

Metastatic Carcinoma of the Neck Node from an Unknown Primary Site

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From 1980 to 1986, 26 patients with metastatic carcinoma of the neck node from an unknown primary site were seen in the Department of Therapeutic Radiology of Seoul National University Hospital. Among these, three patients were excluded from further analysis due to incomplete treatment. So a retrospective analysis was undertaken on 23 patients who had complete treatment with radiation therapy alone or in combination with surgical treatment and chemotherapy. The overall three year actuarial survival rate was 32%. According to the staging system of the American Joint Committee on Cancer, the three year survival rates with N2 and N3 patients were 43% and 13%, respectively. In 16 patients with squamous cell carcinoma and seven with non-squamous cell carcinoma, the three year survival rates were 34% and 29%, respectively. Analysis according to site of nodal involvement was also done. Patients with cervical node and supraclavicular node involvement recorded 44% and 17% of three year survival rate, respectively. In this study, six patients eventually manifested the primary sites (three in the lung, one in the esophagus, one in the stomach, one in the nasopharynx). Presence of the primary site seemed to influence the prognosis (17% vs 38%). In analyzing the prognostic factors, the nodal stage and site of nodal involvement were important prognostic factors, and the presence of a primary site seemed to influence the patients' survival, but histology did not.

Key Words: Unknown primary, Carcinoma of the neck, Neck node metastasis

INTRODUCTION

A primary tumor site can't be identified in 3~4% of the patients presenting with metastatic carcinoma¹⁾. Approximately 10% of these cases form a unique group with metastasis to the cervical lymph nodes from an occult head and neck primary site.

It is now established that over 70% of the patients with metastatic cancer in the neck have a primary tumor somewhere within the head and neck²⁾.

Because of the relatively good prognosis of patients with head and neck cancers compared to those of other anatomical sites, patients in this category can benefit from aggressive local and regional treatment.

This is a report of 23 patients seen at our institution and diagnosed as having metastatic carcinoma of the neck node from an unknown primary site and treated with radiation therapy alone or in combination with surgery and chemotherapy. In this study, we provide a perspective of treatment results and prognostic factors in this disease entity.

MATERIALS AND METHODS

From 1980 to 1986, 26 patients diagnosed as having metastatic carcinoma of the neck node from an unknown primary site were seen in the Department of Therapeutic Radiology of Seoul National University Hospital. Three patients were excluded from the analysis due to incomplete treatment. The remaining 23 formed the basis of this study. The minimum follow-up period for all patients was three years. Actuarial survival was calculated by the life table method; the log-rank test was used for comparison.

There were 20 males and three females. The age distribution ranged from 37 to 76 years with a median age of 54 years. Clinical evaluation of these patients included a complete history and physical examination, as well as a basic hematologic and biochemical study. The radiographic studies performed included simple X-rays, an upper G-I study, barium enema, IVP, C-T scan, and a bone and liver scan. All patients were examined by an ENT specialist. In addition to careful examination of the ENT system, direct laryngoscopy with fiberoptic bronchoscopy and endoscopy were also performed on

any of these patients if indicated. Primary lesions could not be found on the initial work-ups of all the patients. Histologies were obtained from excisional biopsies in nine patients, incisional biopsies in 10 patients, and radical neck dissections in four patients. Of all the patients, squamous cell carcinoma was found in 16, adenocarcinoma in three, and undifferentiated carcinoma in one. Specific cell type could not be determined in three patients. Patients with cervical lymph node metastasis were staged according to the American Joint Committee on Cancer's (AJCC) staging system³⁾ for nodal disease in the head and neck region. There were 14 patients with stage N2 (61%) and nine patients with stage N3 (39%). The patients' characteristics are summarized in Table 1.

TREATMENT

All patients were treated by radiation therapy alone or in combination with surgery and chemotherapy. Radiation therapy was given with Co⁶⁰ or 6-MV linac teletherapy. In radical radiotherapy to 10 patients, the radiation portal included the suspected primary site, usually Waldeyer's ring, and the lower neck area and supraclavicular area. The total tumor doses of 6000~9000 cGy in six to nine weeks were delivered depending on the size

and extent of the involved lymph nodes, reducing the field after tumor doses of 4500~5000 cGy to the suspected primary site⁴⁾. Postoperative radiotherapy was given to five patients with tumor doses of 6000~7000 cGy in seven to eight weeks. Palliative radiotherapy was given to eight patients with tumor doses of 4000~7000 cGy in three to eight weeks. Nine patients underwent surgical excision preceding the radiation therapy. Of these, five were treated by radical neck dissection, two by simple excision and two by wide excision. Three patients received two cycles of neoadjuvant chemotherapy consisting of bleomycin, vincristine, methotrexate, and cisplatin.

RESULTS

The overall three year actuarial survival rate of 23 patients was 32% (Fig. 1). In the 14 patients with N2 stage and the nine patients with N3 stage, the three year survival rates were 42.9% and 13.2%, respectively (Fig. 2). Survival rates according to

Table 1. Patients' Characteristics

Characteristics	No. of Pts.	(%)
Age (years)		
Range	37-76	
Median	54	
Sex		
Male	20	(87)
Female	3	(13)
Histology		
Squamous	16	(70)
Adenoca.	3	(13)
Undiff.	1	(4)
Unspecified	3	(13)
Stage		
N2	14	(61)
N2a	4	(17)
N2b	7	(31)
N2c	3	(13)
N3	9	(39)

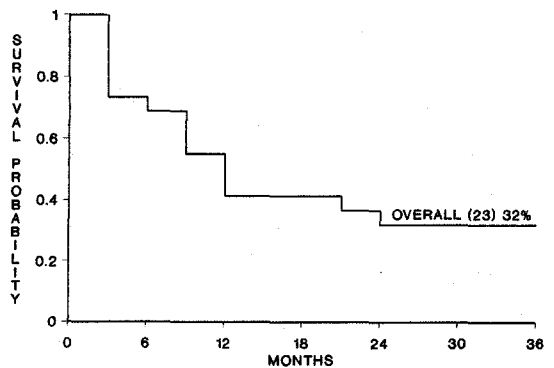


Fig. 1. Actuarial survival of all patients.

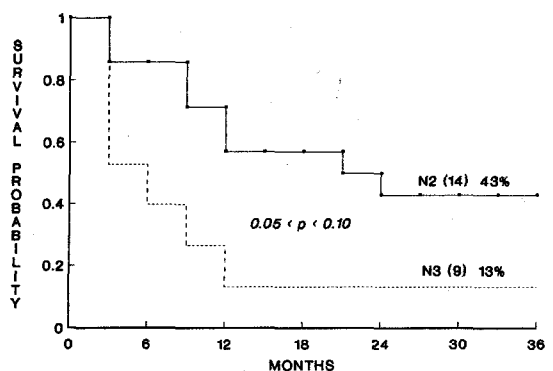


Fig. 2. Actuarial survival according to nodal stage.

histologic type were analyzed. In the 16 patients with squamous cell carcinoma and the seven with non-squamous cell carcinoma, the three year survival rates were 33.7% and 28.6%, respectively (Fig. 3). Survival differences according to the response to radiotherapy were analyzed in 18 patients. Four patients in complete response, 10 in partial response, and four in no response resulted in 50%, 20%, and 0% of three year survival rate, respectively (Fig. 4). Response to radiotherapy versus nodal stage is presented in Table 2. In the 16 patients whose nodal involvement sites could be known, groupings were made arbitrarily into nine patients with cervical node involvement and seven patients with supraclavicular node involvement. The three year survival rates in the group with cervical node involvement and the group with supraclavicular node involvement were 44.4% and 16.9%, respectively (Fig. 5). In this study, six patients (26%) manifested their primary sites eventually, and the details of these patients is presented in Table 3. Survival potential

was analyzed according to the presence of the primary site or not. The 17 patients with primary sites never found and six patients with primary sites found later recorded 37.9% and 16.9% of three year survival rate, respectively (Fig. 6).

DISCUSSION

In interpreting our results, the small sample size, the variety of treatment methods used for each patient, and the inevitable shortcomings in clinical records in this retrospective study are factors that should be considered. In spite of these shortcomings, we offer a perspective of treatment

Table 2. Nodal Stage vs. Response to Radiotherapy

Stage	Response			Total
	C.R.	P.R.	N.R.	
N2	4 (33%)	6 (50%)	2 (17%)	12
N3	0 (0%)	4 (67%)	2 (33%)	6

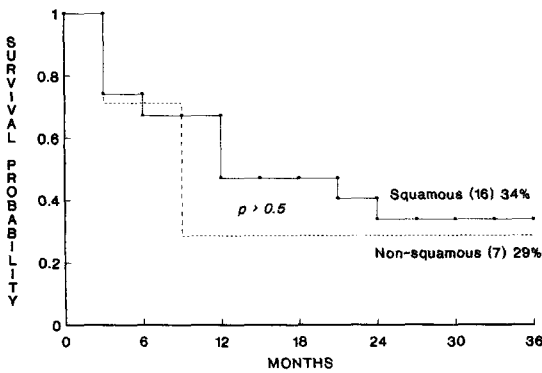


Fig. 3. Actuarial survival according to histology.

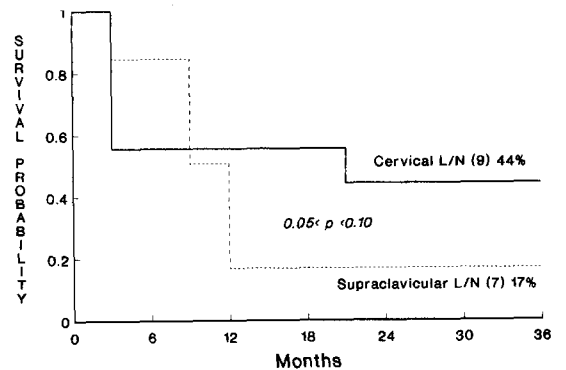


Fig. 5. Actuarial survival by site of nodal involvement.

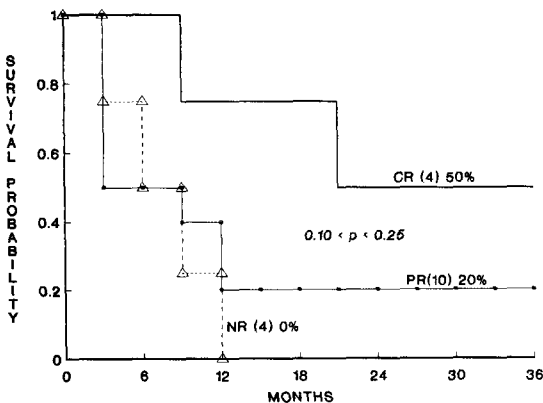


Fig. 4. Actuarial survival by response to radiotherapy.

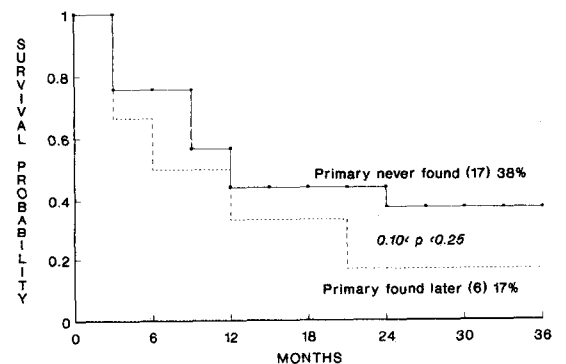


Fig. 6. Actuarial survival by presence of primary site.

Table 3. Primary Sites Found Later

Primary Sites	No. of Pts.	Survival Period
Lung	3	5 mo., 5 mo., 7 mo.
Esophagus	1	14 mo.
Stomach	1	37 mo.
Nasopharynx	1	23 mo.

results and the prognostic factors of metastatic neck node from an unknown primary site.

In reviewing previous data in the literature, it was difficult to interpret them properly because they varied so much, depending on how the unknown or occult primary was defined. The broader the definition, the poorer the end results. In defining the diagnostic criteria, Comess et al⁶⁾, set criteria for the diagnosis of an unknown primary, namely, (1) no history of previous malignancy or of surgical ablation of any indeterminate lesion; (2) no history of definite symptoms related to a specific organ; (3) no clinical or laboratory evidence of a primary neoplasm, proved or not; and (4) one or more cervical masses proved histologically to be cancer. Metastatic cervical nodes from an unknown primary were considered a practically hopeless situation, with patients survival measured in months^{6,7,15)} prior to Jesse's analysis⁸⁾ in 1973. Although Jesse et al. reported 48% with three years free of cancer, the three year survival rates in the literature ranged from 28~31%^{2,9,11)}. The three year survival rate of 32% in our study was comparable with those reported in the literature.

1. Nodal Stage

The important correlation between the nodal stage and survival in patients receiving treatment is indicated in fig. 2. McCunniff et al¹⁰⁾ reports that three out of five patients with N2 stage survived in two years, while none did of the 28 patients with N3 stage. These findings were also in agreement with those of Fried et al¹¹⁾. According to the AJCC, the nodal stage is directly related to the size of the involved node.

Also, it is well-known that early small metastatic nodes can be controlled by radiation therapy alone, but advanced stage are better treated by combined surgery and radiotherapy. If the lymph node size increases, generally its local control by radiation therapy alone becomes more difficult. Since a significant proportion of patients die only from local-regional disease, patients who have

large neck nodes should receive aggressive treatment to improve local control and thereby possibly increase the chance of survival. This conclusion was also confirmed in our study (Table 2, Fig. 4). Four out of 12 patients with N2 stage (33%) showed complete response, but none of the six patients with N3 stage (0%) achieved a complete response. So we could find that the N-stage was closely related with the response to radiotherapy and was an important prognostic factor to survival.

2. Histology

It is suggested in Fig. 3 that histology is not meaningful to prognosis. McCunniff et al¹⁰⁾ reports that six out of 10 patients with squamous cell carcinoma and four out of seven patients with undifferentiated carcinoma survived in two years and that histology is not an important prognostic factor. Coker et al¹²⁾ also reports that prognosis is more dependent on clinical staging than on the histology of the lesion. Our results were in accordance with those reports. However, adenocarcinoma deserves special attention. Fried et al¹¹⁾ reports that nine out of 28 patients with squamous cell carcinoma survived in three years, and none did of the five patients with adenocarcinoma. This poor survival rate in cases of adenocarcinoma is also supported by Spiro et al¹³⁾. Most authors consider adenocarcinoma unfortunate and report a high incidence of supraclavicular node involvement. Currently, it is commonly thought that metastatic cervical lymph nodes with adenocarcinoma indicate the presence of an unknown primary tumor below the clavicle and is associated with a poor prognosis¹⁴⁾. Otherwise it can be explained that because the neck node metastasis of adenocarcinoma mainly originates from the G-I tract and lung, the prognosis of these primaries is generally poorer than those of the head and neck primaries.

3. Site of Nodal Involvement

According to Fig. 5, the site of nodal involvement is significant to prognosis. Jesse et al¹⁵⁾ reports that 21 out of 67 patients with cervical node involvement survived in three years, but only one out of 12 patients did with supraclavicular node involvement. their results are also supported by Yang et al¹⁶⁾. It is generally thought that supraclavicular lymph node involvement means that the origin of the occult primary neck node metastasis may be from the G-I tract and lung rather than a head and neck primary. Like the poor survival prognosis in the histology of adenocarcinoma,

supraclavicular lymph node involvement mainly originating from the G-I tract and lung primary suggests poorer survival than even cervical lymph node involvement from a head and neck primary. Although our study didn't show the following, Jesse et al⁸⁾ and Yang et al¹⁶⁾ report that the incidence of a later appearance of a primary lesion is higher in patients with supraclavicular lymph node involvement than in patients with cervical lymph node involvement.

4. Presence of Primary Site

Cervical lymph node metastasis represents a variety of malignancies arising from different sites of the head and neck regions, and it is well-known that the nasopharynx is the most common site of the primary¹⁷⁾. However, a considerable number of cases might be due to dissemination from tumors situated below the clavicles. Greenberg¹⁸⁾ reports a composite of studies by various authors, citing a figure of 34%, based on the number of primaries found subsequent to treatment. Also he reports that the lung was the most common site, but almost any organ could be responsible. In this study, six out of 23 patients (26%) eventually manifested an occult primary tumor after treatment; the details of these six patients are presented in Table 3. Generally, the primary site is discovered after treatment in 20~40% of patients with metastatic cervical lymph nodes from an occult primary¹⁹⁾. Our results were comparable to others in this respect. Fig. 6 suggests that the group of patients whose primaries were never found had a better survival rate than the group in which primaries were found later. Jesse et al reports that patients with primaries found later and patients with primaries that were never found recorded 12/48 (25%) and 32/79 (40%) in three year survival rates, respectively. In patients treated with surgery only, approximately 20% of all fails in either the nasopharynx, oropharynx or hypoharyngeal areas which would be encompassed in a typical radiotherapy portal. In those patients treated with radiation alone or a combined approach, the incidence of primary appearance in the head and neck region was reduced to 4~14%. Probert et al²⁰⁾ noted a 10% failure in the irradiated volume. Our results were comparable to others with 7% (1/15) of the patients eventually manifesting disease in the irradiated fields. In contrast to in-field failure, it is well-known that the rate of failure below the clavicle is constant regardless of the treatment modality.

In conclusion, this study led us to recognize that

1) the nodal stage and the site of nodal involvement

were important prognostic factors to survival, and 2) patients with N2 stage and cervical node involvement benefited by long-term survival from radical radiotherapy only, but 3) considering the poor survival rate of patients with N3 stage or supraclavicular lymph node involvement, treatment by combined modality should be tried in these cases.

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== 국문초록 ==

확인불능의 원발병소로부터의 경부임파절 전이에 대한 치료 성적

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1980년부터 1986년까지 확인불능의 원발병소로부터의 경부임파절 전이 진단하에 26명의 환자가 서울대학교병원 치료방사선과에서 치료를 받았다. 전체 환자 26명중 불완전한 치료를 받은 3명을 제외하고 방사선치료 단독으로 또는 수술과 화학요법을 병행해서 완전한 치료를 받은 23명을 대상으로 후향적 분석을 시행하여 다음과 같은 결과를 얻었다.

전체환자의 3년 생존율은 32%이며 N-병기에 따라서 보면 N2 병기는 43%, N3 병기는 13%로 나타났다. 조직학적 소견에 따라 편평상피암 환자군과 비편평 상피암 환자군으로 나눌 때 3년 생존율은 각각 34%, 29%로 나타났다. 전이된 임파절 위치에 따라서 분석해보면 경부임파절 전이 환자군과 쇄골상부임파절 전이 환자군은 각각 44%, 17%의 3년 생존율을 나타냈다. 대상 환자 23명중 6명에서 치료후에 원발병소가 나타났는데 3명은 폐장에서, 1명은 식도에서, 다른 2명은 각각 위장과 비인강에서 나타났다. 원발병소의 존재유무에 따른 3년 생존율은 각각 17%, 38%로 예후에 영향을 미치는 것처럼 보였다. 예후인자를 분석해보면 N-병기와 전이된 임파절의 위치가 중요한 예후인자이며 원발병소의 존재유무는 예후와 관계가 있는 것으로 나타났으나 조직학적 소견은 관계가 없는 것으로 나타났다.