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CLINICAL INVESTIGATION **Esophagus**

INFLUENCE OF NUMBER OF METASTATIC LYMPH NODES ON SURVIVAL OF CURATIVE RESECTED THORACIC ESOPHAGEAL CANCER PATIENTS AND VALUE OF RADIOTHERAPY: REPORT OF 549 CASES

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Purpose: To analyze the significance of the number of metastatic lymph nodes on survival with and without the addition of prophylactic postoperative radiotherapy (RT) after radical resection of thoracic esophageal carcinoma.

Methods and Materials: A total of 549 thoracic esophageal squamous cell cancer patients who had undergone radical resection were randomized by the envelope method into a surgery-alone group (S, $n = 275$) and a surgery plus RT group (S+R, $n = 274$). We performed a retrospective review of all patients according to the extent of metastasis. The patients were classified into three groups: Group 1, 269 patients (49.0%) without lymph node involvement; Group 2, 159 patients (29.0%) with one to two positive nodes; and Group 3, 121 patients (22.0%) with three or more positive lymph nodes.

Results: For the same T stage (T3), the 5-year survival rate for Groups 1, 2, and 3 was 50.6%, 29.3%, and 11.7%, respectively ($p = 0.0000$). For patients with Stage III, the 5-year survival rate for Groups 1 (T4N0M0), 2 (T3-T4N1M0), and 3 (T3-T4N2M0) was 58.1%, 30.6%, and 14.4%, respectively ($p = 0.0092$). The 5-year survival rate of the S and S+R groups with positive lymph nodes (Groups 2 and 3) was 17.6% and 34.1% ($p = 0.0378$). In the positive lymph node groups, the incidence of failure by intrathoracic lymph node metastasis and supraclavicular lymph node metastasis in the S+R group (21.5% and 4.6%, respectively) was lower than in the S group (35.9% and 19.7%, respectively; $p < 0.012$). In the negative lymph node group, the incidence of failure by intrathoracic lymph node metastasis in the S and S+R groups was 27.8% and 13.3%, respectively ($p = 0.006$). Hematogenous metastasis was the greatest (27.5%) in Group 3 (three or more positive lymph nodes).

Conclusion: The number of metastatic lymph nodes is one of the important factors affecting the survival of patients with thoracic esophageal carcinoma. In our study, postoperative RT improved the survival of patients with positive lymph nodes. Additionally, postoperative RT reduced the incidence of intrathoracic recurrence and supraclavicular lymph node metastasis for all patients. © 2005 Elsevier Inc.

Esophageal carcinoma, Radical surgery, Postoperative radiotherapy, Number of positive lymph nodes, Metastasis, Survival rate.

INTRODUCTION

Recently, many reports have given conflicting conclusions (1–3) about the influence of the number and extent of positive lymph nodes on the outcomes of esophageal carcinoma patients. It should be noted that the number of positive lymph nodes was a criterion in the 1997 International Union Against Cancer (UICC) (4) staging system for esophageal carcinoma. Consequently, this TNM staging system left something out of the assessment of a patient's prognosis or the need for supplementary treatment. Our objective was to analyze further whether the number of metastatic lymph nodes influences survival of curative resected thoracic esophageal cancer patients. We discussed this previously in Xiao *et al.* (5).

METHODS AND MATERIALS

Clinical data

Between September 1986 and December 1997, 549 patients with esophageal carcinoma who had undergone radical resection were divided randomly, using the envelope method, into two groups: a surgery-alone group (S, $n = 275$) and a surgery plus radiotherapy (RT) group (S+R, $n = 274$). All patients who un-

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Table 1. Clinical characteristics

Characteristic	Group 1 (n = 269)		Group 2 (n = 159)		Group 3 (n = 121)		p
	n	%	*n*	%	*n*	%	
Gender							
Male	202	75.1	120	75.5	103	85.1	0.071
Female	7	24.9	39	24.5	18	14.9	
Age (y)							
<40	16	5.90	7	4.40	3	2.50	0.537
41–50	56	20.8	38	23.9	26	21.5	
51–60	111	41.3	70	44.0	60	49.6	
61–68	86	32.0	44	27.7	32	26.4	
Site							
Upper	46	17.1	20	12.6	6	5.0	0.000
Middle	183	68.0	104	65.4	76	62.8	
Lower	40	14.9	35	22.0	39	32.2	
Length (cm)							
≤5.0	152	56.5	78	49.1	42	34.7	0.000
5.1–7.0	95	35.2	63	39.6	55	45.5	
≥7.0	22	8.20	18	11.3	24	19.8	
Depth of invasion							
T1	4	1.5	1	0.6	1	0.8	0.043
T2	35	13.0	20	12.6	6	5.0	
T3	188	69.9	109	68.6	81	66.9	
T4	42	15.6	29	18.2	33	27.3	
Nodes removed (n)							
≤16	149	55.4	80	50.3	39	32.2	0.000
>16	120	44.6	79	49.7	82	67.8	
Treatment							
S	143	53.2	80	50.3	52	43.0	0.005
S+R	91	33.8	66	41.5	63	52.1	
Not finished	35	13.0	13	8.2	6	5.0	

Abbreviations: S = surgery alone; S+R = surgery plus radiotherapy.

derwent surgery had undergone a complete workup. The preoperative evaluation consisted of a detailed history and physical examination by the assistant resident; complete routine analysis of blood, urine, and stool; and barium swallow, esophagoscopy, chest film, and abdominal ultrasonography. Some patients also underwent thoracic CT from 1986 onward. Later, more and more patients underwent CT, especially since 1997, as the use of CT became generalized. All patients with esophageal cancer who had undergone radical resection were included. Patients meeting the following criteria were randomized by the envelope method: a diagnosis of squamous cell carcinoma confirmed by pathologic evaluation, maximal age of 68 years, tumor at least 4.0 cm, and lesions located in the thoracic segment.

Surgery

Patient selection, surgical approach, and operative procedure were determined by the surgeons. A three-phase abdominothoracic McKeown resection via right thoracotomy using the stomach for esophageal replacement was generally performed for lesions in the upper third of the thoracic segment. For lesions in the mid and lower third, esophagectomy was performed on the left side using the stomach to establish digestive continuation. In each case, the lymph nodes were removed as completely as possible. The juxtatumoral, paraesophageal, superior gastric, left gastric, and paracardial lymph nodes were analyzed individually to arrive at a final stage classification according to the 1997 UICC system. A total of 9700 lymph nodes (median, 17 nodes; range, 2–78 nodes) were dissected for pathologic stage examination using hematoxylin-eosin staining.

A retrospective review of all patients with resected esophageal carcinoma according to the extent of metastasis was performed. All the patients were classified into three groups: Group 1, 269 patients (49.0%) without positive lymph nodes; Group 2, 159 patients (29.0%) with one to two positive lymph nodes; and Group 3, 121 patients (22.0%) with three or more positive lymph nodes (Table 1).

Postoperative RT

Radiotherapy was begun 3–4 weeks after surgery using 6–8-MeV photons delivered by a linear accelerator. The initial portal was cephalad and encompassed the bilateral supraclavicular areas, with the tip of the cricoid cartilage serving as the upper border and the point 1.0 cm below the lower margin of the clavicles serving as the lower border. This field was extended caudad to include the entire mediastinum, site of anastomosis, and left epiploic and paracardiac lymphatics (T3–T12 or L1). An initial midplane dose of 40 Gy in 20 fractions was delivered within 4 weeks. Next, two horizontal portals (5.0 cm wide) were used to administer 20 Gy, also in 20 fractions. 50 Gy was delivered to the supraclavicular areas. The spinal cord dose was kept to not more than 40 Gy in 20 fractions within 4 weeks. The total dose to the mid-plane was 60 Gy in 30 fractions within 6 weeks. The dose was kept to <50 Gy in 25 fractions within 5 weeks if the entire transpositioned stomach had to be included in the same area of RT.