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ORIGINAL ARTICLE

Endoscopic ultrasonography is an independent predictive factor of prognosis in locally advanced esophageal cancer. Results from the randomized FFCD 9102 study from the Fédération Francophone de Cancérologie Digestive

Résultats de l'étude randomisée FFCD 9102 : l'échoendoscopie digestive est un facteur pronostique indépendant chez les patients atteints de cancer de l'œsophage localement invasif

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Summary

Background. — No multivariate study has assessed the independent prognostic role of endoscopic ultrasonography (EUS) in esophageal cancer, even when considering computed tomography (CT).

Objective. — To evaluate the prognostic value of EUS in esophageal cancer before exclusive or preoperative radiochemotherapy.

Methods. — From 1993 to 1999, the FFCD 9102 study enrolled 444 patients who had cancer of the thoracic esophagus, stages T3—4, N0—1 and M0 on CT. The patients received two sessions of chemotherapy in addition to radiotherapy. The 259 patients with objective response and no contraindications for further treatment were randomized to undergo surgery or to continue with radiochemotherapy. EUS was performed in 174 patients enrolled in the trial (mean age: 59 years). Tumor characteristics and lymph node status were prospectively recorded. A Cox statistical model was used to identify any predictive prognostic factors among the clinical, EUS and CT data.

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Results. — In the multivariate analysis, three factors were associated with a poor prognosis: inability to ingest solid food (OR: 1.98; $P = 0.0008$); more than three neoplastic subdiaphragmatic lymph nodes (LN) on EUS (OR: 2.41; $P < 0.0045$) and age > 65 (OR: 1.53; $P < 0.056$). Their prognostic value persisted after adjustment for type of treatment given. Two- and five- year survival rates were 21.5 and 10.5%, respectively, in the presence of three neoplastic subdiaphragmatic LN, and 43 and 30%, respectively, in all other cases.
Conclusion. — Degree of dysphagia, age and presence of neoplastic subdiaphragmatic LN on EUS were independently predictive of the prognosis for locally advanced esophageal cancer. EUS results should be taken into account in future trials.

Résumé
Introduction. — Aucune étude multivariée n'a examiné le rôle pronostique indépendant de l'échoendoscopie digestive (EED) chez les patients atteints de cancer de l'œsophage, en tenant compte des résultats de la tomodensitométrie (TDM).
Objectif. — Evaluer, chez les patients atteints du cancer de l'œsophage, la valeur pronostique de l'EED avant une radiochimiothérapie exclusive ou préopératoire.
Méthodes. — De 1993 à 1999, 444 patients présentant un cancer de l'œsophage thoracique de stade T3—4, N0—1 et M0 sur la TDM ont été inclus dans l'étude 9102 de la FFCD. Les patients ont reçu deux cures de chimiothérapie en plus de la radiothérapie. Les 259 patients présentant une réponse objective et aucune contre-indication pour la poursuite du traitement ont été randomisés en deux groupes : chirurgie ou radiochimiothérapie. Une EED était réalisée chez 174 patients (âge moyen 59 ans). Les caractéristiques tumorales et le statut ganglionnaire ont été notés prospectivement. La recherche de facteurs pronostiques parmi les paramètres cliniques échoendosopiques et tomodensitométriques étaient effectuée avec un modèle de Cox.
Résultats. — A l'analyse multivariée, trois facteurs étaient associés à un mauvais pronostic : l'incapacité d'ingérer des aliments solides (OR : 1,98 ; $p = 0,0008$) ; plus de trois ganglions sous-diaphragmatiques envahis sur l'EED (OR : 2,41 ; $p < 0,0045$) et l'âge supérieur à 65 ans (OR : 1,53 ; $p < 0,056$). Les valeurs pronostiques persistaient après ajustement pour le type de traitement. Les taux de survie à deux et cinq ans étaient respectivement de 21,5 et de 10,2 % en présence de trois ganglions sous-diaphragmatiques envahis et de 43 et de 30 % dans les autres cas.
Conclusion. — L'importance de la dysphagie, de l'âge et de la présence de ganglions sous-diaphragmatiques envahis sur l'EED sont des facteurs indépendants prédictifs du pronostic d'un cancer de l'œsophage localement invasif. Il faut prendre en considération les résultats de l'EED pour les essais à venir.

Introduction

The prognosis for esophageal cancer is poor, with a 5-year survival rate of less than 30% after surgery [1]. However, it has improved with time, mainly because of developments in surgical techniques and adjuvant therapies.

Many prognostic factors have been considered in the choice of therapy, including clinical status [2], age, gender [3], weight loss [4] and dysphagia. The pathological tumor-node-metastasis (pTNM) staging classification is also a good predictor [5,6], but can only be obtained after surgical resection. TNM staging can also be estimated preoperatively by CT [7] and, more recently, by endoscopic ultrasonography (EUS) [5,8—10].

Most of these factors have confirmed their prognostic value in prospective and retrospective studies, but the question of whether new techniques can truly help to identify patients according to their prognosis is still a matter of debate [11,12]. Although it can be assumed that EUS is only a supplementary technique among the various tools for pretherapeutic staging, two recent studies showed that patients investigated by EUS as part of their initial staging of esophageal cancer had a more accurate prognosis than those who did not. The inference is that EUS also allowed for a better choice of therapy, which was not the case with CT [1,13].

There is a good correlation between EUS staging and histopathological examination of the esophagus after surgical resection. Correlation with histopathology may achieve a diagnostic accuracy of 85% for T-stage, and 70—80% for N-stage, cancers [5,8,14,15]. However, these figures may be considered less than ideal. It has also been shown that interobserver agreement is moderate, especially for T2 tumors and lymph nodes located in the superior mediastinum [16,17], although agreement in cases of celiac lymph nodes is better. In spite of these limitations, TNM staging, as estimated by EUS (usTNM), is likely to be a good predictor of the prognosis.

The prognostic significance of EUS results has been suggested in many studies [18—21], but few have taken into account either the already-known factors of prognosis such as clinical features, or CT, which can provide information on parts of the mediastinum not accessible by EUS.

Previous EUS studies only evaluated patients treated by surgery so that usTNM could be readily compared with histopathology. Currently, as many patients are treated by

radiochemotherapy before surgery, downstaging may be observed on EUS. The initial usTNM may then not correspond to the final pTNM. Also, comparisons between EUS and histopathology are not possible after radiochemotherapy as, in this case, EUS may be subject to misinterpretation [22].

At present, four main therapeutic strategies are used for cancers spreading beyond the mucosa: surgical resection, radiochemotherapy alone, adjuvant radiochemotherapy or adjuvant chemotherapy. Several non-randomized prospective and retrospective studies have explored the role of radiochemotherapy, and suggested that this alone might be as effective as radiochemotherapy followed by surgery [23—26]. This is why the Fédération francophone de cancérologie digestive (FFCD) initiated a randomized study comparing radiochemotherapy alone with radiochemotherapy plus surgery in patients with locally advanced resectable cancer (trial FFCD 9102).

Our study was designed to assess the role of EUS as an independent prognostic indicator, while taking into account all known prognostic factors as well as the results of mediastinal CT, even when performed in different centers of varying expertise.

Material and methods

Trial FFCD 9102 aimed to answer the following question: do patients with a potentially operable locally advanced cancer of the esophagus and who respond to induction chemoradiation need surgical resection, or can they be treated with radiochemotherapy alone?

The pretherapeutic workup included routine clinical examination, upper GI endoscopy plus biopsy, thoracic and abdominal CT, barium swallow, chest X-ray and abdominal ultrasound.

The inclusion criteria were: histopathologically confirmed adenocarcinoma or squamous cell carcinoma of the thoracic esophagus; stage T3—T4 and/or N0—N1 on spiral CT scans, according to the Wurtz classification [7]; no contraindications to either surgery or radiochemotherapy and absence of palpable peripheral lymph nodes.

Initial transgastric and transesophageal EUS was performed, using a radial or linear instrument (any Olympus® or Pentax® instrument, Hamburg, Germany), during the preoperative workup at the 38 centers where it was available in France at the time of the study. There was no standardization of how the EUS examination was performed, resulting in the use of different frequencies, instruments and/or intravenous sedation. In fact, EUS was optional in the study. Therefore, as EUS was not considered a routine part of the patient's workup, the decision to perform such an examination was left completely up to the physician. In general, at the time of the study, there was enough data in France to consider this test as offering useful information on patients' resectability. All patients having EUS, for whatever reason, were included in our study.

The degree of extension of the tumor in the esophageal wall was assessed as previously described [14] according to four classifications (usT1—usT4, suggesting the pT aspect of the TNM classification). The endosonographer also had to measure the length, circumference and thickness of the tumor, unless it could not be traversed. Well-rounded, greater than 5 mm in size and hypoechoic lymph nodes were considered neoplastic [14], and were assessed in the mediastinum and celiac areas. The number and maximum size of the lymph nodes were also recorded at these lymphatic sites. In an attempt to replicate the methods used in previously published series [20—27], we grouped lymph nodes a posteriori into two classifications: 0—3 visible neoplastic lymph nodes and greater than three neoplastic lymph nodes.

In cases of non-traversable stenosis, the tumor was classified as T3 at minimum, and Nx if no neoplastic lymph nodes were found above the stenosis.

At the time of the study, fine-needle aspiration (FNA) was not routinely available.

Inclusion in the study was independent of the results of EUS, except where the tumor had clearly spread to an adjacent organ, thereby precluding optimal surgical resection. It was, therefore, possible to include patients with celiac lymph nodes on EUS, but not on CT.

Patients who met the inclusion criteria were registered in the trial and received two courses of chemotherapy (5-FU 800 mg/m^2 per day on days 1—5 and on days 22—26, and cisplatin 75 mg/m^2 on days 2 and 23, or 15 mg/m^2 per day on days 1—5 and on days 22—26). Radiotherapy encompassed the macroscopic tumor and lymph nodes, with 3-cm proximal and distal margins, and a 2-cm radial margin. The use of three to four fields was necessary. Radiotherapy was delivered in two different ways: split-course radiotherapy in two sequences of five daily fractions of 3 Gy, separated by a two-week rest (total dose: 30 Gy) or conventional radiotherapy, delivered in five daily fractions per week, 2 Gy per fraction, for 4—5 weeks (total dose: 45 Gy). The choice of regimen was left to each investigator. After January 1999, only conventional radiotherapy was allowed, in the light of a study having concluded its superiority over split-course regimens [28].

A clinical examination, esophagogram, abdominal ultrasound and chest X-ray were performed as soon as possible after the end of radiotherapy to assess clinical response. Positron emission tomography (PET) was not available at the time of the study.

When an objective response (decrease in tumor size greater than 50%) or improvement in dysphagia was observed, the patient was randomized to receive either surgical resection (arm A) or further radiochemotherapy (arm B), delivering 20 Gy (conventional regimen) or 15 Gy (split-course). In cases of no response, no improvement in dysphagia or a grade-4 toxicity (according to WHO classification), the patients were not randomized and their therapy was freely determined by the physician (usually the oncologist). However, surgery was generally recommended in the protocol. The pathology report determined whether or not the resection was curative, specifying whether there was no residual tumor, microscopic remnants or macroscopic tumor.

Follow-up was performed every three months, and included clinical evaluation, standard endoscopy with biopsy, barium swallow, thoracic CT and abdominal ultrasonography, until death or the study endpoint (30 June 2001) EUS was optional.

The study was designed to establish that arms A and B were equivalent if the two-year survival-rate difference was less than 10% between groups. With alpha and beta errors of 0.05 and 0.20, respectively, the calculated number of patients it needed to randomize was 360. As it was estimated that 25% of the registered patients would not be randomized, the total number of recruited patients had to be 500. An interim analysis, performed in November 2000, showed that the study should be stopped before reaching this figure because of a tendency favoring the non-surgical arm. Results have recently been published.

The study was approved by the Burgundy Ethics Comittee (comité de protection des personnes se prêtant à la recherche biomédicale de Bourgogne, Dijon, France) and patients gave their informed consent before being included in the study.

The *statistical analysis* was performed using the BMDP Statistical Software package. Survival curves were assessed using the Kaplan—Meier method, and comparisons were made by log-rank tests. Multivariate analysis was performed with a Cox regression model on variables already known to be potentially prognostic: age, gender, weight loss, degree of dysphagia, neoplastic lymph nodes and tumor length on CT. All EUS variables significant at $P < 0.25$ in the univariate analysis were also included. Adjustments were always made for center accrual and type of treatment given. This

kind of analysis enabled assessment of the prognostic value of the tested variables without having to perform subgroup low-power analyses. The level of significance used was $P < 0.10$ in the multivariate analysis.

Results

From 1993 to 1999, 444 patients were registered in the FFCD 9102 trial, and 259 were randomized after confirmation of eligibility criteria, including an objective response. The results of this study have already been published [29,30], and showed no statistical differences in survival at five years ($P = 0.44$).

Among the 444 patients registered, an initial EUS examination was performed in 174 patients (mean age 59 ± 9.1 years; range 34—78). Among the 259 patients who were eligible and then randomized, 104 had benefited from EUS examination; an additional 70 EUS examinations were also available from the 185 non-randomized eligible patients, as well as survival data, which were included according to the study protocol.

Table 1 presents the distribution of the 174 patients on inclusion into the study, according to clinical, CT and EUS data.

Univariate analysis (Tables 2 and 3)

Only an inability to ingest solid food was significantly predictive of prognosis among the clinical variables ($P < 0.002$). No CT variable was predictive. Among EUS variables, transmural extent was not predictive, but the presence of neoplastic lymph nodes was significantly predictive of a poor prognosis, especially when patients with neoplastic mediastinal lymph nodes and those with less than three neoplastic celiac lymph nodes were grouped together (similar odds ratios; data not shown in Table 3).

Table 2 Univariate analysis of clinical CT and EUS prognostic factors.
Analyse univariée des facteurs pronostiques cliniques et échoendoscopiques.

	Variable	*p*
Clinical data	Gender (female *vs* male)	0.44
	Age (≤ 65 *vs* > 65 years)	0.41
	Weight loss ($\leq$10% *vs* >10%)	0.10
	Inability to ingest solid food	0.002
CT	Neoplastic lymph nodes (absent *vs* present)	0.29
	Height (≤ 5 cm *vs* >5 cm)	0.24
	Diameter (≤ 20 *vs* 21—50 vs > 50 mm)	0.53
EUS	Non-traversable stenosis	0.24
	If tumor is traversed:	
	transmural extent (T2 *vs* T3 *vs* T4)	0.39[a]
	thickness ($\leq$ 15 mm *vs* >15 mm)	0.13
	height (≤ 5 cm *vs* >5 cm)	0.49

[a] Although P was > 0.25, this variable was forced into the model as it is generally considered a good predictor of prognosis among gastroenterologists.

Multivariate analysis (Table 4)

Based on previously published studies and the results of the univariate analysis, we examined ten variables in the multivariate model: age, gender, weight loss, dysphagia, lymphadenopathy, height of tumor on CT, non-traversable stenosis on EUS, tumor thickness, transmural extension on EUS, and mediastinal and celiac neoplastic lymph nodes on EUS. Adjustments were made for center accrual and type of treatment given.

Table 1 Distribution of patients at the time of study inclusion.
Distribution des patients à l'inclusion.

	Variable	*N*	%
Clinical data	Gender (female)	16	9
	Weight loss >10%	34	20
	Inability to ingest solid food	78	45
CT	Height of tumor >5 cm	76	44
	Presence of lymph nodes	73	42
EUS results	Non-traversable stenosis	61	35
EUS results if tumor traversed ($N = 113$)	T3	104	92
	Height of tumor >5 cm	49	43
	Tumor thickness >15 mm	22	19
	Suspicious lymph nodes:		
	Absence of lymph nodes	8	7
	≤ 3 neoplastic mediastinal lymph nodes	57	50
	>3 neoplastic mediastinal lymph nodes	17	15
	≤ 3 neoplastic celiac lymph nodes	10	9
	>3 neoplastic celiac lymph nodes	21	19

Table 3 Detailed distribution of lymph nodes on EUS.
Distributions détaillés des ganglions à l'EED.

Variable	*N*	OR	95% CI	*P*
No lymph nodes	8	0.62	0.19—1.98	0.38
Neoplastic mediastinal lymph nodes ≤ 3[a]				
Neoplastic mediastinal lymph nodes >3[a]	84[a]	1		
Neoplastic celiac lymph nodes ≤ 3				
Neoplastic celiac lymph nodes >3[a]	21	2.22	1.25—3.93	0.01
Non-traversable stenosis	61	1.41	0.93—2.15	0.11

OR, odds ratio; CI, confidence interval.
[a] Due to a similar risk of death, these three classes were grouped together into a single class.

Table 4 Multivariate analysis of prognostic factors.
Analyse multivariée des facteurs pronostiques.

	OR	95% IC	*p*
Age > 65 *vs* ≤ 65 years	1.53	0.99—2.36	0.0560
Inability to ingest solid food *vs* others	1.98	1.33—2.94	0.0008
Neoplastic celiac lymph nodes > 3 on EUS *vs* others	2.41	1.38—4.21	0.0045

The following variables were introduced into the model: age, gender, weight loss, dysphagia, lymphadenopathy, height of tumor on CT and EUS variables significant at $P < 0.25$ in the univariate analysis.
Adjustments were made for center accrual and type of treatment given.

Only three variables were retained as predictive of a poor prognosis in the multivariate analysis: age more than 65 years, inability to ingest solid food and presence of more than three neoplastic celiac lymph nodes on EUS.

Survival rates

Fig. 1 shows the actuarial survival curves according to lymph node status on EUS.

Two- and five- year survival rates with no neoplastic lymph nodes, presence of up to three celiac neoplastic lymph nodes and more than three celiac neoplastic lymph nodes ($P = 0.0045$) were $52.6 \pm 20.2\%$ and $52.6 \pm 20.2\%$, $48.7 \pm 5.9\%$ and $33.8 \pm 6.3\%$, and $21.5 \pm 9.7\%$ and $10.8 \pm 9.0\%$, respectively. In cases of non-traversable tumor, the survival rates were $34.7 \pm 6.5\%$ and $22.1 \pm 6.6\%$, respectively.

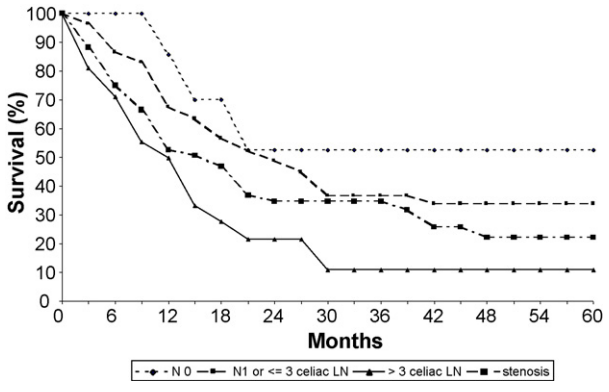

Figure 1 Survival rate as a function of neoplastic lymph node status on EUS.
Taux de survie en function des ganglions envahis à l'EED.

Discussion

The treatment of esophageal cancer is currently not well-standardized, and may explain why multiple treatments have been proposed for prospective investigations. These treatments include surgical resection [1], pre- or postoperative radiochemotherapy [23,24,31], concomitant radiochemotherapy alone [25] and preoperative chemotherapy. It has been suggested that exclusive radiochemotherapy may be similar in efficacy to radiochemotherapy followed by surgical resection [25]. Preoperative radiochemotherapy is now frequently given to patients with locally advanced cancer of the esophagus. This finding was the basis of the FFCD 9102 trial launched in 1993; the results suggest that adding resection to radiochemotherapy does not significantly improve the prognosis when radiochemotherapy alone has induced a clinical response [29,30].

Some recent studies suggest that the transmural extent of the tumor, as assessed by EUS, is not sufficiently predictive of the prognosis when the presence of neoplastic-type lymph nodes in the mediastinum are taken into account. More precisely, it appears that having fewer than three neoplastic mediastinal lymph nodes on EUS is the strongest predictor of prognosis in non-selected patients (resectable and non-resectable patients), regardless of CT results [27,32]. However, the small number of patients in that study precluded any analysis of the predictive value of celiac neoplastic lymph nodes (as suggested by other studies) [20,33].

Therefore, we found it useful to investigate whether, in a subgroup of patients with locally advanced cancer, EUS could isolate any strong independent predictive factors and whether these factors would be more effective than those obtained with spiral CT. The moderate interobserver agreement seen in the staging of esophageal cancer [16,17] justified the participation of non-selected centers in the study to verify the extent of confidence in the results of EUS when performed in multiple centers.

This study showed that age and dysphagia were predictive factors for survival. Other studies had already made similar findings [2,4,6,27,34]. These factors reflect the patient's underlying general status, and the direct consequences of the reduced food intake. No CT factor was retained in the multivariate analysis, which was consistent with a study that showed that spiral CT had limited value in visualizing lymph nodes in cases of T4 tumor [35].

In this study, the usT stage had no effect on the prediction of survival. The prognostic value of the usT stage had, however, been frequently found in other univariate studies [18,19]. There are two potential explanations for this discrepancy. First, inclusion criteria permitted only patients with locally advanced tumor on CT. The consequence of this was that a large proportion of patients (92%) had a T3 tumor on EUS, which decreased the power of the statistical tests. Second, the prognostic power of the T stage may disappear next to that of another, stronger factor such as lymphatic extent. This has already been described in three recent studies involving only EUS variables [20,32,33]. In a recent multivariate study of prognostic factors [27] including spiral CT, we showed that, besides a clinical factor (ASA classification), only the presence of more than three neoplastic lymph nodes was an independent imaging prognostic factor. One study found that T staging was more prognostically predictive than N staging [21], but this might be explained by the fact that the number of neoplastic lymph nodes involved was not considered.

By selecting only patients with locally advanced tumor in the present study, we found positive celiac neoplastic lymph nodes to be predictive of poor survival. This supports the results of four other studies [20,33,34,36]. Three of these studies were multivariate [20,32,33], but did not take into account the information provided by CT and clinical data, and one was retrospective [34]. We were unable to confirm the previous finding that positive neoplastic-type mediastinal lymph nodes were predictors of survival. This was probably due to the higher prognostic significance of neoplastic celiac lymph nodes compared with neoplastic mediastinal lymph nodes. In general, studies distinguish between the absence and presence of neoplastic lymph nodes, whatever their number. We found that setting a cut-off value at three neoplastic lymph nodes on EUS was more predictive of the prognosis than simply the presence of lymph nodes. This finding is in accordance with the fact that, as the number of neoplastic lymph nodes involved increases, the prognosis worsens [5,32,37,38]. Also, as we generally use only the EUS appearance in the absence of pathological confirmation of nodal nature, using the number of neoplastic-type lymph nodes increases the probability of finding at least one positive lymph node on histopathology.

Conversely, the site and size of the lymph nodes on EUS were not found to be predictive in a previous study [27], so this factor was not planned for in the present study.

Although it may play an important role, fine-needle aspiration has not been studied. According to this study and two others [20,32], having more than three neoplastic lymph nodes in the mediastinum and celiac areas is highly predictive of a poor prognosis, whereas having less than three suspicious lymph nodes suggests a better prognosis. So, what is the clinical significance of having no neoplastic lymph nodes versus having one, two or three? Because the diagnostic value of EUS remains less than 80% in most studies, it is possible that FNA could play a role in this specific subgroup. However, at this time, no available study can answer this question.

Conclusion

In locally advanced esophageal cancer, the clinical characteristics are a strong prognostic factor, but the strength of the relationship remains inferior to that of the results of EUS. EUS is superior to CT and allows for a more accurate selection of patients who have a very poor prognosis. Thus, this technique should be used as an initial tool in future therapeutic studies.

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Capsule summary

The prognosis of locally advanced esophageal cancer treated with radiochemotherapy can be easily predicted by age, dysphagia and presence of celiac lymph nodes on EUS independently of the results of CT.

Participating physicians and centers

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Chauvet	Clinique Ste-Catherine	Avignon
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