

Clinicopathologic and prognostic factors of young and elderly patients with esophageal adenocarcinoma: is there really a difference?

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SUMMARY. Evidence suggests a significant difference in the incidence, presentation, and outcome of young and elderly patients with esophageal adenocarcinoma. We aimed to compare clinicopathologic and prognostic factors of young and elderly patients with esophageal adenocarcinoma at a surgical department in Europe. From 1996 to 2006, 223 patients with a resectable esophageal adenocarcinoma were analyzed and divided in three groups: (i) patients ≤ 50 years ($n = 40$); (ii) patients between 50 and 70 years ($n = 131$); and (iii) patients >70 years ($n = 52$). Clinicopathological and prognostic factors were compared between these groups. The total number of patients with esophageal adenocarcinoma increased significantly. Although the total number of patients ≤ 50 years increased over the years, the proportion of young patients with esophageal adenocarcinoma was rather constant. The number of patients with a pT1-tumor was similar among all groups. Young patients had a significantly lower comorbidity and received more often a neoadjuvant radio-chemotherapy. The 5-year survival rate of young patients was significantly higher compared with elderly patients. In this European population, the total number of patients with adenocarcinoma of the esophagus increased dramatically in recent years, but the number of young patients remained rather constant. The better prognosis of young patients is mainly caused by less comorbidity and more frequent use of neoadjuvant therapy.

KEY WORDS: age, esophageal adenocarcinoma, prognostic factor, surgical epidemiology.

INTRODUCTION

Esophageal adenocarcinoma remains the fastest increasing cancer in the western world.^{1–4} In fact, a recent analysis by Pohl and Welch indicates that since 1975, the relative increase in the incidence of esophageal adenocarcinoma is three times that of the next closest cancer, melanoma.⁴ Moreover, recent studies, mostly from North America, suggest a significant difference in the incidence, presentation and outcome of young and elderly patients with esophageal adenocarcinoma. In fact, an analysis by El-Serag *et al.* about the changing epidemiology of esophageal adenocarcinoma from 1977 to 1996 demonstrated a higher incidence rate in more recent birth cohorts of the USA, suggesting that the incidence of esophageal adenocarcinoma is increasing in relatively younger patients.⁵ Portale *et al.* also encountered an increasing number

of young patients with esophageal adenocarcinoma from 1992 to 2002 undergoing surgical therapy at their department.⁶ They revealed that young patients usually present more often with dysphagia, are symptomatic for a longer time before diagnosis, and have more advanced disease compared with elderly patients. In contrast with these findings, Guardino *et al.* demonstrated in a retrospective study about all patients enrolled into the Cleveland Clinic Barrett's esophagus (BE) registry from 1979 to 2002 that older patients had a higher prevalence of dysplasia or adenocarcinoma, while the incidence of dysplasia and adenocarcinoma was similar in young and elderly patients.⁷ Interestingly, their study showed that approximately 25% of BE patients are less than 50 years of age, suggesting future screening strategies for BE and esophageal cancer to recognize that a substantial number of young patients develop BE and therefore, are at higher risk of developing esophageal cancer.

To date, generally studies in the USA were conducted to assess possible differences between young and elderly patients with Barrett's adenocarcinoma. Therefore, the aim of this study was to analyze the

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frequency of young and elderly patients with esophageal adenocarcinoma in a surgical department in Western Europe and to compare clinicopathologic and prognostic factors between these two patient groups. Because the determination of significant differences in the clinical behavior of esophageal adenocarcinoma in young and elderly patients might lead to varying therapeutic strategies.

PATIENTS AND METHODS

Between 1996 and 2006, a total of 272 patients with esophageal adenocarcinoma were admitted to our surgical department. From these, 223 patients with Barrett's adenocarcinoma underwent en-bloc-esophagectomy as a two-cavity operation with intrathoracic esophagogastrotomy, while 35 patients received palliative therapy because of metastasis disease and 14 patients underwent definitive radiochemotherapy because of an abnormal operative risk. There were 20 women and 203 men with a median age of 61 years (range 19–82 years) undergoing surgical therapy. After discharge, patients were under regular follow-up, undergoing esophagogastroscope, chest X-ray, ultrasound of the liver, and computed tomography (CT) of the thorax and abdomen. The study population was divided into three groups, according to the age at time of diagnosis: (i) patients ≤ 50 years ($n = 40$); (ii) patients between 50 and 70 years ($n = 131$); and (iii) patients >70 years ($n = 52$). Afterwards, clinicopathological and prognostic factors were compared between these three groups.

The local Institutional Review Board approved this retrospective study and indicated that individual consent could be waived because individual patients were not identified.

Diagnostic and staging procedures

TNM (T, extent of primary tumor; N, regional lymph node metastasis; M, distant metastasis) staging was performed according to the criteria of the International Union Against Cancer.⁸ Clinical staging consisted of endoscopy, endoscopic ultrasound, barium swallow, CT scanning of the abdomen and thorax, and positron-emission tomography. Adenocarcinomas were considered from esophageal origin if the center of the tumor was located at least 1 cm above the anatomical cardia.⁹

Preoperative risk analysis

An individualized preoperative risk analysis to predict postoperative outcome was performed for each patient undergoing surgical therapy as described previously.^{10–12} Therefore, a composite risk score of all relevant parameters was determined to point out

the relative risk undergoing surgical therapy, including the following: general status $\times 4$, cardiac function $\times 3$, pulmonary and hepatic function $\times 2$, endocrine and renal function $\times 1$, and neoadjuvant radiochemotherapy $\times 1$. Based on this composite risk score, the overall preoperative risk of each patient was classified as 'low' (score 13–16), 'moderate' (score 17–22), or 'high' (score 23–38).

Radiochemotherapy and surgical resection

Patients ($n = 80$) with advanced esophageal cancer (cT3/4, Nx, M0) received a neoadjuvant radiotherapy (36 Gy, cis-Platin, 5-FU).¹³ The surgical treatment of choice was en-bloc-esophagectomy and two-field lymphadenectomy of the mediastinal and abdominal lymph nodes via an abdominal/right transthoracic approach. Since December 2003, all patients underwent laparoscopic mobilization of the stomach including the cardia and preparation of the gastric conduit, followed by conventional right-sided transthoracic en-bloc-esophagectomy after 3–7 days.¹⁴

Statistical analysis

Beginning in 1996, data were collected prospectively according to a standardized protocol. The median with the lower quartile (LQ) and upper quartile (UQ) were used for descriptive statistics. Chi-square statistics were calculated for frequencies of factors with a significance level of $P < 0.05$.

The median follow-up time of all patients was calculated using the time between study entry and the date of the procedure and the time between study entry and the date of censoring for censored patients.¹⁵ The median follow-up time of the patients was 3.3 years (LQ–UQ = 1.2–6.0 years).

Kaplan–Meier plots were used to describe survival distribution.¹⁶ The log-rank test was used to evaluate for survival differences.¹⁷ For multiple comparisons, the Holm–Sidak method was used. In addition, the 95% confidence intervals (95% CI) for the different survival curves were calculated. Postoperative mortality was included in the calculation of prognosis. The 30-day postoperative mortality was 3.0%. The multivariate analysis of survival used Cox-regression analysis to identify independent prognostic variables. The level of significance was set to $P < 0.05$.

All statistical analyses were performed using the statistic program SPSS for Windows version 14.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Frequency of patients with esophageal adenocarcinoma

Among the 223 new cases of esophageal adenocarcinoma between 1996 and 2006, 40 (18%) patients were

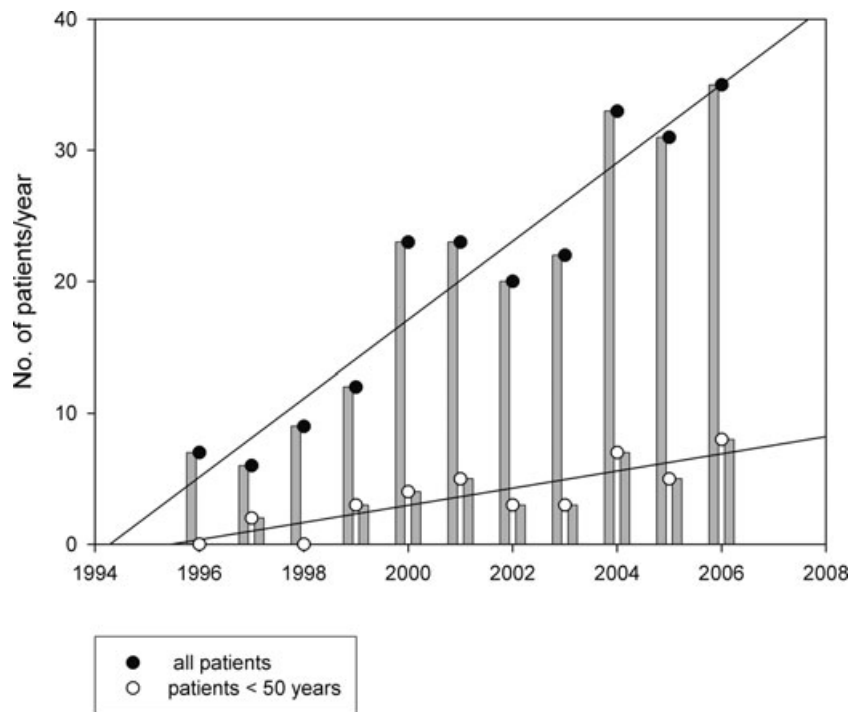


Fig. 1 Frequency of patients with esophageal adenocarcinoma undergoing surgical resection from 1996 to 2006.

reported to be under the age of 50 years, 131 (59%) patients between the age of 50 and 70 years, and 52 patients older than 70 years (23%). As shown in Figure 1, the total number of patients with esophageal adenocarcinoma increased significantly (fourfold increase) in the last 10 years. Although the total number of patients ≤ 50 years increased over the years, the proportion of young patients with esophageal cancer was rather constant at 18%.

Preoperative risk factors

There were significant differences between the three groups with respect to preoperative risk factors. Young patients had a significantly lower composite preoperative risk profile ($P < 0.001$) and a significantly better pulmonary ($P < 0.05$) and cardiac func-

tion ($P < 0.01$) compared with elderly patients. No significant differences were found with respect to the hepatic function (Table 1).

Tumor characteristics

As shown in Table 2, tumor characteristics, i.e. frequency of pT1, pN0/ypN0, or pM0 stage were similar between young and old patients.

Treatment

Of the 223 patients included in the study, 80 (36%) patients received a neoadjuvant radiochemotherapy. Thereby, patients ≤ 50 years underwent significantly more often a preoperative treatment before surgery, as shown in Table 3.

Table 1 Preoperative risk factors in young and elderly patients

	Study groups			P value
	≤ 50 years (n = 40)	51–70 years (n = 131)	70 years (n = 52)	
Normal composite preoperative risk profile [†]	19 (48%)	35 (27%)	10 (19%)	<0.001
Normal pulmonary function [‡]	31 (78%)	88 (67%)	26 (50%)	<0.05
Normal cardiac function [§]	36 (89%)	94 (72%)	14 (27%)	<0.01
Normal hepatic function [¶]	31 (78%)	122 (93%)	47 (92%)	NS

[†]Composite preoperative risk profile was determined by a score as described previously.^{11,12} [‡]Normal pulmonary function: paO₂ >70 mmHg, paCO₂ <45 mmHg, VC percentage and FEV1 percentage of normal. [§]Normal cardiac function: normal electrocardiogram, chest radiograph, and cardiologist's evaluation. [¶]Normal hepatic function: child classification. FEV1, forced expiratory volume in 1 second; NS, not significant; VC, vital capacity.

Table 2 Tumor characteristics in young and elderly patients

	Study groups			P value
	≤50 years (n = 40)	51–70 years (n = 131)	>70 years (n = 52)	
Male : Female	36 : 4	127 : 4	40 : 12	NS
pT1	10 (25%)	33 (25%)	13 (25%)	NS
pN0/ypN0	24 (60%)	68 (52%)	25 (48%)	NS
pM0	39 (98%)	121 (93%)	51 (98%)	NS
R0	35 (88%)	124 (95%)	50 (96%)	NS

NS, not significant.

Survival

The 5-year survival rate for all patients was 42% (95% CI 32–64%). Patients ≤50 years had a significant survival advantage ($P < 0.05$) compared with elderly patients with estimated 5-year survival rates of 61% (27% for patients older than 70 years). Multivariate survival analysis for all patients demonstrated that the (y)pT-category ($P < 0.0001$), (y)pN-category ($P < 0.0001$), M-category ($P < 0.0001$), and the use of neoadjuvant therapy ($P < 0.05$) significantly influenced survival probabilities, while age had no significant influence (Table 4).

DISCUSSION

This is a comprehensive study to evaluate differences in clinicopathologic and prognostic factors of young and elderly patients with esophageal adenocarcinoma undergoing surgical therapy at a department in Western Europe. We were able to demonstrate that in the last 10 years, the total number of patients with esophageal adenocarcinoma increased significantly, while the proportion of younger patients was constant. While our study results showed significant differences in the frequency of preoperative risk factors between the young and elderly patients, tumor characteristics were similar in these groups. However, young patients more often received an aggressive treatment by undergoing more frequently a neoadjuvant radiochemotherapy with having a higher 5-year survival rate.

Several studies have described a dramatic increase in the incidence of esophageal adenocarcinoma in the past decades, which has now surpassed squamous cell carcinoma as the most common histological type of esophageal cancer in Western countries.^{1–4} Moreover, Portale *et al.* recently performed a retrospective study about 263 consecutive patients who underwent esophagectomy for adenocarcinoma from 1992 to 2002 at their surgical department.⁶ They observed a significantly growing proportion of patients with esophageal adenocarcinoma that are ≤50 years old. Similar data were reported by El-Serag *et al.* in a birth cohort analyses for cases with morphologically and histologically confirmed esophageal adenocarcinoma, examining the incidence rates for temporal changes, ethnic, and age distributions.⁵ Their analyses revealed that the adenocarcinoma is characterized by a higher incidence rate in more recent birth cohorts with an increase of the age-specific incidence progressively from 1977 to 1996 among younger subjects in addition to older age groups. Our study results showed indeed a dramatic increase of the total number of patients with esophageal adenocarcinoma, nevertheless, the proportion of younger patients was constant. Interestingly, these conflicting findings are in agreement with a study by Guardino *et al.* demonstrating the incidence of dysplasia and adenocarcinoma was similar in young and elderly patients enrolled into the Cleveland Clinic BE registry from 1979 to 2002.⁷ Thus, at this point, we can only speculate about these disagreeing studies. Among possible reasons to explain are (i) different recommendations regarding screening endoscopy in young patients with symptomatic reflux at the study centers, suggesting that an aggressive diagnostic approach leads to a more frequent and early disease detection; and (ii) possible geographic differences, influencing the incidence of esophageal adenocarcinoma (i.e. USA/west coast–USA/east coast Western Europe).

We have demonstrated that tumor characteristics are similar between young and elderly patients with esophageal adenocarcinoma. In contrast, Portale *et al.* revealed in their study that young patients with esophageal adenocarcinoma are symptomatic for a longer time before diagnosis, and have a more advanced disease compared with older patients.⁶

Table 3 Frequency of and response to neoadjuvant therapy in young and elderly patients

Patients receiving neoadjuvant therapy (%)	Study group			P value
	≤50 years	51–70 years	>70 years	
Of all study patients (n = 223)	21/40 (53%)	50/131 (38%)	9/52 (17%)	<0.001
Of patients with cT3/4 stage (n = 135)	21/26 (81%)	50/77 (65%)	9/32 (28%)	<0.001
With minor response†	17/21 (81%)	31/50 (62%)	6/9 (67%)	NS
With major response†	4/21 (19%)	19/50 (38%)	3/9 (33%)	NS

†Histomorphologic regression was defined as major response when resected specimens contained less than 10% of residual vital tumor cells and minor response when resected specimens contained more than 10% of residual vital tumor cells.¹ NS, not significant.

Table 4 Multivariate survival analysis of study patients with R0-resection

Factor	Hazard ratio	95% CI	Significance <i>P</i>
T-category			0.001
pT2-pT1	3.0	1.3–7.2	0.014
pT3-pT1	4.6	2.1–10.1	0.000
pT4-pT1	7.8	1.2–77.2	0.078
N-category			0.001
pN1-pN0	2.4	1.4–4.2	
M-category			0.000
pM1-pM0	3.0	1.8–5.1	
Preoperative RTx/CTx			0.014
Yes-No	0.7	0.4–0.9	
Age groups			0.083

However, despite the higher prevalence of late-stage disease in young patients, they detected an identical survival rate in the older group, possibly influenced by a more aggressive treatment with a more frequent use of en-bloc-esophagectomy in young patients, while approximately 20% of patients in both groups received neoadjuvant therapy. Interestingly, our young study patients more often received a neoadjuvant radiochemotherapy compared with elderly patients. Furthermore, multivariate survival analysis demonstrated that beside the TNM-category, the use of neoadjuvant therapy significantly influenced survival probabilities, possibly being the most important factor responsible for the significantly longer 5-year survival rate in young patients.

Our findings, in conjunction with the work by Sabel *et al.*, may further influence decisions on mainly the treatment of elderly patients.¹⁸ In fact, the study by Sabel *et al.*, comparing clinical data, perioperative details, and postoperative courses for patients older and younger than 70 years with esophageal cancer, showed that the benefit in multimodal therapy of this malignancy is the same in both groups, without a significant increase in operative morbidity or mortality.¹⁸ Therefore, age alone should not preclude an aggressive therapy, including a neoadjuvant therapy, for this cancer in otherwise healthy patients. However, this hypothesis has to be answered by a prospective, randomized trial with the use of neoadjuvant therapy in young and old patients.

One potential criticism of our study is that we used an institutional database for our analyses regarding possible epidemiologic changes in the frequency and age-related differences of patients with esophageal adenocarcinoma. Therefore, our data are hypothesis generating and should therefore be validated in larger clinical studies, using European cancer registries.

In conclusion, this study at a surgical department in Western Europe showed indeed that the number of patients with esophageal adenocarcinoma increased significantly in the last 10 years, while on the con-

trary, the proportion of young patients was rather constant. While tumor characteristics of young and old patients tended to be similar, young patients received a more aggressive treatment with a more frequent use of neoadjuvant therapy, which may be one reason leading to a significant survival benefit compared with elderly patients. These findings might influence future therapeutic strategies for patients with esophageal cancer to include even elderly patients in a more aggressive treatment.

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