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Induction Chemo-Radiotherapy for Squamous Cell Carcinoma of the Thoracic Esophagus: Long-Term Results of a Phase II Study

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Background: This study was done to evaluate the results of the combined use of chemo- and radiotherapy before surgery in a group of patients with squamous cell esophageal carcinoma after a median follow-up period of more than 5 years.

Methods: Between June 1987 and January 1995, 111 patients with squamous cell carcinoma of the thoracic esophagus were submitted to a preoperative course of radiotherapy (3000 cGy) and chemotherapy (cisplatin and 5-FU) before surgery in the First Division of General Surgery at the University of Verona.

Results: The neoadjuvant treatment was completed in 90.9% of the cases (101/111). After an average of 29 days, 87 patients underwent surgery (operability rate: 78.3%) and, of these, 80 underwent esophagectomy (resectability rate: 91.9%). Histopathologic studies showed no residual disease in the specimen (T0) in 17 cases (21.2%), only microscopic clusters of neoplastic cells within the esophageal wall (Minimal Residual Disease, MRD) in 14 cases (17.5%) and in 5 cases the tumor did not extend beyond the submucosal layer (T1).

The median overall survival time of the 111 patients who were eligible for the study protocol was 14 months, and the 2- and 5-year survival rates were 32.0% and 17.5%, respectively. Kaplan-Meier determination of survival showed a statistically significant difference between the good responders (T0, T1, and MRD) to the neoadjuvant treatment and the remaining cases. The 2- and 5-year survival rates were 50.3% and 34.9%, respectively, in the good responder group compared with 26.7% and 10.7%, respectively, in the other cases, with a median survival time of 24 months vs. 13 months, respectively.

Conclusions: The neoadjuvant treatment showed promising results, especially in the group of patients that had a good response. The identification of these patients may be the key to selecting which patients should be submitted to preoperative radio- and chemotherapy.

Key Words: Esophagus, Carcinoma, Chemotherapy, Radiotherapy, Surgery.

In an attempt to improve the very disappointing results of treatment of esophageal carcinoma, several trials have been conducted over the past decade according to therapeutic protocols in which chemotherapy, radiotherapy, and surgery have been used in various combinations.

Combined chemo- and radiotherapy before surgery (induction or neoadjuvant therapy) is the treatment which perhaps has yielded the best results, with survival rates that are often better than those obtained by surgery or radiotherapy alone[1–9] and many phase II studies have demonstrated their feasibility and promising results.

In a previous study,[10] we described our preliminary experience with the treatment of squamous cell carcinoma of the thoracic esophagus on the basis of a protocol using preoperative chemo- and radiotherapy.

The present article reports the final results of this study with particular reference to the patients' compliance with such treatment, the associated long-term mor-

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bidity, and the modes and characteristics of recurrence of the disease.

MATERIALS AND METHODS

Patient Selection Criteria and Study Period

From January 1987 to January 1995, a total of 415 patients who suffered from squamous cell carcinoma of the thoracic esophagus were observed in our department and assessed for inclusion in the study protocol.

The most important inclusion criteria were: histologically proven squamous cell carcinoma, age less than 70 years old, a Karnofsky Performance Status >60, possibility of follow-up, and the consent of the patient. The exclusion criteria of the 304 patients not enrolled in the study are described in Table 1. In particular, patients with squamous cell carcinoma located in the cervical esophagus and hypopharynx, as well patients with remote metastases (stage IV), were excluded from the study.

The eligible 111 patients were recruited for the study and followed up from June 1987 to February 1998.

Pretreatment Evaluation and Staging

All patients were assessed at entry by having a full blood chemistry investigation, chest roentgenograms, a study of respiratory function with global spirometry, and a cardiological evaluation with ECG.

For the purpose of tumor staging, each patient underwent upper digestive roentgenography, esophagogastroscopy and tracheobronchoscopy, esophageal ultrasonography, thoracoabdominal computer tomography (CT) scans, and transcutaneous cervical ultrasonography. Bone scintigraphy was performed only when indicated by the patient's symptoms.

The same investigations were performed at restaging, on average 1–2 weeks after the end of preoperative treatment, to assess the response to induction therapy and the effective operability of the patient.

All patients were staged according to the clinical and pathological criteria of the UICC TNM classification system.[11] Moreover, patients with complete disappearance of the malignancy (T0), those with residual tumor confined to the more superficial layers of the wall (T1), or those with residual microscopic clusters of neoplastic cells (MRD), were regarded as "good responders."

TABLE 1. *Exclusion criteria * in 304 patients not enrolled in the study*

	No. cases
Distant metastasis	184
Tracheo-esophageal fistula	38
Age >70 years	20
SCC of hypopharynx and/or cervical esophagus	16
No possibility of follow-up	12
Contraindications chemotherapy	10
Surgery only (EEC, esophageal rupture)	7
Karnofsky Performance status <60	7
Absence of consent	5
Previous history of secondary malignancy	5

* The most important cause was considered; SCC, squamous cell carcinoma.

Treatment Plan

The treatment plan has already been described in detail in our previous study.[10]

The chemotherapy consisted of two courses of cisplatin (CDDP) and 5-Fluorouracil (5-FU). 5-FU was administered intravenously in doses of 1000 $mg \cdot m^{-2} \cdot day^{-1}$ on days 1–4 and 29–32, CDDP in doses of 100 $mg \cdot m^{-2} \cdot day^{-1}$ on days 1 and 29. Toxicity was monitored and treatment modified on the basis of the findings of hematological, renal, or gastrointestinal toxicity.

Radiotherapy was initiated concurrently on the first day of chemotherapy. Parallel opposing portals were used to deliver a total midpalmar dose of 30 Gy with a daily fraction of 2.0 Gy. The radiation field was based on a practical barium swallow with chest computed tomography (CT) scan to cover the primary tumor with margins of at least 5.5 cm above and below the lesion.

The surgical resection was scheduled at least 21 days after the end of the second course of chemotherapy. The aim of the resection was complete extirpation of the tumor in all cases. The choice of surgical technique was generally dictated by the site and extent of the tumor. In the case of lesions of the lower third, a subtotal esophagectomy was performed with an intrathoracic anastomosis via the abdominal and right thoracic route. In the case of tumors located in the middle or upper third, or both, an esophagectomy with cervical anastomosis was performed via the right thoracic, abdominal, and cervical route.

The esophageal resection was combined with a mediastinal and upper abdominal lymphadenectomy in all cases. A cervical lymphadenectomy was carried out only in cases of carcinoma of the supracarinal thoracic esophagus with clinical and ultrasound evidence of cervical lymphadenopathy.

Only in patients with poor respiratory function or a compromised general medical condition was a transhiatal esophagectomy performed and regarded in all cases as a palliative resection, inasmuch as, in our opinion, lymphadenectomy would invariably be of only limited value in this type of resection.

Gastrointestinal continuity was restored by a gastric transposition. A coloplasty was used only in patients with previous gastric surgery or concomitant gastric disease.

All patients received a tube jejunostomy for postoperative alimentation.

In patients with unresectable disease or with any form of contraindication to surgical resection, an endoscopic prosthesis was inserted, or a surgical bypass was constructed.

Further postoperative chemotherapy and/or radiotherapy (which consisted of a further course of CDDP and 5-FU and an additional 2000–3000 cGy of radiation) was administered to the following three groups of patients: (1) patients unsuitable for surgery; (2) patients with unresectable disease; and (3) patients who underwent only palliative resection.

Evaluation of the Response and Toxicity After Neoadjuvant Therapy

The evaluation of the response to preoperative therapy was carried out 2–3 weeks after completion of the treatment: the patients' subjective anamnestic findings (improvement of dysphagia, weight recovery) and restaging investigations (esophagogastroscopy with 4–8 biopsies, esophageal roentgenograms, esophageal ultrasonography, CT) were considered. On the basis of these assessments, the patients were assigned to one of three groups:

- *Complete response*: disappearance of dysphagia, no radiological or endoscopic evidence of malignancy;
- *>50% Partial response*: improvement of dysphagia, marked regression of tumor size in both volumetric and longitudinal terms;
- *<50% Partial response-progression*: no improvement of symptoms, only slight reduction or increase in tumor size.

Regarding the evaluation of the toxicity of the neoadjuvant treatment, the Eastern Cooperative Oncology Group criteria were adopted.[12]

Follow-Up and Statistical Analysis

Patients were followed up prospectively in the outpatient clinic, which they attended regularly at least once every 6 months. Examination of the upper gastrointestinal tract by means of endoscopy and thora-abdominal CT scans was performed at 6-month intervals to detect cancer recurrence. There was 100% follow-up of patients until February 1998, with a median follow-up period of 74 months in surviving patients (range: 32–117 months).

Survival data included postoperative mortality whereas the overall survival of the series also included preoperative deaths due to the induction treatment.

The results are presented as 5-year survival rates with 95% confidence intervals. The probability of survival was calculated for the different subgroups according to the Kaplan-Meier method[13] and the respective survival curves were compared using the log rank test.

RESULTS

The clinical and demographic characteristics of the 111 patients are shown in Table 2.

The neoadjuvant treatment was completed in 90.9% of cases (101/111). The causes of discontinuation were: death of the patient in 3 cases (2 due to digestive tract hemorrhage and 1 to severe kidney and medullary failure), severe postchemotherapy toxicity in 6 cases, and voluntary withdrawal of the patient after radiotherapy in 1 case.

The morbidity rate associated with the chemo-radiotherapy was 37%. Table 3 gives details of the complications and the clinical responses observed.

After an average of 29 days (range: 18–63 days) after the second course of chemotherapy, 87 patients underwent surgery (operability rate 78.3%). Twenty-four patients did not undergo operation: 4 died during or after the induction treatment, 5 had a progression of the disease, 6 were judged not suitable for operation due to general medical conditions, and 9 patients refused surgery.

Eighty patients (resectability rate: 91.9%) underwent esophagectomy (Ro resection in 61.2% of the cases). Five patients were unresectable because of local invasion by the tumor of mediastinal structures, and two patients

TABLE 2. *Patients' characteristics*

No. of patients:	111
Mean age (years):	58.4 (range: 41–70)
Male/female:	1/11.7
Average duration of dysphagia (months):	2.6
Performance Status (Karnofsky)	>80 37%
	60–80 63%

Location of cancer		Pre-treatment stage*		
Upper	28 (25.2%)	Stage I	(T1N0)	6 (5.4%)
Middle	49 (44.1%)	Stage IIa		41 (36.9%)
Lower	34 (30.6%)			
			T2N0	13
			T3N0	28
		Stage IIb	(T2N+)	2 (1.8%)
		Stage III		62 (55.8%)
			T3N+	34
			T4N+	28

* EGDS, TBS, EUS, CT (see text).

TABLE 3. *Results of induction radio-chemotherapy in 111 patients*

	Grade 2–3*	Grade 4*
Granulocytopenia/Thrombocytopenia	28 (27.4%)	6 (5.8%)
Esophagitis	6 (5.8%)	3 (2.9%)
Renal failure	10 (9.8%)	—
Nausea/vomiting	35 (34.3%)	—
Grade of response		
Complete (CR)	15 (13.8%)	
Partial >50% (PR >50%)	44 (40.7%)	
Partial <50% (PR <50%)	42 (38.8%)	
Progression (P)	7 (6.4%)	

* According to ECOG criteria (12).

because of unresectable abdominal nodal metastasis. Palliative resection with a residual tumor was performed in 31 patients: 7 received a transhiatal esophagectomy (a palliative procedure), 18 had a neoplastic infiltration of surrounding organs, 5 had unresectable mediastinal lymph node metastasis, and, finally, 1 patient had residual tumor at the proximal esophageal stump.

The median number of dissected lymph nodes after esophagectomy was 18.2 (range: 8–27).

The intraoperative mortality rate was zero, whereas the postoperative hospital mortality amounted to 10.3% (9/87). The major postoperative surgical complications were pulmonary in 16 patients and anastomotic leakage in 22 (17 of 45 cervical anastomosis and 5 of 35 thoracic anastomosis).

Resumption of oral feeding occurred, on average, 13.8 days postoperatively, after radiological evaluation of the digestive tract anastomosis with a water-soluble contrast medium.

According to the indications outlined above, after a mean period of 25.4 days (range: 17–42 days) from the date of discharge, 39 patients (44.8%) underwent subsequent adjuvant treatments (radiotherapy alone in 27 cases and radio- plus chemotherapy in 12).

TABLE 4. *Histologic staging (pTNM) on 88 patients*

Stage 0	(T0N0)	12 (13.6%)
Stage I	(T1N0)	8 (9.0%)
Stage IIa	20 (22.7%)	
	T2N0	10
	T3N0	10
Stage IIb		11 (12.5%)
	T0N+	5
	T1N+	2
	T2N+	4
Stage III		33 (37.5%)
	T3N+	9
	T4N0	6
	T4N+	18
Stage IV	T any N any M1	4 (4.5%)

Eighty-seven patients operated on and 1 autoptic study.

The histological findings, obtained in 88 cases (87 operations and 1 autopsy), are summarized in Table 4.

In 17 cases there was complete remission of the tumor at the esophageal wall level with no residual malignancy (T0); in 5 cases the tumor did not extend beyond the submucosal layer (T1), and only microscopic clusters of neoplastic cells within the esophageal wall (minimal residual disease [MRD]) were found in 14 cases, which were staged according to the outermost layer in which neoplastic cells were found (T1-T2-T3). The downstaging of T after neoadjuvant treatment (Fig. 1), though devoid of statistical significance, shows a substantial reduction of stage with an increase in the number of tumors confined to the most superficial layers of the esophageal wall.

In 47.7% of the cases (42/88), there was nodal involvement and the most commonly involved nodes were those in lower mediastinal and subcarinal stations. In 19 patients diagnosed N1 after clinical staging, the pathological staging did not show any nodal involvement (N0).

In each group, which we regarded as "good responders," we found cases presenting involvement of mediastinal lymph nodes (five in the T0 group, one in the T1 group and four in the MRD group). These tumors were obviously staged as IIb or III according to the T class.

The longest survival period was 122 months obtained in a stage 0 patient (T0/N0). The median overall survival time of the 111 patients eligible for the study protocol was 14 months (Fig. 2), and the 2- and 5-year survival rates were 32.0% and 17.5%, respectively.

Kaplan-Meier determination of survival in relation to the degree of tumor infiltration of the esophageal wall (T) (Fig. 3) shows a significant difference between patients with tumors confined to the innermost layers of the wall (T0-T1-T2) and those with more extensive tumors. The respective 5-year survival rates were 36.5% for T0, 45.7% for T1, 28.6% for T2, 14.0% for T3, and 0% for T4.

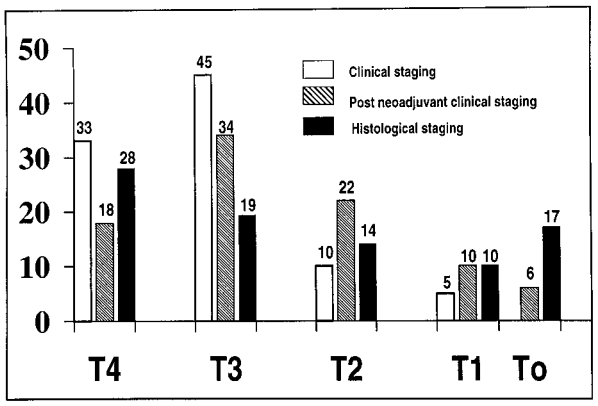

FIG. 1. Neoplastic downstaging after neoadjuvant treatment.

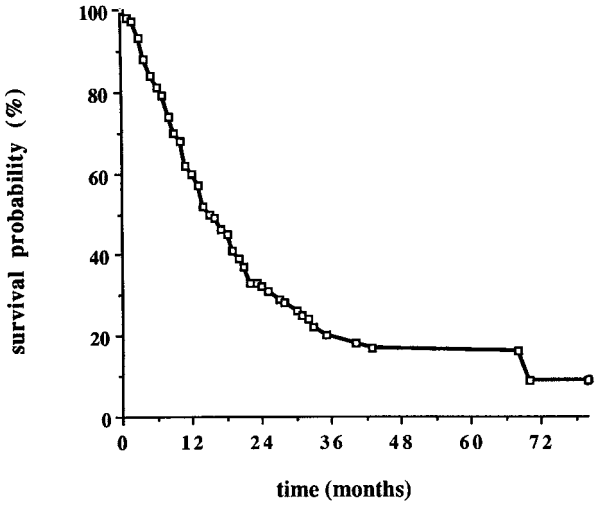

FIG. 2. Kaplan-Meier plot of overall survival (111 patients).

The difference in survival between T0 and T1, which is apparently paradoxical, may be due, in our opinion, to the small number of patients and to the presence, in the T0 group, of as many as five cases with lymph node involvement.

Even more marked are the differences between good responders to the neoadjuvant treatment (T0, T1, and MRD) and the remaining cases (Fig. 4). The 2- and 5-year survival rates were 50.3% and 34.9%, respectively, in the good responder group compared with 26.7% and 10.7%, respectively, in the other cases, with a median survival time of 24 vs. 13 months, respectively.

Survival according to lymph node state confirms better prognosis in N0 patients compared with N1 patients

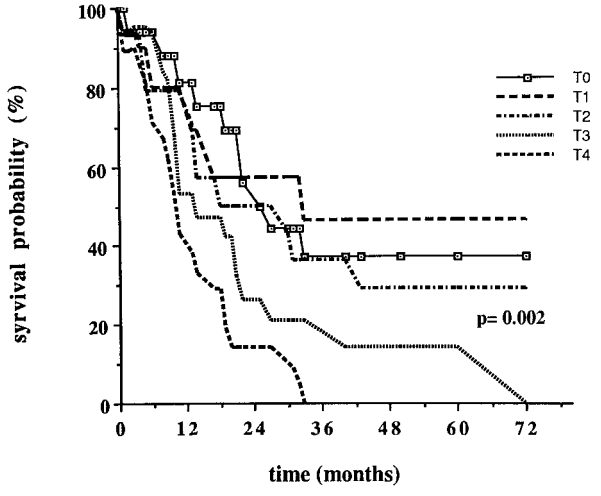

FIG. 3. Kaplan-Meier plot of survival in 80 resected patients (including postoperative deaths) according to the depth of invasion of the tumor in the oesophageal wall.

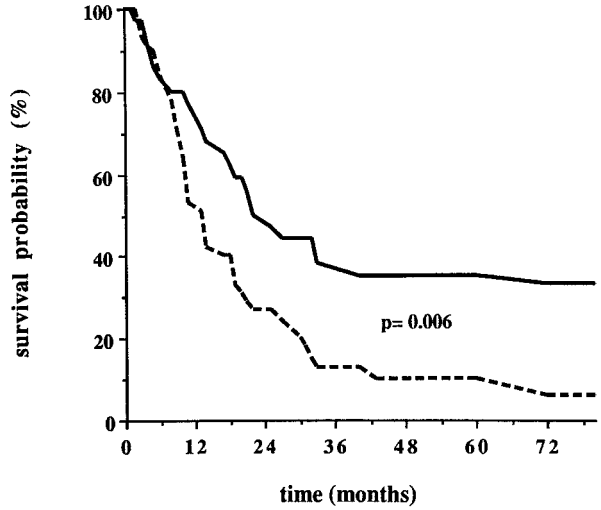

FIG. 4. Kaplan-Meier plot of 80 resected patients (including postoperative deaths) according to the grade of response to the neoadjuvant treatment. Good responders (solid line); bad responders (dashed line).

with 2-year and 5-year survival of 45% and 34%, and 23% and 12%, respectively.

The cause of death in the 57 nonsurvivors was recurrence of the disease in 96.4% of cases (55 patients). In the other two cases, the cause of death was unrelated to the tumor.

The overall incidence of recurrence was 85.9% (61/71 patients). The sites of the recurrences are listed in Table 5.

DISCUSSION

Contrary to what was believed in the past, it is now becoming increasingly clear that the best results in the treatment of squamous cell carcinoma of the esophagus can only be achieved through the combined use of different treatment modalities used in a complementary and synergistic manner.

Among the multimodal treatments available, the combination of radiotherapy, chemotherapy, and surgery has been the one most often adopted and the one which seems to yield the best results.[7,9,14–15]

The trials reported in the literature, almost all phase II, have as a rule been conducted in small patient samples, which were not always homogeneous in terms either of

TABLE 5. *Relapses in 71 resected patients*

Total relapses	85.9% (61/71)
Location	
Loco-regional	32.7% (20/61)
Distant	44.2% (27/61)
Both	22.9% (14/61)

(excluded p.o. deaths)

patient recruitment (stage, general medical condition, etc.) or of histological type, and in many cases were studied over very short follow-up periods.

Though far from definitively clarifying the effective role of such treatment, our single-arm uncontrolled phase II trial conducted in 111 cases that were followed up for a minimum period of almost 2 years, has enabled us to gain strongly indicative impressions and has brought to light new problems which, in our opinion, this type of treatment regimen poses.

The first issue worthy of comment has to do with the mortality and morbidity rates associated with radiotherapy and chemotherapy, which are by no means negligible and necessarily call for great care in the selection of patients for treatment. In our study, three patients died during or after the end of treatment as a result of causes directly related to the treatment itself, and adverse reactions of varying degrees of severity occurred in almost half the cases, which in some patients prompted us to discontinue the treatment or prolong the hospital stay, or both. Our results are comparable with those reported in other studies where the mortality rates range from 0% to 6% and severe morbidity (WHO 3–4) is reported on average in 30% of cases.[4,5,16–18]

Furthermore, though the compliance of study populations is generally very satisfactory, with preoperative treatment completion rates at times exceeding 95%,[4,16,18] we cannot overlook the fact that, by prolonging the hospitalization period, such treatment gives rise to by no means negligible psychological problems for the patient, who fails to perceive any change in the state of his or her disease in the short term.

Postoperative mortality, as reported by other authors[5,6,19] using this type of treatment, was higher if compared to that obtained in a previous experience in patients who underwent surgery (10% vs. 6%). In the last 4 years of this study, the postoperative mortality has been $< 3\%$.

Different from other experiences, the most frequent postoperative complication we had was anastomotic leakage. Preoperative treatment could play an important role, especially for intrathoracic leakages: the incidence of this complication was about double after induction treatment compared with our experience with surgery alone (14.3% versus 6%). The high percentage of cervical leakage probably could be due to the use at the beginning of our experience of stapler. As we showed in a randomized controlled trial conducted in our institution,[20] mechanical anastomosis has a higher incidence of dehiscence compared with the manual anastomosis.

Despite the distinctly positive response to preoperative treatment with a successful downstaging of the lesions, the percentage of curative resections obtained in our experience was lower than the average reported in other studies (90%).[4,5,16–18] Among the likely causes of this difference may be the lower dose of radiotherapy administered in our study.

This factor might have affected the rate of recurrence that in our series was higher than the rates reported in the literature.[4,5,19] In contrast to the data reported by other authors, our study's regional recurrence rates were similar to the remote ones, thus belying what, according to the various rationales, should have been one of the advantages of the preoperative use of radio- and chemotherapy.

Comparing results of the present series to those obtained in an historic control group of 97 patients treated with surgery alone in our same institution between 1976 and 1987, we saw many differences, such as resectability (72% vs. 66.4%), median survival (14 months vs. 9 months), and 3-year survival (42% vs. 13%). Although this comparison of the benefits and advantages is not optimal, we think our present results suggest a trend toward improving the treatment for esophageal cancer and could indicate a new approach to explore.

As reported elsewhere[4,6,8,17,21–22] and in our study, the best results were achieved in the patients regarded as "good responders," i.e., in patients with complete disappearance of the malignancy (T0), those with residual tumor confined to the more superficial layers of the wall (T1), or those with residual microscopic clusters of neoplastic cells (MRD).

On the other hand, regarding the remaining patients who were not operated on because of the progression of the disease or those with residual tumor, unfortunately we can only confirm that the results were no different from those obtained with traditional therapies, with a 5-year survival rate below 5%.

In light of these results, it is reasonable to assume that the early identification of patients with prospects of a good response, as identified by means of molecular markers (*p35*, *HER-2/nen*, *bcl-2*) or instrumental procedures, may be the key to selecting which patients should have neoadjuvant treatment and which are likely to be able to do without surgery which, at present, remains mandatory because there is no substitute.[16,23–24]

Again, from this standpoint, some reflection is warranted with regard to the preoperative staging, which, after induction treatment, proves highly inaccurate. In fact, in addition to not having any valid diagnostic means of recognizing T0 and MRD cases, even for the more advanced forms of malignancy, it is also impossible to differentiate precisely between periesophageal fibrous tissue and the true extent of the tumor. This limitation,

which has already been noted by ourselves[25] and by others,[26–27] has modified our surgical activity. It has prompted us to perform, in the absence of remote metastases or contraindications of a general nature, an exploratory thoracotomy and visual and manual assessment of the macroscopic extent of the tumor in all cases.

The very few prospective randomized trials (phase III) reported in the literature[28–32] confirm some of our results as the important downstaging, and the better long-term results, for patients with complete response.

On the other hand, some of these trials have failed to demonstrate any particular benefit for long-term survival. Bosset et al.,[32] who showed the results of a large multicenter randomized trial, documented no improvement of the overall survival with preoperative radio- and chemotherapy, but only a significant prolongation of disease-free survival. We cannot consider these studies as definitive because of various reasons, such as the excessively short period of follow-up,[31] flaws in methodology such as the pooling of patients with squamous cell carcinoma and adenocarcinoma,[28] and the use of pharmacological and radiation doses lower than those most commonly administered.[30]

CONCLUSIONS

The following conclusions can be drawn from this single-arm phase II study. (1) This phase II study documents the possibility of the application of a neoadjuvant therapy approach to the treatment of squamous cell carcinoma of the esophagus and shows high downstaging rates and promising survival rates, especially in selected groups of patients. Because of the uncontrolled nature of study, it is impossible to draw definite conclusions on the real advantages for the patients. (2) The results, which were not always optimal for mortality and morbidity associated with preoperative treatment, should prompt greater care in the selection of patients, both clinically and psychologically. Patients should be given detailed explanations of all aspects of the treatment. (3) In the light of the shortcomings exhibited by tumor staging after induction treatment, both of overstaging and understaging, we believe that surgery is still the mainstay of therapy for this disease. The role of surgery could be modified after a phase III study compares groups of patients treated with radio- and chemotherapy with or without surgery. (4) The high incidence of recurrences, whether regional or remote, should certainly prompt us to use the radio- and chemotherapy with larger doses, new drugs, or new combinations. (5) Currently, we feel that such treatment must be regarded as experimental and should be administered only in specialized centers, pending definitive validation by the prospective comparative studies presently under way. (6) We think that future efforts have to be dedicated to the preoperative identification of patients labeled “good responders” by molecular markers and/or improving the accuracy of postinduction staging tools when selecting patients who really could benefit from surgical treatment.

REFERENCES

1. Popp MB, Hawley D, Reiseng J. Improved survival in squamous oesophageal cancer. *Arch Surg* 1986;121:1330–5.
2. Austin JC, Postier RG, Elkins RC. Treatment of oesophageal cancer: the continued need for surgical resection. *Am J Surg* 1986;152:592–6.
3. Wolfe WG, Burton GV, Seigler HF, Croker IR, Vaughn A. Early result with combined modality therapy for carcinoma of the oesophagus. *Ann Surg* 1987;205:563–71.
4. Forastiere AA, Orringer MB, Perez-Tamayo C, Urba SG, Zahurak M. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the oesophagus: final report. *J Clin Onc* 1993;11:1118–23.
5. Stahl M, Wilke H, Fink U, Stuschke M, et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced oesophageal cancer: interim analysis of a phase II trial. *J Clin Oncol* 1996;14:829–37.
6. Roth JA, Pass HI, Flanagan MM, Graeber GM, Rosemberg JC, Steinberg S. Randomised clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the oesophagus. *J Thor Cardiovasc Surg* 1988;96:242–8.
7. Tubiana M. The role of local treatment in the cure of cancer. *Eur J Cancer* 1992;28A:2061–9.
8. Swisher SG, Holmes CE, Kelly KH, Doty JE, Zinner MJ, McFadden DW. The role of neoadjuvant therapy in surgical resectable oesophageal cancer. *Arch Surg* 1996;131:819–25.
9. Ide H, Nakamura T, Hayashi K. Neoadjuvant chemotherapy with cisplatinum/5-Fluorouracil/low-dose leucovirin for advanced squamous cell carcinoma of the oesophagus. *Semin Surg Oncol* 1997; 13:263–9.
10. Laterza E, Griso C, Urso SU, de Manzoni G, Malagò Massimo, Oliani C, Cordiano C. Induction therapy for squamous carcinoma of the thoracic oesophagus. *Ann thorac Surg* 1994;57:1126–32.
11. Hermanck P, Sobin LH, eds. *Union Internationale Contre le Cancer. TNM classification of malignant tumors*.; 4th ed. Geneva, Springer-Verlag, 1987.
12. Podolski WJ, Xavier AM, Wittlinger PS, Padmanabhan A. Radiotherapy alone and chemoradiation for nonmetastatic oesophageal carcinoma. *Cancer* 1989;63:2397–403.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457–81.
14. Kelsen DP, Ilson DH. Chemotherapy and combined-modality therapy for oesophageal cancer. *Chest* 1995;107:224S–32S.
15. Vokes EE, Weichselbaum RR. Concomitant chemoradio-therapy: rationale and clinical experience in patients with solid tumours. *J Clin Oncol* 1990;8:911–34.
16. Naunheim KS, Petruska PJ, Roy TS, Andrus CH, Johnson FE, Schlueter JM, Baue AE. Preoperative chemotherapy and radiotherapy for oesophageal carcinoma. *J Thorac Cardiovasc Surg* 1992; 103:887–5.
17. Bedenne L, Milan C, Brriè F, Seitz JF, Renard P, Conroy T, Herr JP. Preoperative radiotherapy and chemotherapy in epidermoid oesophageal cancers. Result of a phase II multicentric trial by the French Foundation for Carcinology of the Digestive Tract (FFDC). *Proc Am Soc Clin Oncol Proc* 1993;199:(Abstr 587).

18. Malhaire JP, Labat JP, Lozac'h P, Simon H, Lucas B, Topart P, Volant A. Preoperative concomitant radiochemotherapy in squamous cell carcinoma of the oesophagus: result of a study of 56 patients. *Int J Rad Oncol Biol Phys* 1996;34:429–37.
19. Kavanagh B, Anscher M, Leopold K, et al. Patterns of failure following combined modality therapy for oesophageal cancer. *Int J Rad Oncol Biol Phys* 1992;24:633–36.
20. Laterza E, de Manzoni G, Veraldi GF, Guglielmi A, and Cordiano C. Manual versus mechanical cervical esophago-gastric anastomosis: a randomised trial. *Eur J Surg* 1999 (in press).
21. Van Raemdonck D, Van Cutsem E, Menten J, Ectors N, Coosemans W, De Leyn P, Lerut T. Induction therapy for clinical T4 oesophageal carcinoma, a plea for continued surgical exploration. *Eur J Car Thor Surg* 1997;11:828–37.
22. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumour regression after preoperative chemoradiotherapy of oesophageal carcinoma: clinicopatologic correlation. *Cancer* 1994; 73:2680–6.
23. Lam KY, Law S, Ma LT. Pre-operative chemotherapy for squamous cell carcinoma of the oesophagus: do histological assessment and p53 over-expression predict chemo-responsiveness? *Eur J Can* 1997;33(8):1221–5.
24. Wu GS, El-Deiry WS. Apoptic death of tumours cell correlates with chemosensitivity, independent of p53 or Bcl-2. *Clin Can Res* 1996;2:623–3.
25. Laterza E, de Manzoni G, Guglielmi A, Rodella L, Tedesco P, Cordiano C. Endoscopic ultrasonography in the staging of oesophageal carcinoma after preoperative and radio- chemotherapy. *Ann Thorac Surg* 1999;67:1466–9.
26. Rosch T, Classen M. Oesophageal carcinoma, in gastroenterologic endosonography. Stuttgart: Georg Thieme Verlag, 1992;45–62.
27. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for oesophageal adenocarcinoma. *N Engl J Med* 1996;15:462–7.
28. Urba SG, Orringer MB, Perez-Tamayo C. Concurrent preoperative chemotherapy and radiation therapy in localised oesophageal adenocarcinoma. *Cancer* 1992;69:285–91.
29. Apinop C, Puttisack P, Preecha N. A prospective study of combined therapy in oesophageal cancer. *Hepato-gastroenterol.* 1994; 41:391–3.
30. Le Prise E, Etienne PL, Meunier B, et al. A randomised study of chemotherapy, radiation therapy, and surgery versus surgery for localised squamous cell carcinoma of the oesophagus. *Cancer* 1994;73:1779–84.
31. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. Multimodality Treatment Plus Surgery Versus Surgery Alone for Oesophageal Squamous Cell Carcinoma. In A. Peracchia, eds. *Recent Advances in Disease of the Oesophagus*. Monduzzi 1995:451–456.
32. Bosset J-F, Gignoux M, Triboulet J-P, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the oesophagus. *NEJM* 1997;337:161–7.