



## Does baseline quality of life predict the occurrence of complications in resectable esophageal cancer?

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### ► To cite this version:

W.G. Sheng, Emerline Assogba, O. Billa, Bernard Meunier, J. Gagnière, et al.. Does baseline quality of life predict the occurrence of complications in resectable esophageal cancer?. *Surgical Oncology*, 2022, 40, pp.101707. 10.1016/j.suronc.2021.101707 . hal-03634089

**HAL Id: hal-03634089**

**<https://hal.science/hal-03634089>**

Submitted on 8 Apr 2022

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**1 Title Page**

**2 Title: Does baseline quality of life predict the occurrence of complications in resectable**  
**3 esophageal cancer?**

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## Abstract and keywords

**Background:** The aim of this study was to assess the impact of baseline health related quality of life (HRQOL) on the occurrence of postoperative complications and death in patients with resectable esophageal cancer.

**Methods:** Existing data from a prospective, multicenter, open label, randomized, controlled phase III trial comparing hybrid versus open esophagectomy in patients with resectable esophageal cancer from 2009 to 2012 in France were used. A Cox regression model was used to assess the prognostic value of the baseline HRQOL score on the occurrence of major complications (MC), and major pulmonary complications (MPC) at 30 days post-surgery, as well as on 1-year postoperative overall survival (OS).

**Results:** Every 10-point increase in the baseline role functioning score was associated with a 14% reduction in the risk of MC, while every 10-point increase in fatigue or pain score was associated with an 18% increase in the risk of MC. Similarly, higher scores on fatigue and pain were associated with a higher risk of MPC. Compared with the hybrid procedure, patients undergoing open esophagectomy had a significantly higher risk of MC and MPC. Patients diagnosed with esophageal adenocarcinoma were at significantly lower risk of MC or MPC compared to patients with esophageal squamous cell carcinoma. Higher pain (HR=1.23,  $p=0.035$ ) and insomnia (HR=1.16,  $P=0.031$ ) scores were associated with increased 1-year OS.

**Conclusion:**

Fatigue, pain, insomnia, and squamous cell pathology were indicators of poor prognosis, and that the presence of these findings might possibly change the management plan towards other forms of treatment and warrant close attention.

**Keywords:**

Health Related Quality of Life, esophagectomy, major complications, overall survival, prognostic factor.

**Acknowledgements:** This research was set up using existing data on a prospective, multicenter, open label, randomized, controlled phase III trial comparing hybrid procedure and open procedure in patients with resectable esophageal cancer from 2009 to 2012 in France (the MIRO trial). We thank all the investigators in MIRO trial, special the co-PI who are not listed in the authors: Doctor Thierry Perniceni, Nicolas Carrère, Jean-Yves Mabrut, Simon Msika, Frédérique Peschaud, Michel Prudhomme, and the Fédération de Recherche en Chirurgie (FRENCH) and French Eso-Gastric Tumors (FREGAT) Working Groups. We also thank Fiona Ecartot, PhD (University of Franche-Comté, France) for editorial assistance.

## Main Text

### 1. Introduction

Esophageal cancer was the 8<sup>th</sup> most common cancer diagnosed, and the 6<sup>th</sup> leading cause of cancer-related death worldwide in 2020 [1]. Esophageal cancer is a highly fatal disease, with 5-year standardized net survival of 16% and 20% in men and women respectively in France [2].

Esophagectomy remains the primary curative treatment option for patients with esophageal cancer. Five-year survival has increased to 40% among patients undergoing surgery compared to those without surgery [3]. Standard esophagectomy consists in an open surgical excision (laparotomy + right thoracotomy) for subcarinal thoracic esophageal cancer. It is associated with a significant risk of postoperative morbidity (30% to 50%) and mortality (2% to 10%) [4-6]. In recent years, minimally invasive approaches have been evaluated for esophagectomy, and have resulted in a decreased incidence of overall morbidity, pulmonary complications and a shorter length of hospital stay [7-10].

The MIRO trial was a prospective, randomized, controlled, open-label, multicenter phase III study conducted in France to compare the morbidity, overall and disease-free survival, and health related quality of life (HRQOL) of patients undergoing open esophagectomy (open procedure) versus hybrid minimally invasive esophagectomy (hybrid procedure). The MIRO trial showed that the hybrid procedure resulted in a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complications, compared to open esophagectomy, without compromising overall and disease-free survival or HRQOL over a period of 3 years [7].

Previous studies have shown that baseline HRQOL can predict overall survival in patients with advanced cancer, such as glioblastoma, lung cancer, metastatic colorectal cancer, and

esophageal cancer [11-15]. However, data are lacking regarding the impact of baseline HRQOL on the occurrence of complications in patients with resectable esophageal cancer. Therefore, we used the data from MIRO trial to assess the prognostic value of baseline HRQOL on the occurrence of major complications (MC) at 30 days after surgery in patients with resectable esophageal cancer. The secondary aims were to assess the prognostic value of baseline HRQOL on major pulmonary complications (MPC) at 30 days, and on 1-year overall survival (OS).

## 2. Methods

### 2.1 Study design and population

This study used data from MIRO. Briefly, the MIRO trial was a prospective, multicenter, open label, randomized, controlled phase III trial comparing the hybrid procedure to the open procedure in patients with resectable esophageal cancer. The patients were randomized from October 2009 through April 2012 in France, then followed up for 3 years after esophagectomy. MIRO inclusion criteria were patients aged 18-75 years with WHO performance status 0 to 2; diagnosed with squamous cell carcinoma (SCC) or adenocarcinoma of the middle or lower third of the esophagus with clinical stage I, II or III ( $T_1$ ,  $T_2$ ,  $T_3$ ;  $N_0$  or  $N_1$ ;  $M_0$ ), with the tumor judged as resectable pre-operation; with or without neoadjuvant therapy.

In the MIRO trial, patients were randomized intraoperatively after a laparoscopic exploration of the abdominal cavity to confirm the absence of contraindications to curative surgery (hepatic cirrhosis, hepatic or peritoneal metastasis, or non-resectable tumor extension), in a 1:1 ratio to either the open procedure (with open gastric mobilization and thoracotomy) or the hybrid procedure (laparoscopic gastric mobilization and open thoracotomy). All patients were followed up to 30 days after surgery and every 6 months for 3 years postoperatively. The design and the results of the MIRO trial have been previously published elsewhere [7, 16-17].

The present study included all patients who were randomized in the MIRO trial. Data on HRQOL, complications, and OS were collected.

## 2.2 Endpoints

The primary endpoint for this study was major complications during surgery or within 30( $\pm$ 3) days after surgery. A major intraoperative and/or postoperative complication was defined as a surgical or medical complication classed as grade II or higher on the five-grade Clavien-Dindo classification (including grade 1, 2a, 2b, 3 and grade 4, higher grades indicate more life-threatening complications) [18].

The secondary endpoints were major pulmonary complications during surgery or within 30( $\pm$ 3) days after surgery, and 1-year overall survival.

## 2.3 Study Instruments

Baseline HRQOL was measured within 30 days before resection using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, Version 3.0) and the esophageal cancer module-18 (EORTC QLQ-OES18).

EORTC QLQ-C30 is a 30-item questionnaire including five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom and six single item scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties), and a global health status item. The QLQ-OES18 module includes 10 symptom scales and is used among patients with esophageal cancer undergoing any single treatment, or combination of treatments including: esophagectomy, chemo-radiation, endoscopic palliation, or palliative chemotherapy and/or radiotherapy [19]. The score ranges from 0 to 100; high scores on functional scales (like role functioning) represent a high/ healthy level of functioning,

whereas high scores on symptom scales (like fatigue, pain, or insomnia) represent a high level of symptomatology/ problems.

## 2.4 Statistical Analysis

Sociodemographic and clinical characteristics of patients at inclusion are described in the whole sample, as well as baseline HRQOL scores for each scale. Age (in years), body mass index (BMI, in kg/m<sup>2</sup>), and baseline HRQOL scores are described as mean  $\pm$  standard deviation (SD). Sex, WHO status, clinical tumor stage, presence of nodes on clinical examination, histological tumor type, tumor location, American Society of Anesthesiologists (ASA) score and type of neoadjuvant therapy are described as number and percentage. Survival curves were plotted using the Kaplan Meier Method.

Considering that among patients who reported “a small” change in HRQOL for better or for worse, the average change in scores was 5-10 points on the EORTC QLQ-C30 scales, we divided the initial scores of EORTC QLQ-C30 and EORTC QLQ-OES18 by ten, then used the quotient thus obtained for the assessment of prognostic value [20]. This methodology is used to obtain a minimum clinically important difference [21].

Univariable and multivariable Cox models were used to assess the prognostic value of the baseline HRQOL score on the occurrence of MC, MPC and on 1-year OS. Univariable analysis was performed on each dimension of baseline EORTC QLQ-C30 and EORTC QLQ-OES18, and on the baseline demographic and clinical characteristics. The significance threshold was set at 0.05 for HRQOL and at 0.20 for the baseline demographic and clinical characteristics in univariable analysis. We used Spearman’s correlation coefficient and the chi square or Fisher’s exact test to test candidate variable independence. Next, we conducted a separate multivariable analysis for each dimension of the EORTC QLQ-C30 and QLQ-OES18 that was significant by univariable analysis. Analyses were adjusted for baseline demographic and clinical



characteristics that were associated with the occurrence of MC or MPC at 30 days, or with 1-year OS with a p-value  $<0.20$  in univariable analysis. Multivariable analyses were systematically adjusted for age, ASA score, TNM stage and neoadjuvant therapy for the assessment of complications.

Final multivariable models were chosen based on clinical considerations and Harrell's C index. Results are presented as Hazard Ratios (HR) and 95% confidence interval. The significance threshold was set at 0.05 for multivariable analyses. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

### **3. Results**

#### **3.1 Baseline patient characteristics**

In total, 207 patients were included in this study. The mean age was 60.37 (SD=8.81) years and 84.54% of patients were male. Forty one percent of patients were diagnosed with squamous cell carcinoma and 59% with adenocarcinoma. Two hundred and five patients underwent esophagectomy: 103 had an open procedure and 102 had a hybrid procedure; two patients were randomized but did not undergo surgery. The details of the baseline clinical characteristics are shown in Table 1.

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**Table 1.** Patients' baseline demographic and clinical characteristics (n=207):

Characteristic		N	Percentage (%)
Gender			
	Male	175	84.54
	Female	32	15.46
Age, years			
	Mean (SD)	207	60.37 (8.81)
	≤ 60	96	46.38
	> 60	111	53.62
WHO performance status score			
	0	120	57.97
	1	79	38.16
	2	8	3.86
BMI, kg/m <sup>2</sup>	Mean (SD)	25.31 (3.93)	
ASA risk score			
	1	59	28.50
	2	119	57.49
	3	29	14.01
Dysphagia score, Atkinson			
	Able to eat a normal diet	104	50.24
	Able to eat some solid food	68	32.85
	Able to eat some semi solids only	22	10.63
	Liquid feed possible	11	5.31
	Complete dysphagia	2	0.97
TNM Classification			
T	T <sub>0</sub>	4	1.93
	T <sub>1</sub>	33	15.94
	T <sub>2</sub>	63	30.43
	T <sub>3</sub> +T <sub>4</sub>	98	47.34
	Missing data	9	4.35
N	N <sub>0</sub>	89	43.00
	N <sub>1</sub>	102	49.27
	N <sub>2</sub>	8	3.86
	Missing data	8	3.86
	Location of tumor in esophagus		
	Upper third	1	0.48
	Middle third	63	30.43
	Lower third	143	69.08
Tumor histology			
	Squamous cell carcinoma	84	40.58
	Adenocarcinoma	123	59.42
Neoadjuvant therapy			
	Chemotherapy only	86	41.54
	Chemo-radiotherapy	66	31.88
	None	55	26.57
Surgery type			
	Hybrid procedure	102	49.28
	Open procedure	103	49.75
	None	2	0.97

Abbreviations: SD, standard deviation; WHO, World Health Organization; BMI, body mass index; ASA, American Society of Anesthesiologists.

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178 Overall, baseline HRQOL scores were good. The best functional score was the physical  
 179 functioning, at 91.82 (SD=12.17), and the lowest symptomatic score was trouble talking, at

2.76 (SD=9.22). “Global health status”, with a mean of 69.49 (SD=19.66), was the worst functioning score, and dysphagia 76.6 (SD=27.28) was the highest symptomatic score (Table 2).

**Table 2.** Baseline HRQOL score and the relation between baseline HRQOL scores and major complications, major pulmonary complications, and 1-year overall survival by univariable analysis:

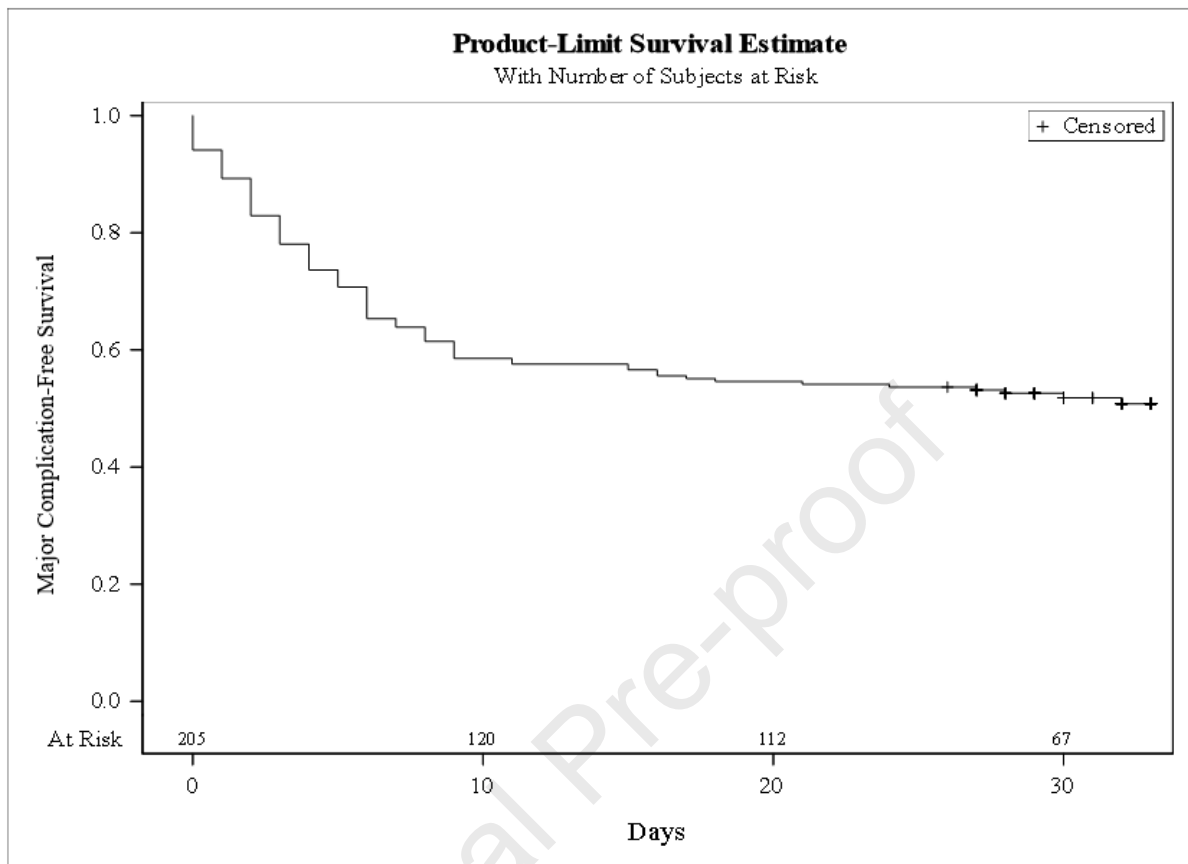
Dimensions	Baseline HRQOL	P-value from univariable analysis		
	Mean (SD)	MC	MPC	1-year OS
<b>QLQ-C30 Questionnaire</b>				
Global Health Status	69.49 (19.66)	0.1139	0.6277	0.1030
Physical Functioning	91.82 (12.17)	0.1298	0.961	0.2113
Role Functioning	88.41 (19.26)	<b>0.0425</b>	0.5958	<b>0.0387</b>
Emotional Functioning	74.34 (22.65)	0.7510	0.9791	0.9679
Cognitive Functioning	91.08 (14.51)	0.4197	0.9473	0.2606
Social Functioning	87.54 (22.00)	0.6634	0.5053	0.2469
Fatigue	23.88 (19.91)	<b>0.0330</b>	<b>0.0424</b>	0.3824
Nausea and Vomiting	11.68 (22.88)	0.1146	0.4850	<b>0.0007</b>
Pain	11.53 (17.46)	0.0517	<b>0.0023</b>	<b>0.0486</b>
Dyspnoea	11.11 (19.58)	0.5706	0.5709	<b>0.0107</b>
Insomnia	21.94 (26.80)	0.0840	0.9149	<b>0.0063</b>
Appetite Loss	19.93 (30.41)	0.3405	0.9557	0.1173
Constipation	20.54 (30.30)	0.5224	0.5970	<b>0.0147</b>
Diarrhoea	10.32 (20.50)	0.9892	0.9756	0.7006
Financial Difficulties	8.84 (21.38)	0.0690	0.1531	0.8756
<b>QLQ OES-18 Questionnaire</b>				
Dysphagia	76.60 (27.28)	0.3887	0.7703	<b>0.0091</b>
Eating	19.49 (23.50)	0.4001	0.7678	<b>0.0241</b>
Reflux	18.28 (24.90)	0.6103	0.4365	0.2456
Pain	11.34 (15.26)	<b>0.0380</b>	0.0557	0.2437
Trouble Swallowing Saliva	8.12 (24.00)	0.6088	0.3821	0.9626
Choked when swallowing	7.81 (17.47)	0.5403	0.7865	0.3961
Dry Mouth	18.88 (25.28)	0.7532	0.5349	<b>0.0446</b>
Trouble with Taste	16.92 (29.38)	0.6793	0.2238	0.6796
Trouble with Coughing	4.30 (12.65)	0.5608	0.5070	0.5680
Trouble Talking	2.76 (9.22)	0.7135	0.2025	0.0613

Abbreviations: HRQOL, Health Related Quality of Life; SD, standard deviation; MC, Major Complication; MPC, Major Pulmonary Complication; OS, Overall Survival; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QLQ OES-18, European Organisation for Research and Treatment of Cancer-Esophageal Cancer module-18.

### 3.2 Primary and secondary endpoints

Among the 207 patients, 99 (47.83%) had one or more major complications 30 days after the esophagectomy, and more than 70% of complications occurred during the first week after surgery (Figure 1). Forty-nine of the 99 cases of major complications were pulmonary complications. At 1-year post surgery, 31 patients (14.98%) had died.

195 **Figure 1.** Kaplan Meier curve showing major complication-free survival.



### 197 3.3 Assessment of prognostic value

#### 198 3.3.1 HRQOL and complications

199 In univariable analysis, role functioning ( $p=0.0425$ ) and fatigue ( $p=0.033$ ) on the QLQ-C30,  
 200 and pain ( $p=0.038$ ) on the QLQ-OES18 were significantly associated with the occurrence of  
 201 MC. For MPC, only the fatigue ( $P=0.0424$ ) and pain ( $p=0.0023$ ) dimensions of the QLQ-C30  
 202 were statistically significant (Table 2).

203 The same dimensions were found to be associated with MC and MPC by multivariate analysis  
 204 after adjusting for type of surgery, tumor histology, age, ASA score, and TNM classification  
 205 (T and N), for both MC and MPC.

Patients with higher role functioning scores (every 10 point) were at lower risk of MC (HR=0.86; 95% CI [0.77-0.96]; P=0.007), while every 10-point increase in fatigue (HR=1.18; 95% CI [1.06-1.31]; P=0.002) and OES-18 pain scores was associated with an increased risk of MC (HR=1.18; 95% CI [1.03-1.34]; P=0.014). Similarly, patients with higher scores on the fatigue (HR=1.20; 95% CI [1.06-1.36]; P=0.004) and pain (HR=1.24; 95% CI [1.09-1.40]; P=0.001) dimensions of the QLQ-C30 were at higher risk of MPC (Table 3).

**Table 3.** Multivariable analysis of the impact of baseline HRQOL on the occurrence of major complications and major pulmonary complications

	Major complications						Major pulmonary complications			
	Role functioning		Fatigue		OES-18_Pain		Fatigue		Pain	
	HR [95% CI]	P value	HR [95% CI]	P value	HR [95% CI]	P value	HR [95% CI]	P value	HR [95% CI]	P value
HRQOL*	0.86 [0.77;0.96]	<b>0.007</b>	1.18 [1.06;1.31]	<b>0.002</b>	1.18 [1.03;1.34]	<b>0.014</b>	1.20 [1.06;1.36]	<b>0.004</b>	1.24 [1.09;1.40]	<b>0.001</b>
Surgery type										
Hybrid	1		1		1		1		1	
Open	2.30 [1.46;3.62]	<b>&lt;0.001</b>	2.48 [1.57;3.92]	<b>&lt;0.001</b>	2.14 [1.47;3.66]	<b>&lt;0.001</b>	1.97 [1.03;3.79]	<b>0.042</b>	1.94 [1.01;3.74]	<b>0.047</b>
Tumor histology										
SCC	1		1		1		1		1	
Adeno- carcinoma	0.55 [0.35;0.85]	<b>0.007</b>	0.54 [0.34;0.83]	<b>0.006</b>	0.59 [0.38;0.92]	<b>0.021</b>	0.42 [0.22;0.81]	<b>0.009</b>	0.46 [0.24;0.88]	<b>0.018</b>
Age (years)										
≤ 60	1		1		1		1		1	
> 60	1.35 [0.87;2.07]	0.186	1.37 [0.88;2.13]	0.164	1.33 [0.85;2.08]	0.206	1.55 [0.85;2.84]	0.157	1.55 [0.82;2.93]	0.177
ASA										
I	1		1		1		1		1	
II	1.13 [0.69;1.85]	0.627	1.14 [0.70;1.86]	0.607	1.31 [0.79;2.18]	0.291	1.02 [0.52;2.02]	0.948	1.08 [0.55;2.15]	0.820
III	0.49 [0.21;1.15]	0.10	0.53 [0.23;1.22]	0.134	0.58 [0.25;1.33]	0.198	0.50 [0.14;1.86]	0.305	0.46 [0.14;1.58]	0.210
TNM-T										
T0/T1	1		1		1		1		1	
T2	0.80 [0.42;1.52]	0.501	0.80 [0.42;1.50]	0.483	0.97 [0.5;1.80]	0.916	0.67 [0.29;1.55]	0.347	0.75 [0.34;1.62]	0.458
T3/T4	0.91 [0.47;1.76]	0.777	0.89 [0.46;1.69]	0.713	0.96 [0.49;1.87]	0.900	0.59 [0.26;1.39]	0.228	0.70 [0.30;1.62]	0.399
TNM-N										
N0	1		1		1		1		1	
N1 /N2	0.88 [0.54;1.43]	0.600	0.89 [0.55;1.45]	0.641	0.98 [0.60;1.62]	0.947	1.19 [0.62;2.30]	0.600	1.21 [0.63;2.35]	0.562

\*In each model with HRQOL for the occurrence of major complication and major pulmonary complication.

Abbreviations: HRQOL, Health Related Quality of Life; OES-18, Esophageal Cancer module-18; HR, Hazard Ratio; SCC, Squamous Cell Carcinoma; ASA, American Society of Anesthesiologists.

Multivariable analyses also showed that, compared with the hybrid procedure, patients who underwent an open procedure had a significantly higher risk of both MC and MPC. In the model with fatigue, the HR for the occurrence of MC was 2.48 (95% CI 1.57 -3.92,  $p<0.001$ ). In the model with role functioning and OES18-pain, the HRs for MC were respectively 2.30 and 2.14 ( $p<0.001$  for both). For risk of MPC, type of surgery showed a similar impact. Patients diagnosed with esophageal adenocarcinoma were at significantly lower risk of MC or MPC after surgery compared to patients with SCC. No difference was found for age, ASA score and TNM stage (Table 3).

### 3.3.2 HRQOL and 1-year postoperative OS

By univariable analyses, role functioning, nausea and vomiting, pain, dyspnoea, insomnia, and constipation on the QLQ-C30, and dysphagia, eating, and dry mouth on the QLQ-OES18 were the dimensions of HRQOL that were significantly associated with 1-year OS (Table 2).

By multivariable analysis, pain (HR=1.23; 95% CI [1.02-1.50];  $p=0.035$ ) and insomnia (HR=1.16; 95% CI [1.01-1.32];  $P=0.031$ ) on the QLQ-C30 were significant after adjustment for age, occurrence of major complications and pN stage. Patients with higher pain or insomnia scores (per 10-point increase) were at significantly higher risk of death at 1 year after surgery.

We also found pN stage to be a significant prognostic factor, whereby patients with more advanced pN stage (mainly for N<sub>2</sub>) had a higher risk of death at 1 year after surgery compared to patients with N<sub>0</sub> stage. In the model with insomnia, node stage N<sub>2</sub> was associated with a hazard ratio of 10.51 (95% CI 2.30-47.90,  $p=0.002$ ) for 1-year death compared to node stage N<sub>0</sub>. The occurrence of major complications was significantly associated with an increased risk of death in both models ( $p=0.008$  in the model with pain, and  $p=0.015$  in the model with insomnia). Age over 60 years was a significant prognostic factor for death only in the model with the pain dimension, but not in the model with insomnia (Table 4).

**Table 4.** Multivariable analysis of the impact of baseline HRQOL on the occurrence of death at 1 year after surgery

	Pain		P value	Insomnia	
	HR	[95% CI]		HR	[95% CI]
HRQOL*	1.23	[1.02;1.50]	<b>0.035</b>	1.16	[1.01;1.32]
Age (year)					
≤ 60	1			1	
> 60	2.80	[1.10;7.15]	<b>0.031</b>	2.18	[0.87;5.48]
Major complication					
No	1			1	
Yes	3.23	[1.36; 7.66]	<b>0.008</b>	2.99	[1.24;7.20]
TNM-N					
N0	1			1	
N1	2.08	[0.86;5.04]	0.103	2.69	[1.05;6.93]
N2	10.43	[2.37;45.87]	<b>0.002</b>	10.51	[2.30;47.90]

\*Under each model with HRQOL for the occurrence of death at 1 year.

Abbreviations: HRQOL, Health Related Quality of Life; HR, Hazard Ratio.

#### 4. Discussion

In this study, we found that the initial HRQOL score (specifically, role functioning, fatigue and pain scales), surgical approach and histological type of esophageal cancer were significant predictors of the occurrence of MC and MPC. The results also showed that the baseline HRQOL score (specifically pain and insomnia) were predictors of 1-year overall survival after surgery.

In our study, every 10-point increase in the baseline role functioning score was associated with a 14% reduction in the risk of MC. Conversely, every 10-point increase in fatigue or OES18-pain symptoms at baseline was associated with an 18% increase in the risk of MC. Similarly, every 10-point increase in pain or fatigue symptom scores was associated with a higher risk (20-24%) of MPC.

After esophagectomy for cancer, postoperative complications can directly affect long term oncological outcomes and HRQOL [22]. Patients' HRQOL could be influenced between 6 months and 3 years after surgery, and even after 10 years, patients still experience reduced

HRQOL with persisting symptoms [23-24]. Postoperative complications after esophagectomy mainly include in the short-term pulmonary and cardiac complications, anastomotic leakage, chylothorax, and delayed gastric emptying, which mostly occurred during the first week after surgery [7]. In the long-term, anastomotic stenosis and reflux oesophagitis can occur and potentially impair patients' HRQOL. Postoperative anastomotic leakage is one of the most important complications leading to death [25]. The higher the incidence of postoperative pulmonary complications, the greater the harm. Reported risk factors for pulmonary complications include patients' smoking history, forced expiratory volume (FEV), chronic obstructive pulmonary disease (COPD), age, obesity, and lung diseases, while lymph node dissection status and preoperative serum albumin levels are risk factors for anastomotic leakage [26-28]. In the present randomized, controlled study, strict inclusion/ exclusion criteria were applied, and a standardized perioperative pathway was proposed for all patients, including alcohol and smoking cessation for at least 1 month prior to surgery, oral immuno-nutrition and enteral nutritional assistance, intraoperative respiratory and cardiovascular monitoring and an algorithm of treatment for post-operative complications. Together, these contributed to minimizing differences between patients, leading to more convincing results. We focused our analysis on MC, including MPC, and found that nearly 50% of MC are pulmonary complications. In addition to the type of surgical approach and tumor histology, the initial HRQOL score (role functioning, fatigue and pain) could also play a role in the occurrence of complications. When performing preoperative assessment, in addition to routine tumor and clinical examinations, special attention should be paid to patients' HRQOL, such as pain and fatigue.

In our study, patients with higher baseline scores on the pain or insomnia dimensions were observed to be at greater risk (23% and 16% respectively) of death at one year after surgery. Pain is a common symptom among patients with cancer, and adequate pain assessment and



management are thus critical to improve the quality of life and health outcomes in this population [29]. In our analysis, lymph node status was shown to be an important risk factor for death at 1 year, whereby patients with more advanced N stage (N<sub>2</sub>), had an approximately 10-fold increase in the risk of death. Furthermore, patients who experienced a MC had around a 3-fold increase in the risk of death at 1 year compared to patients who suffered no complication. In the multivariable model on the pain dimension, older age (> 60 years) was associated with a higher risk of death at 1 year. Previous studies have identified age, pathological T stage, clinical lymph node involvement and treatment modality (surgery versus definitive chemoradiotherapy) as predictive factors of death in esophageal cancer [30-31]. The study by Tamagawa et al showed that the development of postoperative pneumonia was a risk factor for decreased 5-year OS in patients who underwent curative surgery for esophageal cancer [32]. In our analysis, age was a risk factor for 1-year overall survival in certain conditions. In clinical practice, management and treatment of MC, especially for older patients, is of paramount importance.

In a previous study assessing baseline HRQOL to predict OS in patients with advanced cancer, the dimensions such as global health status, physical functioning, fatigue, nausea, appetite loss and constipation were prognostic indicators of OS [13-15]. In the present study, we included patients with clinical tumor stage I, II or III. Generally, patients' baseline HRQOL scores were good in our study; and their health status were better than patients with advanced cancer. Nevertheless, our results also provide evidence that there is a need to be mindful of patients' overall syndromes, such as complaining of pain and insomnia, to ensure longer survival for patients undergoing esophagectomy.

Our study findings are in line with the previous MIRO and TIME studies [7,9], which showed that the hybrid procedure resulted in a lower incidence of MC or MPC compared to open esophagectomy.

## 5. Conclusion

In conclusion, the role functioning, fatigue and pain were independent prognostic factors of complications in patients with resectable esophageal cancer treated with surgery. Role functioning had a protective effect against MC, while fatigue and pain were associated with an increased risk of the occurrence of MC or MPC. Regarding 1-year OS after surgery, pain and insomnia were prognostic risk factors for death; patients with squamous cell pathology, older age, and more advanced lymph node status were indicators of poor prognosis of OS. To patients with these presences, special attention should be paid, and it might possibly change the management plan towards other forms of treatment.

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**Title: Does baseline quality of life predict the occurrence of complications in resectable esophageal cancer?**

**Highlights**

Quality of life predicts the postoperative complications in esophageal cancer patients.

Baseline role functioning had a protective effect against complications.

Fatigue and pain were the risk factors of postoperative complications.

Squamous cell pathology, pain and insomnia were risk factors for 1-year OS.



**Title:** Does baseline quality of life predict the occurrence of complications in resectable esophageal cancer?

**Author statement:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.