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

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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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### 31 **Abstract and keywords**

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

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

41 **Results:** Every 10-point increase in the baseline role functioning score was associated with a  
42 14% reduction in the risk of MC, while every 10-point increase in fatigue or pain score was  
43 associated with an 18% increase in the risk of MC. Similarly, higher scores on fatigue and pain  
44 were associated with a higher risk of MPC. Compared with the hybrid procedure, patients  
45 undergoing open esophagectomy had a significantly higher risk of MC and MPC. Patients  
46 diagnosed with esophageal adenocarcinoma were at significantly lower risk of MC or MPC  
47 compared to patients with esophageal squamous cell carcinoma. Higher pain (HR=1.23,  
48 p=0.035) and insomnia (HR=1.16, P=0.031) scores were associated with increased 1-year OS.

**49 Conclusion:**

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

**53 Keywords:**

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

56

**57 Acknowledgements:** This research was set up using existing data on a prospective, multicenter,  
58 open label, randomized, controlled phase III trial comparing hybrid procedure and open  
59 procedure in patients with resectable esophageal cancer from 2009 to 2012 in France (the  
60 MIRO trial). We thank all the investigators in MIRO trial, special the co-PI who are not listed  
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65

**Main Text**

66

**1. Introduction**

67 Esophageal cancer was the 8<sup>th</sup> most common cancer diagnosed, and the 6<sup>th</sup> leading cause of  
68 cancer-related death worldwide in 2020 [1]. Esophageal cancer is a highly fatal disease, with  
69 5-year standardized net survival of 16% and 20% in men and women respectively in France  
70 [2].

71 Esophagectomy remains the primary curative treatment option for patients with esophageal  
72 cancer. Five-year survival has increased to 40% among patients undergoing surgery compared  
73 to those without surgery [3]. Standard esophagectomy consists in an open surgical excision  
74 (laparotomy + right thoracotomy) for subcarinal thoracic esophageal cancer. It is associated  
75 with a significant risk of postoperative morbidity (30% to 50%) and mortality (2% to 10%) [4-  
76 6]. In recent years, minimally invasive approaches have been evaluated for esophagectomy,  
77 and have resulted in a decreased incidence of overall morbidity, pulmonary complications and  
78 a shorter length of hospital stay [7-10].

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

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

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

## 96 **2. Methods**

### 97 **2.1 Study design and population**

98 This study used data from MIRO. Briefly, the MIRO trial was a prospective, multicenter, open  
99 label, randomized, controlled phase III trial comparing the hybrid procedure to the open  
100 procedure in patients with resectable esophageal cancer. The patients were randomized from  
101 October 2009 through April 2012 in France, then followed up for 3 years after esophagectomy.  
102 MIRO inclusion criteria were patients aged 18-75 years with WHO performance status 0 to 2;  
103 diagnosed with squamous cell carcinoma (SCC) or adenocarcinoma of the middle or lower  
104 third of the esophagus with clinical stage I, II or III (T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>; N<sub>0</sub> or N<sub>1</sub>; M<sub>0</sub>), with the tumor  
105 judged as resectable pre-operation; with or without neoadjuvant therapy.

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

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

## 115 **2.2 Endpoints**

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

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

## 123 **2.3 Study Instruments**

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

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

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

## 138 **2.4 Statistical Analysis**

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

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

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



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

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

### 168 **3. Results**

#### 169 **3.1 Baseline patient characteristics**

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

176

**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)	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.

177

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

180 2.76 (SD=9.22). “Global health status”, with a mean of 69.49 (SD=19.66), was the worst  
 181 functioning score, and dysphagia 76.6 (SD=27.28) was the highest symptomatic score (Table  
 182 2).

183 **Table 2.** Baseline HRQOL score and the relation between baseline HRQOL scores and major  
 184 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

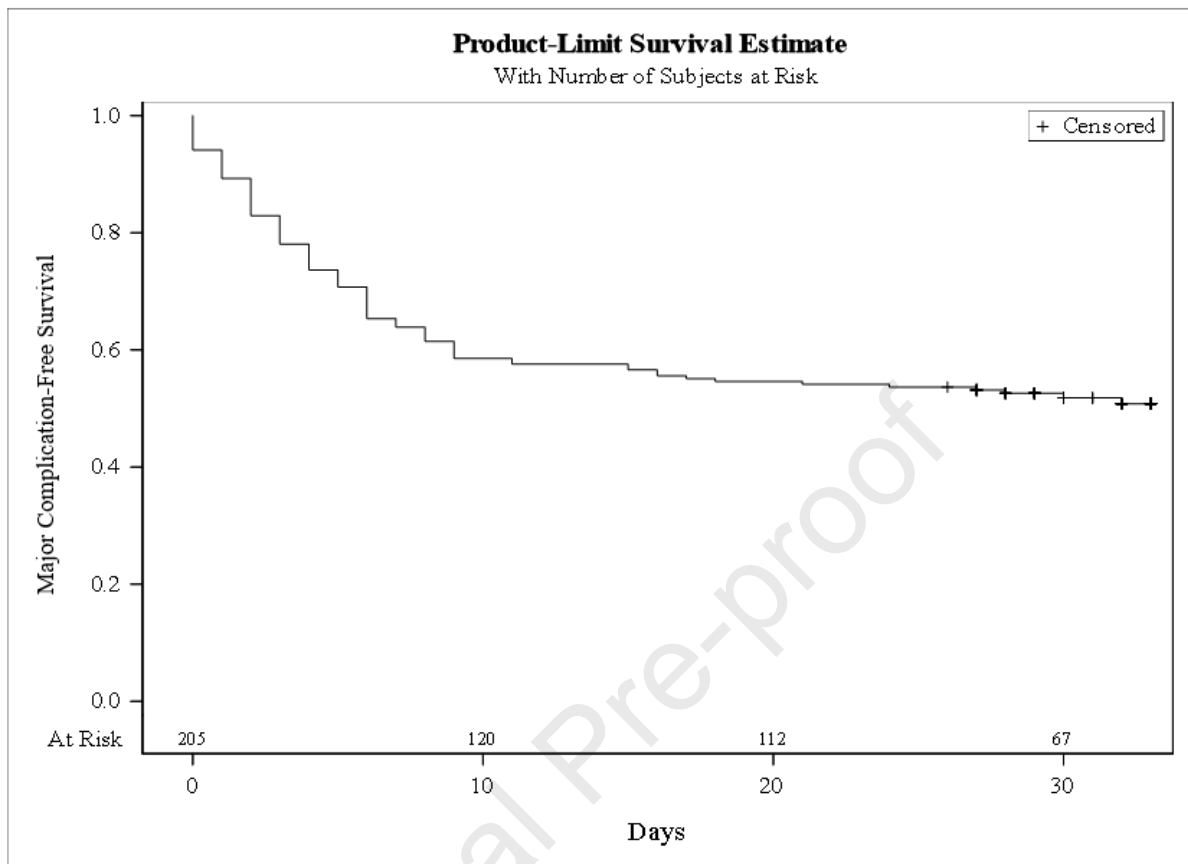
185 Abbreviations: HRQOL, Health Related Quality of Life; SD, standard deviation; MC, Major Complication; MPC,  
 186 Major Pulmonary Complication; OS, Overall Survival; QLQ-C30, European Organisation for Research and  
 187 Treatment of Cancer Quality of Life Questionnaire Core 30; QLQ OES-18, European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

189

### 190 3.2 Primary and secondary endpoints

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

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



196

### 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.

206 Patients with higher role functioning scores (every 10 point) were at lower risk of MC  
 207 (HR=0.86; 95% CI [0.77-0.96]; P=0.007), while every 10-point increase in fatigue (HR=1.18;  
 208 95% CI [1.06-1.31]; P=0.002) and OES-18 pain scores was associated with an increased risk  
 209 of MC (HR=1.18; 95% CI [1.03-1.34]; P=0.014). Similarly, patients with higher scores on the  
 210 fatigue (HR=1.20; 95% CI [1.06-1.36]; P=0.004) and pain (HR=1.24; 95% CI [1.09-1.40];  
 211 P=0.001) dimensions of the QLQ-C30 were at higher risk of MPC (Table 3).

212 **Table 3.** Multivariable analysis of the impact of baseline HRQOL on the occurrence of major  
 213 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

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

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

217

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

### 226 3.3.2 HRQOL and 1-year postoperative OS

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

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

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

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

	Pain		Insomnia	
	HR [95% CI]	P value	HR [95% CI]	P value
HRQOL*	1.23 [1.02;1.50]	<b>0.035</b>	1.16 [1.01;1.32]	<b>0.031</b>
Age (year)				
≤ 60	1		1	
> 60	2.80 [1.10;7.15]	<b>0.031</b>	2.18 [0.87;5.48]	0.098
Major complication				
No	1		1	
Yes	3.23 [1.36; 7.66]	<b>0.008</b>	2.99 [1.24;7.20]	<b>0.015</b>
TNM-N				
N0	1		1	
N1	2.08 [0.86;5.04]	0.103	2.69 [1.05;6.93]	<b>0.040</b>
N2	10.43 [2.37;45.87]	<b>0.002</b>	10.51 [2.30;47.90]	<b>0.002</b>

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

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

246

#### 247 4. Discussion

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

253 In our study, every 10-point increase in the baseline role functioning score was associated with  
 254 a 14% reduction in the risk of MC. Conversely, every 10-point increase in fatigue or OES18-  
 255 pain symptoms at baseline was associated with an 18% increase in the risk of MC. Similarly,  
 256 every 10-point increase in pain or fatigue symptom scores was associated with a higher risk  
 257 (20-24%) of MPC.

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

261 HRQOL with persisting symptoms [23-24]. Postoperative complications after esophagectomy  
262 mainly include in the short-term pulmonary and cardiac complications, anastomotic leakage,  
263 chylothorax, and delayed gastric emptying, which mostly occurred during the first week after  
264 surgery [7]. In the long-term, anastomotic stenosis and reflux oesophagitis can occur and  
265 potentially impair patients' HRQOL. Postoperative anastomotic leakage is one of the most  
266 important complications leading to death [25]. The higher the incidence of postoperative  
267 pulmonary complications, the greater the harm. Reported risk factors for pulmonary  
268 complications include patients' smoking history, forced expiratory volume (FEV), chronic  
269 obstructive pulmonary disease (COPD), age, obesity, and lung diseases, while lymph node  
270 dissection status and preoperative serum albumin levels are risk factors for anastomotic leakage  
271 [26-28]. In the present randomized, controlled study, strict inclusion/ exclusion criteria were  
272 applied, and a standardized perioperative pathway was proposed for all patients, including  
273 alcohol and smoking cessation for at least 1 month prior to surgery, oral immuno-nutrition and  
274 enteral nutritional assistance, intraoperative respiratory and cardiovascular monitoring and an  
275 algorithm of treatment for post-operative complications. Together, these contributed to  
276 minimizing differences between patients, leading to more convincing results. We focused our  
277 analysis on MC, including MPC, and found that nearly 50% of MC are pulmonary  
278 complications. In addition to the type of surgical approach and tumor histology, the initial  
279 HRQOL score (role functioning, fatigue and pain) could also play a role in the occurrence of  
280 complications. When performing preoperative assessment, in addition to routine tumor and  
281 clinical examinations, special attention should be paid to patients' HRQOL, such as pain and  
282 fatigue.

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



286 management are thus critical to improve the quality of life and health outcomes in this  
287 population [29]. In our analysis, lymph node status was shown to be an important risk factor  
288 for death at 1 year, whereby patients with more advanced N stage (N<sub>2</sub>), had an approximately  
289 10-fold increase in the risk of death. Furthermore, patients who experienced a MC had around  
290 a 3-fold increase in the risk of death at 1 year compared to patients who suffered no  
291 complication. In the multivariable model on the pain dimension, older age (> 60 years) was  
292 associated with a higher risk of death at 1 year. Previous studies have identified age,  
293 pathological T stage, clinical lymph node involvement and treatment modality (surgery versus  
294 definitive chemoradiotherapy) as predictive factors of death in esophageal cancer [30-31]. The  
295 study by Tamagawa et al showed that the development of postoperative pneumonia was a risk  
296 factor for decreased 5-year OS in patients who underwent curative surgery for esophageal  
297 cancer [32]. In our analysis, age was a risk factor for 1-year overall survival in certain  
298 conditions. In clinical practice, management and treatment of MC, especially for older patients,  
299 is of paramount importance.

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

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

**311 5. Conclusion**

312 In conclusion, the role functioning, fatigue and pain were independent prognostic factors of  
313 complications in patients with resectable esophageal cancer treated with surgery. Role  
314 functioning had a protective effect against MC, while fatigue and pain were associated with an  
315 increased risk of the occurrence of MC or MPC. Regarding 1-year OS after surgery, pain and  
316 insomnia were prognostic risk factors for death; patients with squamous cell pathology, older  
317 age, and more advanced lymph node status were indicators of poor prognosis of OS. To patients  
318 with these presences, special attention should be paid, and it might possibly change the  
319 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.

Journal Pre-proof



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

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Journal Pre-proof