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First-Line Chemotherapy Improves the Resection Rate and Long-Term Survival of Locally Advanced (T4, any N, M0) Squamous Cell Carcinoma of the Thoracic Esophagus

Final Report on 163 Consecutive Patients With 5-Year Follow-Up

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Objective

The objective of this prospective, nonrandomized study was to evaluate the immediate and long-term results of first-line chemotherapy and possible surgery in locally advanced, presumably T4 squamous cell esophageal cancer.

Summary Background Data

Locally advanced esophageal cancer is rarely operable and has a dismal prognosis. For this reason, neoadjuvant cytoreductive treatments are more and more frequently used with the aim of downstaging the tumor, increasing the resection rate, and possibly improving survival.

Methods

From January 1983 to December 1991, 163 consecutive patients with a presumedly T4 squamous cell carcinoma of the thoracic esophagus (group A) received on average 2.5 cycles (range, 1–6) of first-line chemotherapy with cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 per day, in continuous infusion from day 1 through day 5). Chemotherapy was followed by surgery when adequate downstaging of the tumor was obtained.

Results

Chemotherapy toxicity was WHO grade 0 to 2 in 80% of cases, but 3 toxic deaths (1.9%) occurred. Restaging suggested a downstaging of the tumor in 101 of 163 patients (62%), but only 85 patients (52%) underwent resection surgery; it was complete or R0 in 52 (32%) and incomplete or R1–2 in 33. Overall postoperative mortality was 11.7% (10 of 85), morbidity 41% (35 of 85). Complete pathologic response was documented in 6 patients, and significant downstaging to pStage I, IIA, or IIB occurred in 25 more patients. The overall 5-year survival was 11% (median, 11 months). After resection surgery, the 5-year survival was 20% (median, 16 months); none of the nonresponders survived 4 years after palliative treatments without resection (median survival, 5 months). The 5-year survival rate of the 52 patients undergoing an R0 resection was 29% (median, 23 months). Stratifying patients according to the R, pT, pN, and pStage classifications, the survival curves were comparable to the corresponding data obtained in the 587 group B patients with "potentially resectable" esophageal cancer who underwent surgery alone during the same period. Furthermore, the results were improved in comparison with 136 previous or subsequent patients with a locally advanced tumor who did not undergo neoadjuvant treatments (group C). In these patients, the R0 resection rate was 7%, and the overall 5-year survival was 3% (median, 5 months).

Conclusion

Although nonrandomized, these results suggest that in locally advanced esophageal carcinoma, first-line chemotherapy increases the resection rate and improves the overall long-term survival. In responding patients who undergo R0 resection surgery, the prognosis depends on the final pathologic stage and not on the initial pretreatment stage.

Until a few decades ago, the results of esophageal cancer therapy were discouraging: resection surgery was possible only in a minority of patients, postoperative mortality was >30%, and cure was rarely mentioned.[1–3] Recent diagnostic and therapeutic advances have improved the short-term prognosis for esophageal tumors, especially as a result of reduced postoperative mortality.[4] At present, esophagectomy is the treatment of choice in suitable patients, as it gives the best functional results and the only hope of cure. However, the overall long-term results of surgical treatment for cancer of the esophagus are still poor, mostly because it is generally diagnosed late.[5,6]

Between 1980 and 1995, 2285 squamous cell carcinomas of the esophagus were observed at the Center for the Diseases of the Esophagus of the Veneto Region. Of these patients, 543 (24%) had a locally advanced, T4 tumor documented by pretreatment workup (personal unpublished data). At this stage, only a palliative treatment is feasible, and the mean survival time is only 3 to 5 months.[7–9]

Because palliative procedures offer only a minor benefit to patients who cannot undergo resection surgery, we performed a prospective study of first-line chemotherapy with the aim of downstaging locally advanced, unresectable T4 esophageal cancer and making it resectable. We used the cisplatin–fluorouracil combination, as it was reported to produce an objective tumor regression in 35% to 70% of patients by Hellerstein et al.[10] and by other subsequent authors.[11–18]

We report herein the final results of a prospective, nonrandomized, single-institution study of first-line chemotherapy possibly followed by surgery that was carried out between 1983 and 1991 in patients with locally advanced, presumably T4 squamous cell carcinoma (SCC) of the thoracic esophagus. The goals of the study were to evaluate the toxicity and activity of the chemotherapy regimen, the overall resection rate and the rate of complete tumor resections, postoperative morbidity and mortality, and survival time.

PATIENTS AND METHODS

From January 1983 to December 1991, patients with locally advanced, presumably T4 SCC of the thoracic esophagus were administered a cisplatin–fluorouracil combination followed by surgery whenever possible. One hundred sixty-three consecutive patients satisfying the following selection criteria entered the study and were defined as group A: 1) biopsy-proven SCC of the thoracic esophagus (*i.e.*, located below the cervicothoracic inlet and above the gastroesophageal junction; 2) clinical tumor stage: presumably T4, any N, M0 according to the latest UICC classification[19]; 3) patients with tracheobronchial

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or mediastinal fistula were excluded; 4) age <75 years; 5) Karnofsky performance status >60 and general condition permitting for both chemotherapy and surgery; 6) no malignancies diagnosed during the 5 years preceding the diagnosis of the esophageal cancer, excluding in situ carcinoma of the cervix and cutaneous basal cell tumors; 7) no prior chemotherapy, radiation therapy, or surgery for the esophageal cancer; and 8) informed consent obtained. All the patients entered in the study had initially been considered unfit for complete tumor resection by the same team of surgeons who performed the operation if they responded to chemotherapy.

One hundred thirty more patients with a T4, M0 SCC of the thoracic esophagus did not satisfy the selection criteria of the study for the following reasons: esophagorespiratory fistula (29), esophagomediastinal fistula (17), advanced age (12), low Karnofsky performance status or concomitant diseases (53), previous or synchronous malignancies in other organs (9), prior chemotherapy or radiation therapy for the esophageal cancer (7), and informed consent denied (3).

The primary goal of the study was to evaluate the treatment's efficacy in improving survival. Secondary goals were to evaluate its activity in downstaging the tumor, the surgical resection rate, the toxicity of chemotherapy, the morbidity and mortality after surgery, and the rates of local and at-distance control of the disease. All patients have now had follow-up of at least 5 years and have been evaluated for treatment results. Patient and tumor characteristics are shown in Table 1.

Pretreatment workup showed that the tumor infiltrated or caused a rigid encagement–indentation of the tracheobronchial tree in 88 patients (54%); infiltrated the recurrent laryngeal nerve, causing dysphonia in 23 (14%); infiltrated the aorta in 10 (6%); and caused mediastinal spread-out in 42 (26%). As for the tracheobronchial tree, biopsy-proven infiltration was present in 21 patients, gross infiltration (no biopsy taken) in 10, and rigid encagement–indentation in 57. In all patients the chance of performing a complete R0 resection was very unlikely. Overall, at least part of the tumor was located behind the tracheobronchial tree (*i.e.*, at or above the tracheal bifurcation) in 85% of cases.

The results of the present study (group A patients) were compared with those obtained in 587 patients retrospectively selected from our database who fulfilled the following selection criteria (group B patients): 1) same observation period (January 1983 to December 1991); 2) histologically proven SCC of the thoracic esophagus; 3) clinical stage below T4 (''potentially resectable'' tumor); 4) no distant visceral metastasis; 5) no concomitant diseases contraindicating surgery; 6) no malignancies diagnosed during the 5 years preceding the diagnosis of esophageal cancer; and 7) no neoadjuvant chemotherapy or radiation therapy given before surgery. Group B patients had a significantly better Karnofsky performance status and a significantly more favorable tumor location (*i.e.*, fewer tumors located at or above the tracheal bifurcation) than group A patients (see Table 1).

Table 1. PATIENT AND TUMOR CHARACTERISTICS IN GROUP A (LOCALLY ADVANCED TUMOR, TREATED WITH FIRST LINE CHEMOTHERAPY AND POSSIBLE SURGERY) AND IN GROUP B ("POTENTIALLY RESECTABLE" TUMOR, TREATED WITH SURGERY ONLY)

	Group A	Group B	p
Number of patients	163	587	
Mean age (yr) (range)	56 (35–75)	59 (32–85)	
Sex (male/female)	138/25	474/113	0.254
Karnofsky Performance Status [number (%)]			0.005
100–90	53 (32.6)	278 (47.4)	
80–70	78 (47.8)	234 (39.8)	
60	32 (19.6)	75 (12.8)	
Histology [number (%)]			0.071
Squamous cell, G1	34 (21)	141 (24)	
Squamous cell, G2	98 (60)	295 (50)	
Squamous cell, G3	31 (19)	151 (26)	
Tumor location [number (%)]			0.001
Upper thoracic	64 (39)	129 (22)	
Mid-thoracic	76 (47)	269 (46)	
Lower thoracic	23 (14)	189 (32)	

The results were also compared with those obtained in 136 patients with a clinical stage T4 (*i.e.*, locally advanced) SCC of the thoracic esophagus who were observed before or after the study period and who were retrospectively selected from our database using the same selection criteria adopted for group A patients. These patients were defined as group C. The two groups were comparable in terms of sex ($p = 0.514$), Karnofsky performance status ($p = 0.109$), tumor histologic grading ($p = 0.09$), and tumor location ($p = 0.836$).

Chemotherapy

The treatment schedule consisted of cisplatin 100 mg/m^2 administered intravenously with hyperhydration on day 1 and 5-fluorouracil 1000 mg/m^2 per day in continuous intravenous infusion for 5 days. The course was repeated on days 21 and 43. The serotonin receptor-3 antagonists were not available at the time of the study, and as antiemetics we used metoclopramide, diazepam, and dexamethasone.

Toxicity was graded according to WHO guidelines.[20]

In the presence of a white blood cell count $<4000/mm^3$ or platelets $<100,000/mm^3$, the next course of chemotherapy was delayed until bone marrow recovery took place. Treatment was postponed by 8 days in the case of grade 3 mucositis or grade 1 or 2 renal toxicity. Treatment was stopped if cardiotoxicity or renal toxicity greater than grade 2 occurred.

All the patients were included in response analysis. Symptomatic response to chemotherapy was not considered; however, objective tumor response was evaluated according to the restaging protocol, outlined in the evaluation protocols section below.

Surgical Procedures

In the presence of adequate tumor downstaging, suggesting that the tumor had become potentially resectable, surgery was planned 3 to 4 weeks after completion of the last chemotherapy course. Before surgery, a second risk analysis was performed to ensure the medical operability of patients.

At least 6 to 8 cm of healthy esophagus were resected above the proximal edge of the tumor to avoid neoplastic involvement of the section margin. A right transthoracic approach was used in conjunction with laparotomy and a left cervical incision, when indicated. Lymph node dissection included routinely the periesophageal, infracarinal, posterior mediastinal, paracardial, left gastric, and celiac nodes. Alimentary tract reconstruction was performed during the same operative session, preferably using the stomach. Complete tumor resection was defined as R0 resection; incomplete resections, with microscopic or gross residual disease, were defined as R1–2 resections.

Postoperative mortality was defined as any death occurring before the patient's discharge, independent of the length of time elapsed after surgery, or after discharge if there was any relation with the operation itself. We included among anastomotic leaks both radiologic leaks and those causing local or systemic signs of sepsis. Pneumonia, atelectasis, respiratory failure, and adult respiratory distress syndrome were included among respiratory complications. Acute myocardial infarction, severe arrhythmias, cardiovascular failure, and acute cerebrovascular accident were included among cardiovascular complications.

Evaluation Protocols

Initial pretreatment evaluation included a thorough analysis of the patient's past medical history, a physical examination, complete blood cell and platelet counts, analysis of serum electrolytes, urinalysis, and evaluation of renal (blood urea nitrogen, creatinine), liver (sGOT, sGPT, sALP), pulmonary, and cardiac functions. During chemotherapy, complete blood cell and platelet counts, serum electrolytes, and renal and liver function were monitored before every cycle and repeated after a week if altered.

Clinical tumor stage was routinely evaluated by means of chest x-ray, barium swallow, esophagogastroscopy with biopsies, tracheobronchoscopy, head and neck examination, computed tomography (CT) scan of the chest and upper abdomen, and ultrasonography of the neck. Magnetic resonance imaging (MRI) and endoscopic ultrasonography were used in some of the more recent patients. Tumor invasion into the tracheobronchial tree was defined as evidence of biopsy-proven or macroscopic infiltration by bronchoscopy (true T4), or rigid encagement–indentation (potential T4) by bronchoscopy and CT scan. Invasion of the aorta was assumed if the CT scan or MRI showed 90° or greater contact, with obliteration of the fatty plane between the esophagus and the aorta.[21]

Restaging of esophageal cancer was performed 20 days after completion of the third course of chemotherapy, repeating the pretreatment workup. Complete response was defined as disappearance of any tumor evidence on barium esophagogram, endoscopies with biopsy, and CT scan. Partial response was defined as a tumor regression, with downstaging of the T category according to the TNM staging system, without evidence of new lesions or progression of any known lesion. Surgery was planned when restaging documented tumor regression, with a downstaging of the tumor suggesting that a potentially complete resection had become possible.

After surgery, all patients were monitored to detect local or at-distance neoplastic recurrence every 2 to 4 months during the first year and every 4 to 6 months afterward. Follow-up evaluations included a physical examination, hematologic tests, chest x-ray, barium esophagogram alternating with esophagoscopy, tracheobronchoscopy, and ultrasonography of the neck and upper abdomen. CT scan of the chest and upper abdomen was performed every 6 months to 1 year, or more frequently if clinically indicated.

Statistics

Beginning in 1980, data for any esophageal cancer patients observed at our center were collected and entered prospectively into a dedicated database. In all patients, both the clinical tumor stage and the pathologic stage were reassessed using the most recent UICC TNM criteria.[19]

Differences between groups were examined using the chi square test, and p values <0.05 were considered significant. Survival was calculated from the first date of treatment to the date of death or the last date of follow-up.

Table 2. TOXIC EFFECTS OF CHEMOTHERAPY (HIGHEST WHO GRADE) IN THE 407 CYCLES OF CHEMOTHERAPY GIVEN TO THE 163 PATIENTS WITH LOCALLY ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Type of Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	328 (80.5)	55 (13.5)	21 (5.1)	3 (0.7)	—
Granulocytes	328 (80.5)	51 (12.5)	22 (5.4)	5 (1.2)	1 (0.2)*
Platelets	387 (95.0)	6 (1.5)	14 (3.4)	—	—
Renal	295 (72.5)	47 (11.5)	37 (9.1)	28 (6.9)	—
Mucositis	320 (78.6)	40 (9.8)	38 (9.3)	8 (1.9)	1 (0.2)
Hepatic	387 (95.0)	9 (2.2)	11 (2.7)	—	—
Nausea–vomiting	129 (31.7)	72 (17.7)	96 (23.6)	110 (27.0)	—
Cardiac	395 (97.1)	—	5 (1.2)	5 (1.2)	2 (0.5)*

Values are number (%).
* Toxic deaths: one from leukopenic sepsis and two from cardiac toxicity.

Toxic deaths related to chemotherapy and postoperative deaths were included in survival analysis. Survival data were examined using the product limit method of Kaplan and Meier, and differences in survival were assessed using the log rank test. Again, a p value <0.05 was considered statistically significant. All statistical analyses were performed using the SAS statistical package (SAS Institute, Cary, NC).

RESULTS

Chemotherapy

A total of 407 courses of chemotherapy were administered to the 163 group A patients. The mean number of courses per patient was 2.5 (range, 1 to 6). Ten patients received only 1 course of chemotherapy because of WHO grade 3 or 4 toxicity: cardiac in 6 patients (2 deaths), leukopenia-related sepsis in 2 (1 death), renal in 1, and mucositis with diarrhea in 1. As noted above, there were three toxic-related deaths (1.9%). A 25% dose reduction of chemotherapy or a delay of the second or third course of chemotherapy was necessary in 41 patients (25%) because of toxicity. The most common side effects are listed in Table 2. Overall, chemotherapy toxicity was WHO grade 0 to 2 in 80% of cases.

Restaging after chemotherapy suggested an objective tumor response, with significant downstaging making the tumor potentially resectable, in 101 of 163 patients (62%). Of these, 4 refused surgery, 2 were deemed inoperable because of increased operative risk after chemotherapy, and 10 underwent explorative surgery that disclosed an unresectable tumor or distant metastasis.

Surgery After Chemotherapy

Eighty-five of the 163 group A patients (52%) underwent resection surgery. It was complete or R0 in 52 patients (32%) and incomplete in 33 (20%) (Table 3). For patients with pretreatment evidence of tracheobronchial involvement, the R0 resection rate was 19% (4 of 21) in the presence of biopsy-proven infiltration, 30% (3 of 10) in the presence of macroscopic infiltration, and 28% (16 of 57) in the presence of rigid encagement–indentation ($p = 0.495$).

The overall postoperative mortality rate after resection surgery was 11.8%. Five (9.6%) postoperative deaths occurred in the 52 patients undergoing an R0 resection, and 5 (15.1%) in the 33 patients undergoing an R1–2 resection. These mortality data are comparable with those obtained in group B patients, who had a "potentially resectable" SCC of the thoracic esophagus and underwent resection surgery only (see Table 3). In group B patients, the overall postoperative mortality rate was 8.3% ($p =$

Table 3. RESECTION RATE, TYPE OF RESECTION, AND POSTOPERATIVE MORBIDITY AND MORTALITY IN GROUP A AND IN GROUP B

	Group A	Group B	p
Number of patients	163	587	
No resection	78 (47.8)	42 (7.1)	0.001
R0 resection	52 (31.9)	419 (71.4)	0.001
R1–2 resection	33 (20.3)	126 (21.5)	0.736
Total resections	85 (52.2)	545 (92.8)	0.001
Complications after resection surgery			
Overall	35 (41.0)	250 (45.9)	0.510
Anastomotic leak	12 (14.1)	65 (11.9)	0.381
Pulmonary complications	15 (17.6)	78 (14.3)	0.420
Postoperative mortality	10 (11.8)	45 (8.3)	0.287

Values are number (%).

Table 4. HISTOPATHOLOGICAL STAGING IN THE 85 GROUP A PATIENTS WHO UNDERWENT FIRST LINE CHEMOTHERAPY AND RESECTION SURGERY

pT	pN	pM	p Stage	Number of Patients
0	0	0	0	6
1	0	0	I	2
2–3	0	0	IIA	15
1–2	1	0	IIB	8
3	1	0	III	21
4	0	0	III	27
Any T	Any N	1	IV	6

0.287), after R0 resection it was 6.9% (29 of 419; p =0.479), and after R1–2 resection it was 12.7% (16 of 126; p = 0.711).

Major or minor postoperative complications were observed in 41% of group A patients and consisted of 10 cervical anastomotic leaks (14.9%), which were fatal in 2 cases; 2 intrathoracic anastomotic leaks (11.1%), which were fatal in 1 case; 1 partial necrosis of the esophageal substitute; 15 pulmonary complications (17.6%), which were fatal in 7 cases; 6 cases of sepsis; 6 wound infections; 4 cardiovascular complications; 2 cases of chylothorax; 2 acute pulmonary embolisms; 2 cases of bleeding; 1 case of renal failure; 1 case of liver failure; and 1 case of multiple organ failure. The overall postoperative morbidity and the incidence of anastomotic leaks and pulmonary complications were comparable to those observed in group B patients (see Table 3).

The histopathologic tumor stage is shown in Table 4. Complete pathologic response was documented in 6 patients (3.7%), and significant downstaging to pStage I, IIA, or IIB occurred in 25 patients (15.3%). Downstaging to pT3, N1, M0 was documented in 21 more patients (12.9%). The overall response rate, as confirmed by pathologic examination of the operative specimen, was therefore 32% (52 of 163).

After resection surgery, 15 patients received adjuvant chemotherapy, 10 adjuvant radiation therapy, and one adjuvant chemoradiotherapy. Ten of these patients had undergone an R1–2 resection.

Table 5 shows the palliative procedures that were performed in the 78 patients who did not undergo resection surgery. Three patients (3.8%) died as a result of these palliative procedures. Only 2 patients lived more than 2 years: both initially had biopsy-proven infiltration of the tracheobronchial tree, and response to chemotherapy was graded as minimal. In one patient, surgical exploration revealed neoplastic spread-out with infiltration of the prevertebral fascia, mediastinum, and apex of the lung. The patient underwent a bypass procedure and died from cancer after 24 months. In the other patient, a tracheo-esophageal fistula developed after chemotherapy, and a bypass operation was performed; the patient died after 41 months from unknown causes. It is possible that in this patient the actual response to chemotherapy had been underestimated, mistaking fibrosis and necrosis for cancer.

Survival and Failure Patterns

Of the 52 patients who underwent R0 resection surgery, 12 (23%) are still alive and disease-free, 5 (9.6%) died of postoperative complications, 7 (13.5%) died of causes unrelated to the esophageal cancer or its treatment, 15 (29%) died with locoregional tumor recurrence, 4 (7.7%) died with distant metastases, and 8 (15.4%) died with both locoregional recurrence and distant metastases; in 1 case the cause of death was unknown. Five of the 6 patients with complete histologic response are alive and disease-free 60, 67, 80, 91, and 100 months after surgery; the last patient died after 111 months from causes unrelated to esophageal cancer. In contrast, only 2 of the 28 patients who survived an R1–2 resection are alive; the other patients died from locoregional tumor progression, either alone (16 patients) or combined with distant metastases (10 patients).

The overall median survival of all 163 patients was 11 months. The overall survival rate at 1, 3, and 5 years was 43%, 13%, and 11%, respectively. The 52 patients who had an R0 resection achieved a median survival time of 23 months and a 5-year survival rate of 29%. The 33 patients who had an R1–2 resection achieved a median survival time of 11 months and a 5-year survival rate of 6% (Table 6). The difference in survival between patients

Table 5. PALLIATIVE TREATMENT ADOPTED IN THE 78 GROUP A PATIENTS WITH LOCALLY ADVANCED TUMOR WHO FAILED TO RESPOND TO FIRST LINE CHEMOTHERAPY

Treatment	Number
Bypass operation	9*
Endoscopic intubation	22
Explorative thoracotomy + intubation	8
Alimentary gastrostomy	6
Nd:Yag laser therapy	5
Endoscopic dilations	5
Medical supportive care	29

* Cervical esophagogastrostomy, 7; cervical esophagocolostomy, 2. Two bypass operations were performed during explorative thoracotomy.

Table 6. SURVIVAL AFTER RESECTION SURGERY IN GROUP A AND IN GROUP B

	1 yr (%)	2 yr (%)	3 yr (%)	4 yr (%)	5 yr (%)	Median (mo)	p
R0 resection							0.5854
Group A (n = 52)	75	46	33	29	29	23	
Group B (n = 419)	68	44	30	27	24	22	
R1–2 resection							0.3922
Group A (n = 33)	45	12	6	6	6	11	
Group B (n = 126)	36	13	6	6	6	9	

who underwent an R0 resection and those who underwent an R1–2 resection was significant ($p < 0.001$). Stratifying patients according to the type of resection (R0 *vs.* R1–2), the survival data are quite similar to those obtained in group B patients (see Table 6).

The overall survival was comparable in patients with the pretreatment finding of biopsy-proven infiltration (median, 11 months), macroscopic infiltration (median, 6 months), or rigid encagement–indentation (median, 8 months) of the tracheobronchial tree ($p = 0.592$). Also, the survival after R0 resection was comparable in patients with the pretreatment finding of biopsy-proven infiltration (median, 18 months), macroscopic infiltration (median, 27 months), or rigid encagement–indentation (median, 24 months) of the tracheobronchial tree ($p = 0.407$).

Tables 7 and 8 show the survival data of the 52 patients who underwent an R0 resection, stratified by depth of esophageal wall penetration (pT), lymph node status (pN), and pathological TNM stage. Tables 7 and 8 also show that stratifying patients according to the pT, pN, and pStage categories, the survival curves are in all respects comparable to the corresponding data obtained in the 587 group B patients with "potentially resectable" cancer of the thoracic esophagus who underwent surgery only during the same period.

The 78 patients who did not undergo resection surgery had a median survival time of 5 months; the 1-, 3-, and 5-year survival rate was 21%, 3% (1 patient), and 0, respectively. The survival of the 85 patients who underwent resection surgery was significantly better, with a median survival time of 16 months and a 5-year survival rate of 20%, than the survival of patients who did not ($p < 0.0001$).

The results obtained in group A patients compare favorably with those obtained in the 136 group C patients with a locally advanced, presumedly T4 SCC of the thoracic esophagus who did not undergo neoadjuvant treatments. The overall resection rate was 53% *versus* 19% (26 of

Table 7. SURVIVAL AFTER R0 RESECTION IN GROUP A AND IN GROUP B; DATA STRATIFIED BY PATHOLOGICAL DEPTH OF WALL PENETRATION (pT) AND LYMPH NODE STATUS (pN)

	1 yr (%)	2 yr (%)	3 yr (%)	4 yr (%)	5 yr (%)	Median (mo)	p
pT0–pT1							0.8085
Group A (n = 10)	80	60	50	50	50	>60	
Group B (n = 56)	82	68	61	59	54	>60	
pT2							0.8287
Group A (n = 12)	92	58	42	33	33	25	
Group B (n = 106)	73	55	39	33	30	26	
pT3–pT4							0.6025
Group A (n = 30)	67	37	23	20	20	16	
Group B (n = 257)	63	34	20	17	15	15	
pN^-							0.7348
Group A (n = 24)	87	71	54	50	50	>60	
Group B (n = 182)	81	63	49	44	42	35	
pN^+							0.882
Group A (n = 28)	64	25	14	11	11	15	
Group B (n = 237)	58	30	16	13	11	14	

Table 8. SURVIVAL AFTER R0 RESECTION IN GROUP A AND IN GROUP B; DATA STRATIFIED BY PATHOLOGICAL TNM STAGE

	1 yr (%)	2 yr (%)	3 yr (%)	4 yr (%)	5 yr (%)	Median (mo)	p
p stage 0–I							0.8512
Group A (n = 8)	87	75	63	63	63	>60	
Group B (n = 49)	84	75	67	65	59	>60	
p stage IIA							0.945
Group A (n = 14)	86	64	50	43	43	37	
Group B (n = 125)	82	59	43	38	37	30	
p stage IIB							0.6125
Group A (n = 7)	71	29	14	14	14	19	
Group B (n = 42)	67	47	32	27	22	22	
p stage III–IV*							0.4284
Group A (n = 23)	65	30	17	13	13	16	
Group B (n = 203)	56	27	13	11	9	15	

* p stage IV includes patients with distant lymph node metastasis.

136; p = 0.001), and the R0 resection rate was 33% *versus* 6.6% (9 of 136; p = 0.001). In 6 of 9 group C patients who underwent an R0 resection, a patch of pericardium or a segment of the lung had to be resected *en bloc* with the tumor because of direct infiltration, as opposed to none of the 52 group A patients. The overall 1-, 3-, and 5-year survival rate was 43%, 13%, and 11% in group A *versus* 15%, 5%, and 3.6% in group C (p = 0.0001); the overall median survival was 11 months and 5 months, respectively. After resection surgery, the 1-, 3-, and 5-year survival rate was 63%, 22%, and 20% *versus* 40%, 12%, and 12% (p = 0.0296). After an R0 resection, the 1-, 3-, and 5-year survival rate was 75%, 33%, and 29% *versus* 55%, 22%, and 22% (p = 0.245).

Results in Patients Excluded From the Study

Only 5 of the 130 patients with locally advanced SCC of the thoracic esophagus who did not satisfy the selection criteria of the study could undergo an R0 resection. In 3 of the 5 patients, the resection had to be enlarged to include a patch of pericardium or a segment of the lung because of direct tumor infiltration. The overall median survival of these 130 patients was 4 months, with a 1- and 3-year survival of 14% and 3%, respectively.

Discussion

Available data concerning multimodal treatment of locally advanced, T4, M0 esophageal carcinoma are limited,[22–24] mostly because different histologic types and tumor stages have been frequently considered together. The cisplatin–fluorouracil combination is one of the most commonly used chemotherapy regimens for esophageal cancer.[13,15–17,24–28] The toxic effects observed are mucositis, myelotoxicity, and nephrotoxicity. The reported response rate is 49% to 67%, with a complete response rate of 7% to 10%.[16,17,25] Unfortunately, to date there are no reliable criteria to predict response to cytoreductive treatments.[29]

The aim of our study was to assess the activity, toxicity, and efficacy of cisplatin–fluorouracil combination chemotherapy, followed by surgery whenever possible, in patients with locally advanced, presumably unresectable SCC of the thoracic esophagus. This chemotherapy regimen was the most effective in esophageal carcinoma when we started the study. We recorded only a mild toxicity, which was easily manageable. Significant renal dysfunction was observed in <7% of patients, and only 3 (1.8%) toxic deaths occurred. The major dose-limiting toxicities were myelosuppression and mucositis. Comparable data are reported in the literature.[16,17,24,25]

Postoperative morbidity and mortality rates after chemotherapy were comparable to those observed in group B patients, who had a "potentially resectable" tumor and were treated with surgery only. Other studies report that neoadjuvant cisplatin–fluorouracil treatment does not adversely affect the postoperative mortality rate in comparison with patients undergoing surgery alone.[16,17,25,26,30] Postoperative pulmonary complications occurred in nearly 17% of our patients; other studies reported higher rates of pulmonary complications, up to 25%.[31] Therefore, the utmost care should be taken to prevent these complications.

Significant tumor downstaging was thought to be obtained in 101 of the 163 patients (62%) who initially had a tumor that was not eligible for complete tumor resection;

however, a complete histologic response was documented in only 3.7% of our patients (6 of 163). Resection surgery was performed in 52% of cases (85 of 163), and it was potentially curative or R0 in 32% of cases (52 of 163). Comparable data are reported in the literature.[16,17,26,30] The rate of complete R0 resections, the overall survival, and the survival after R0 resections were comparable in patients with the pretreatment finding of biopsy-proven infiltration, macroscopic infiltration, or rigid encagement–indentation of the tracheobronchial tree. These results indirectly demonstrate that clinical staging of T4 esophageal cancer may be considered rather accurate.

The study confirms the results already reported by our group in 1986[12] and by other phase II studies[23,24,26]: first-line chemotherapy produces tumor regression in a significant percentage of patients and makes possible subsequent complete resection surgery in previously unresectable tumors. A significant survival advantage was found in patients who responded to preoperative chemotherapy and who underwent resection surgery (median survival time, 16 months) compared with unresponsive patients who could not be operated on (median survival time, 5 months). The median survival after complete R0 resection was 23 months, and the 5-year survival rate was 29%. Similar results are reported in other retrospective studies performed in locally advanced esophageal tumors.[30] This was also observed in the otherwise negative randomized trials of preoperative chemotherapy *versus* surgery alone that were carried out in patients with "potentially resectable" tumor.[31–36] Because most of our patients who responded to preoperative chemotherapy had gross or microscopic tumor detected on the operative specimen, it should be emphasized that surgery has a central role in the multimodal treatment of esophageal cancer.[29,37,38]

The survival after resection surgery, if stratified by type of resection (R0, R1–2), was comparable to the survival obtained in the corresponding cohorts of group B patients with "potentially resectable" cancer who underwent surgery alone during the same period. The same finding was observed after an R0 resection, when patients were stratified by depth of wall invasion (pT), lymph node status (pN), and pathologic TNM stage. This demonstrates that the prognosis of patients with locally advanced cancer of the esophagus who undergo first-line chemotherapy depends on the final stage that is found on pathologic examination of the operative specimen.

The fact that 50% of our patients with locally advanced esophageal cancer developed local recurrence after first-line chemotherapy and an R0 resection suggests that more aggressive multimodal protocols may be indicated.[39–44]

In conclusion, these results, although nonrandomized, suggest that in locally advanced esophageal carcinoma, first-line chemotherapy increases the resection rate and improves the overall long-term survival. In responding patients who undergo R0 resection surgery, the prognosis appears to depend on the final pathologic tumor stage and is comparable to that of patients with "potentially resectable" cancer who are treated with surgery alone. The results of this study provide additional support for multimodal treatment, including resection surgery, in patients with esophageal cancer.

Acknowledgment

The authors wish to dedicate this paper to Piero De Besi, medical oncologist, who had made substantive contributions to the study and died prematurely in 1992.

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Discussion

PROF. J. WONG (Hong Kong): Thank you very much for the opportunity to discuss this paper. This paper reflects once again the large experience of Professor Peracchia's service and, as usual, there is some useful information from this study that he has presented. He conceded both at the presentation and in the manuscript (which I had the chance to read beforehand) that as this was not a randomized controlled trial, the conclusions drawn are probably not as strong as it could have been if this had the vigor of such a trial. There are a couple of points that should be clarified in the manuscript, although these were not addressed in the presentation. The first is that you equated advanced disease as being unresectable and vice versa, and that potentially curable patients are resectable. By just applying this definition, there would be some, and may be considerable, overlap. Some of the patients, even so-called unresectable, when explored were resectable and vice versa. Therefore, the conclusions drawn depend very much on how large this overlapping group was. If this overlap group is large, then I think your definition of what is advanced, what is unresectable, what is resectable, what is potentially curable, would not be tight and you could not then conclude with conviction. We have done a randomized controlled trial on preoperative chemotherapy *versus* surgery alone, and our overall result is that there is no statistically significant difference in survival; that paper will be coming out in the *Journal of Thoracic and Cardiovascular Surgery,* 114(2):210–219, 1997.

What I would like to ask is, what is the outcome of the nonresponders, and when you add the responders to the nonresponders, was their survival significantly different from the group that had no chemotherapy beforehand? This morning we heard the good results of liver transplant and liver resection