: 1080–1084.
- Coster, J. R., Foote, R. L., Olsen, K. D., Jack, S. M., Schaid, D. J., DeSanto, L. W. (1992) Cervical nodal metastasis of squamous cell carcinoma of unknown origin: indications for withholding radiation therapy. *International Journal of Radiation Oncology Biology Physics* **23**: 743–749.
- De Braud, F., Heilbrun, L. K., Ahmed, K., Sakr, W., Ensley, J. F., Kish, J. A., Tapazoglou, E., Al-Sarraf, M. (1989) Metastatic squamous cell carcinoma of an unknown primary localized to the neck. Advantages of an aggressive treatment. *Cancer* **64**: 510–515.
- Harper, C. S., Mendenhall, W. M., Parsons, J. T., Stringer, S. P., Cassisi, N. J., Million, R. R. (1990) Cancer in neck nodes with unknown primary site: Role of mucosal radiotherapy. *Head and Neck* **12**: 463–469.
- Jesse, R. H., Perez, C. A., Fletcher, G. H. (1973) Cervical lymph node metastases: Unknown primary cancer. *Cancer* **31**: 854–859.
- Leipzig, B., Winter, M. L., Hokanson, J. A. (1981) Cervical nodal metastases of unknown origin. *Laryngoscope* **91**: 593–598.
- Maulard, C., Housset, M., Brunel, P., Huart, J., Ucla, L., Rozec, C., Delanian, S., Baillet, F. (1992) Post-operative radiation therapy for cervical lymph node metastases from an occult squamous cell carcinoma. *Laryngoscope* **102**: 884–890.
- Silverman, C. L., Marks, J. E., Lee, F., Ogura, J. H. (1983) Treatment of epidermoid and undifferentiated carcinomas from occult primaries presenting in cervical lymph nodes. *Laryngoscope* **93**: 645–648.
- Spiro, R. H., DeRose, G., Strong, E. W. (1983) Cervical node metastasis of occult origin. *American Journal of Surgery* **146**: 441–446.
- Wang, R. C., Goepfert, H., Barber, A. E., Wolf, P. (1990) Unknown primary squamous cell carcinoma metastatic to the neck. *Archives of Otolaryngology, Head and Neck Surgery* **116**: 1388–1393.

Address for correspondence:

Yoav P. Talmi, M.D.,  
 Department of Otolaryngology,  
 Head and Neck Surgery,  
 The Chaim Sheba Medical Center,  
 Tel Hashomer, 52621  
 Israel.

Fax: 972-3-5376515