

Esophageal Surgery Division

Introduction

More than 300 new patients with esophageal carcinoma were admitted to the National Cancer Center Hospital in 2003. Treatments were determined by the stage of the tumor. This division cooperates with the Gastrointestinal Oncology Division, the Radiation Oncology Division and other divisions to use a multidisciplinary team approach to treating patients. 56 patients underwent endoscopic esophageal mucosal resection by the Endoscopy Division in 2003. 113 patients received chemo-radiotherapy as their primary treatment. We have also cooperated with the Head and Neck Surgery Division for cervical esophageal carcinomas and with the Gastric Surgery Division for tumors in the esophagogastric junction. In Japan, squamous cell carcinomas constitute the largest proportion of esophageal tumors, and the proportion of adenocarcinomas was still 3% in our institution in 2003.

Routine Activities

The Esophageal Surgery Division consists of three staff surgeons, one chief resident and three rotating senior residents. A division conference is held every week in which surgeons, medical oncologists, radiation oncologists, endoscopists, radiologists, and pathologists who are involved in the treatment of esophageal diseases meet and discuss the diagnosis, staging, and treatment plans for patients with esophageal tumors. A monthly conference, clinical diagnosis, and pathology demonstration of the esophagus is held to discuss various themes.

Every week, three patients with esophageal carcinoma undergo surgery. A hundred and twenty-eight patients underwent esophagectomy with 2 operation-related deaths in 2003. A curative resection was completed for 96% of the patients undergoing esophagectomy reflecting strict preoperative staging. Ten patients received salvage esophagectomy after failure of chemo-radiotherapy as their primary treatment. Fourteen patients received esophagectomy after preoperative chemotherapy.

Since 1982, the area of lymph node dissection has been extended to the whole upper mediastinum and

neck in addition to the lower mediastinum and abdomen. The three-field dissection was completed in 91% of transthoracic esophagectomy.

Research Activities

We performed a multicenter randomized controlled trial (JCOG 9204) to determine whether postoperative adjuvant chemotherapy improves outcome in patients with esophageal squamous cell carcinoma undergoing radical surgery. The 5-year disease-free survival rate was 45% with surgery alone, and 55% with surgery plus chemotherapy including two courses of cisplatin and fluorouracil (one-sided log-rank, $P = .037$). The 5-year overall survival rate was 52% and 61%, respectively ($P = .13$). Risk reduction by postoperative chemotherapy was remarkable in the subgroup with lymph node metastasis. Postoperative adjuvant chemotherapy with cisplatin and fluorouracil is better able to prevent relapse in patients with esophageal cancer than surgery alone. The efficacy and toxicity of chemo-radiotherapy with 5FU and cisplatin in patients with Stage I esophageal squamous cell carcinoma were studied by a multicenter randomized controlled trial (JCOG 9708). CR rate was 96%. The 2-year overall survival rate was 93%, and the 2-year recurrence-free survival rate was 75%. This regimen could be considered as a test arm of phase III study to compare with surgery in patients with Stage I esophageal squamous cell carcinoma.

Clinical T1 and T2 tumors may be good candidates for complete resection of the lesion and removal of metastatic nodes by extensive lymphadenectomy. The efficacy of esophagectomy with 3-field lymph node dissection for patients with clinical T1 and T2 squamous cell carcinoma of the thoracic esophagus was evaluated. The overall 5-year survival rate was 61%. Number of lymph node metastases most strongly affected survival. Esophagectomy with 3-field lymph node dissection accomplishes a high feasibility of complete resection of primary tumor and removal of metastatic nodes.

Pulmonary complications, a major component of morbidity and mortality, were studied after esophagectomy with 3-field lymph node dissection. Pulmonary complications developed in 7.3% of

the patients and 62.4% of all mortality were caused by pulmonary complications. Pulmonary complications can be kept at a low level, but still account for most of the mortality after 3-field lymph node dissection. The incidence of serious infection and respiratory failure was significantly higher in secondary pulmonary morbidities as compared with primary pulmonary morbidities and was associated with a higher death rate (47.1% versus 15.8%, $p=0.047$). Primary and secondary pulmonary complications are two distinct entities that should be managed differently.

Inactive ALDH2 encoded by ALDH2*1/2*2 and the low-activity form of alcohol dehydrogenase (ADH)-2 encoded by ADH2*1/2*1 enhance the risk for esophageal cancer in Japanese light to heavy drinkers, a significant association that emphasizes the importance of screening tests for inactive ALDH2 based on alcohol flushing. The reliability of a simple questionnaire that asks about both current and past flushing for detecting inactive ALDH2 was evaluated to predict cancer risk based on flushing in a case-control manner. Those who also had ADH2*1/2*1 (both cases and controls) tended not to report current flushing, and those who did not report current flushing (controls only) tended to be heavier drinkers. As

compared with overall never or rare drinking, the cancer risks for drinkers with current or former flushing significantly exceeded the risks for those who had never flushed. The flushing questionnaire may be used in large-scale epidemiological studies as a surrogate marker of ALDH2 genotype to predict individual cancer risk.

Clinical Trials

The trial of postoperative adjuvant chemotherapy after radical esophagectomy (JCOG 9204) revealed better 5-year disease-free survival rate. The next multi-institutional randomized controlled trial comparing preoperative and postoperative chemotherapy with cisplatin and 5-FU with radical esophagectomy (JCOG 9907) is in registration in cooperation with the Gastrointestinal Oncology Division.

The trial of chemoradiotherapy without surgery for a Stage I lesion (JCOG 9708) showed that chemoradiotherapy could be considered as a test arm of phase III study to compare with surgery. The multi-institutional randomized controlled comparison between surgery and chemoradiotherapy for a Stage I lesion is planned for the next trial.

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	2002 (n=102)	2003 (n=129)
Histology		
Squamous cell carcinoma	92	118
Adenocarcinoma	7	3
Others	3	8
Tumor location		
Cervical	4	2
Upper thoracic	16	14
Middle thoracic	40	57
Lower & Junctional	42	56
Clinical TNM Stage		
Stage I	14	22
Stage IIA	18	18
Stage IIB	20	15
Stage III	33	72
Stage IV	17	17
Operative procedure		
Right thoracotomy	89	122
Left thoracotomy	2	2
Transhiatal	6	2
Cervical	2	1
Abdominal	3	2
Salvage esophagectomy	11	10

The Over-all 3-year and 5-year Survival Rates for Patients Who Underwent Esophagectomy (1994-1998)

cTNM Stage	Cumulative survival rate (%)		
	Pts	3-yr	5-yr
cI	85	76.5	72.9
cIIA	55	61.8	45.3
cIIB	49	69.4	52.7
cIII	119	38.6	28.9
cIVA	17	35.3	29.4
cIVB	52	32.7	18.4