ORIGINAL ARTICLE

Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer

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ABSTRACT

BACKGROUND

Postoperative complications, especially pulmonary complications, affect more than half the patients who undergo open esophagectomy for esophageal cancer. Whether hybrid minimally invasive esophagectomy results in lower morbidity than open esophagectomy is unclear.

METHODS

We performed a multicenter, open-label, randomized, controlled trial involving patients 18 to 75 years of age with resectable cancer of the middle or lower third of the esophagus. Patients were randomly assigned to undergo transthoracic open esophagectomy (open procedure) or hybrid minimally invasive esophagectomy (hybrid procedure). Surgical quality assurance was implemented by the credentialing of surgeons, standardization of technique, and monitoring of performance. Hybrid surgery comprised a two-field abdominal–thoracic operation (also called an Ivor–Lewis procedure) with laparoscopic gastric mobilization and open right thoracotomy. The primary end point was intraoperative or postoperative complication of grade II or higher according to the Clavien–Dindo classification (indicating major complication leading to intervention) within 30 days. Analyses were done according to the intention-to-treat principle.

RESULTS

From October 2009 through April 2012, we randomly assigned 103 patients to the hybrid-procedure group and 104 to the open-procedure group. A total of 312 serious adverse events were recorded in 110 patients. A total of 37 patients (36%) in the hybrid-procedure group had a major intraoperative or postoperative complication, as compared with 67 (64%) in the open-procedure group (odds ratio, 0.31; 95% confidence interval [CI], 0.18 to 0.55; P<0.001). A total of 18 of 102 patients (18%) in the hybrid-procedure group had a major pulmonary complication, as compared with 31 of 103 (30%) in the open-procedure group. At 3 years, overall survival was 67% (95% CI, 57 to 75) in the hybrid-procedure group, as compared with 55% (95% CI, 45 to 64) in the open-procedure group; disease-free survival was 57% (95% CI, 47 to 66) and 48% (95% CI, 38 to 57), respectively.

CONCLUSIONS

We found that hybrid minimally invasive esophagectomy resulted in a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complications, than open esophagectomy, without compromising overall and disease-free survival over a period of 3 years. (Funded by the French National Cancer Institute; ClinicalTrials.gov number, NCT00937456.)

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Esophageal cancer is among the cancers with the most rapidly increasing incidence in the Western world.[1,2] Overall survival among patients with esophageal cancer remains poor; the 5-year survival is 10 to 15% among all patients but increases to 40% among patients who undergo curative surgery.[3,4] Improvements in overall survival after esophagectomy have been observed in recent years because of centralization of practice to high-volume centers[5,6] and the increased use of treatments involving multiple approaches.[3,4,7]

Randomized, controlled trials have previously shown that a minimally invasive surgical approach to colorectal and gastric cancer reduces surgical trauma and results in reduced blood loss, fewer complications, shorter length of hospital stay, and a faster recovery to normal activity.[8-10] The randomized TIME trial showed that totally minimally invasive esophagectomy (both thoracoscopic and laparoscopic) was associated with a lower incidence of pulmonary complications than open esophagectomy.[11] In the current era, esophagectomy is most commonly a two-field (abdominal and thoracic) surgical procedure, and it remains unclear whether the maximal benefit of a minimally invasive approach is in the abdominal or thoracic phase. Hybrid minimally invasive esophagectomy combines a laparoscopic abdominal phase with an open thoracotomy, which may have specific advantages, including a lower rate of pulmonary complications, laparoscopic tumor dissection limiting potential tumor spillage, and easier reproducibility of the technique.[12] In this large, prospective, randomized, controlled trial, we hypothesized that hybrid minimally invasive esophagectomy would result in a lower incidence of major intraoperative and postoperative complications than open esophagectomy, without compromising rates of cancer recurrence.

Methods

Trial Design

In this prospective, open-label, multicenter, randomized, controlled, phase 3 trial, we compared hybrid minimally invasive esophagectomy (laparoscopic gastric mobilization and open thoracotomy) with open esophagectomy (open gastric mobilization and thoracotomy) in patients with thoracic esophageal cancer who were undergoing esophagectomy by means of an abdominal and right thoracic approach (Ivor–Lewis procedure). In both trial groups, patients underwent an open right thoracic approach.

The trial was conducted at 13 centers in France (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol has been published previously[13] and is available at NEJM.org. The trial was funded by the French National Cancer Institute.

The trial complied with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice. The trial was approved by the institutional review board, the Nord-Ouest II ethics committee, in March 2009 and by the Agence Française de Sécurité Sanitaire des Produits de Santé in May 2009. The last author vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

The trial included patients with squamous-cell carcinoma or adenocarcinoma of the middle or lower third of the esophagus who were eligible to undergo surgical resection. Specific inclusion criteria were the following: squamous-cell carcinoma or adenocarcinoma of thoracic esophagus with a clinical stage of I, II, or III (tumor stage 1 through 3 [T1, T2, or T3], no nodal involvement [N0] or presence of cancer in lymph nodes [N1] or in distant lymph nodes [≥5 cm from the tumor; N2], and no metastases [M0]) before the receipt of any induction treatment; esophageal cancer in the middle or lower third of the esophagus or junctional (Siewert's type I) tumor; the receipt or nonreceipt of neoadjuvant radiotherapy, chemotherapy, or both; tumors that were considered to be resectable with a curative intention at the time of preoperative evaluation; an age of 18 to 75 years; a World Health Organization performance-status score of 0, 1, or 2 (on a 5-point scale, with higher numbers indicating greater disability); ability to provide written informed consent; ability to undergo one of the investigated surgical procedures; and ability to attend the follow-up visits.

The patient-associated exclusion criteria were the following: a partial pressure of arterial oxygen of less than 60 mm Hg while the patient was breathing ambient air; a partial pressure of arterial carbon dioxide of more than 45 mm Hg; a forced expiratory volume in 1 second of less than 1000 ml; liver cirrhosis; myocardial infarction

or progressive coronary artery disease; peripheral arterial occlusive disease of Leriche–Fontaine stage II or higher (in this four-stage system, higher numbers indicate worse symptoms); weight loss exceeding 15% in the 6 months before cancer diagnosis; the presence of another malignant tumor; and receipt of any other simultaneous experimental treatment. The disease-associated exclusion criteria were the following: another histologic subtype of esophageal cancer apart from squamous-cell carcinoma or adenocarcinoma; tumor located at the pharyngoesophageal junction, the cervical esophagus, the upper third of the esophagus, or the esophagogastric junction (Siewert type II or III); distant metastases, including peritoneal carcinomatosis or metastasis to the supraclavicular and celiac lymph nodes; recurrent laryngeal nerve palsy; and tumor involvement of adjacent mediastinal structures. Exclusion criteria associated with surgical technique were a contraindication to laparoscopy and a history of supraumbilical laparotomy.

RANDOMIZATION

Randomization was performed centrally, with the use of the stratified-field block-randomization method (blocks of four) for each participating center. A randomization list was generated for each center, and numbered envelopes were prepared. The blinded assignment to a trial group was done during surgery, according to serial inclusion. All the eligible patients were randomly assigned intraoperatively after the surgeon performed laparoscopic exploration of the abdominal cavity to confirm the absence of contraindications to curative surgery. Patients, physicians, and investigators were aware of the assigned treatment group during or immediately after surgery.

PROCEDURES AND QUALITY CONTROL

Patients with esophageal cancer were considered for curative surgery after a complete preoperative workup, as described in the published protocol.[13] Clinical tumor staging (with the tumor–node–metastasis [cTNM] system) was based on data obtained from computed tomography (CT), endoscopic ultrasonography, and positron-emission tomography. The use of neoadjuvant therapy was determined locally by the multidisciplinary cancer board at each participating center,[14,15] according to national and international guidelines, and applied to all patients, regardless of group in the trial.

Preoperative care for all the patients included the treatment of dental, head, and neck or bronchial infections; immunonutrition (Oral Impact, Nestlé Health Science) 5 to 7 days before surgery; advice to cease smoking and drinking alcohol for at least 1 month before surgery; and insertion of a percutaneous gastrostomy or jejunostomy tube for nutrition in malnourished patients (those with weight loss of >10% over the 6-month period before the cancer diagnosis). General anesthetic induction and maintenance, along with intraoperative analgesia with thoracic epidural, was performed as described in the published protocol.[13] Cardiovascular variables were standardized and carefully controlled in a similar way in each treatment group, both intraoperatively and postoperatively, with single lumen ventilation during thoracotomy.[13]

After laparoscopic abdominal exploration and confirmation of tumor resectability, patients were randomly assigned to undergo hybrid minimally invasive esophagectomy (hybrid-procedure group) or open esophagectomy (open-procedure group). Despite the difference in approach to the abdominal component of the surgical procedure, the surgical technique was standardized between groups and performed as described previously.[13] All the patients were scheduled to receive a transthoracic en bloc esophagectomy with an extended two-field lymphadenectomy and terminolateral anastomosis in the upper chest with the use of a gastric conduit in all cases. No pyloric drainage procedures were routinely performed in either group, and the anastomosis was either sutured or stapled at the discretion of the operating surgeon.

Guidelines for enhanced recovery after surgery were followed at all the participating centers.[13] Oral intake was progressively introduced on day 5 after the removal of the nasogastric tube if no anastomotic leak was suspected, and early mobilization was performed on postoperative day 1.

All the participating centers had surgeons who were experienced in esophageal-cancer surgery and in laparoscopic gastric mobilization, with at least 25 procedures performed at each center before it was included in the trial. A technical surgical video of the abdominal minimally invasive phase was sent to each participating center

to standardize surgical technique, and during the initial cases, surgical technical supervision was undertaken by the principal investigator at each center, as stipulated in the protocol.

END POINTS

The primary end point was major complication during surgery or within 30 days after surgery. A major intraoperative and postoperative complication was defined as a surgical or medical complication with a Clavien–Dindo grade of II or higher (this five-grade system includes subgrades in grades III and IV, and higher grades indicate more life-threatening complications).[16] The most severe complication in a patient was considered for the classification of the primary end point.

Secondary end points included postoperative death within 30 days, intraoperative and postoperative overall complications (major and minor) within 30 days, major pulmonary complications within 30 days, disease-free survival (defined as the time between randomization and the first tumor recurrence [local, regional, or distant], second cancer, or death from any cause), and overall survival (defined as the time between randomization and death from any cause). Standardized definitions of complications were used for classification, as previously described (see the protocol).[13]

FOLLOW-UP

Patients were followed up at 30 days after surgery and every 6 months for 3 years after surgery. Follow-up included physical examination; thoracoabdominal CT scan every 6 months; an ear, nose, and throat examination once per year; bronchoscopy for squamous-cell cancer every 2 years; and esophagogastroduodenoscopy every 2 years. Other examinations, including positron-emission tomographic scanning or visits that were earlier than scheduled according to the protocol, were done on demand.

STATISTICAL ANALYSIS

On the basis of published literature,[11] we postulated that we would observe a clinically meaningful difference of 20 percentage points in the incidence of major complications between the open-procedure group (45%) and the hybrid-procedure group (25%). To show this between-group difference using a bilateral alpha type I error of 5%, at a power of 80% on the basis of the chi-square test, we calculated that the sample size for each group was 98. We anticipated losing a maximum of 4 patients to follow-up, and thus the estimated sample size for the trial was 200.

All the analyses were performed on an intention-to-treat basis; the analyses included all the patients who had undergone randomization, regardless of the surgery performed and eligibility criteria. Discrete end points including the primary end point were described with the use of frequencies and percentages with 95% confidence intervals and were compared by the chi-square test or Fisher's exact test. Univariate and multivariate logistic regressions were done to account for potential confounding variables affecting binomial end points. Continuous end points were described with the use of means (with standard deviations) and medians (with ranges). A random effect for center was introduced in the multivariate logistic regressions to account for within-center correlation among outcomes, and multivariate analyses were also adjusted according to potential confounding factors.

Kaplan–Meier analysis was used to estimate time-to-event end points. The survival end points were described by their median value and rate at specific time points with 95% confidence intervals. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratio with 95% confidence intervals. Because the initial statistical analysis plan did not include a provision for correcting for multiple comparisons when tests for secondary or other end points were conducted, P values were not provided, and results are reported as point estimates with 95% confidence intervals. All the statistical analyses were performed with the use of Stata software, version 13.1 (StataCorp). The statistical analysis plan is available with the protocol.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The flow of patients through the trial is described in Figure 1. From October 2009 through April 2012, we assessed 219 patients for eligibility; 12 patients were excluded, with 7 excluded because of a contraindication to curative surgery, 4 because of cirrhosis, and 1 because no laparoscope was available at the time of surgery.

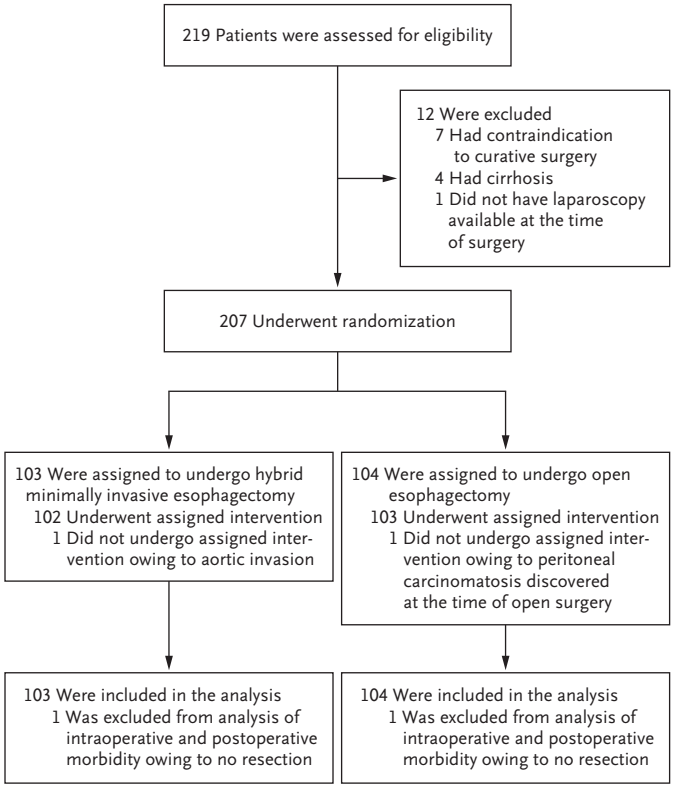


Figure 1. Screening, Randomization, and Follow-up of the Patients.

Therefore, 207 patients underwent randomization — 103 patients to the hybrid-procedure group and 104 to the open-procedure group. Two patients (1 in each group) did not undergo resection; this was due to aorta invasion in a patient in the hybrid-procedure group and due to peritoneal carcinomatosis that was discovered at the time of open surgery in a patient in the open-procedure group.

The demographic and clinical characteristics of the two groups did not differ significantly at baseline, except for the American Society of Anesthesiologists risk score (Table 1). The percentage of patients receiving neoadjuvant therapy was similarly high in the two groups (75% in the hybrid-procedure group and 72% in the open-procedure group) (Table 1). A total of 3 patients (3%) who had been assigned to the hybrid-procedure group underwent intraoperative conversion to the open procedure: 1 underwent laparotomy without resection because of advanced disease, 1 underwent intraoperative conversion to the open procedure because of subcutaneous emphysema, and 1 underwent intraoperative conversion to the open procedure, as decided by the surgeon on the basis of intraoperative physiological stress of the patient. According to the intention-to-treat principle, these patients were included in the hybrid-procedure group.

SHORT-TERM OUTCOMES

A total of 312 serious adverse events were recorded in 110 patients. The primary end-point analysis showed that hybrid minimally invasive esophagectomy was associated with major intraoperative and postoperative morbidity at 30 days that was significantly lower than that with open esophagectomy (36% vs. 64%; $P<0.001$ by the chi-square test; odds ratio, 0.31; 95% confidence interval [CI], 0.18 to 0.55; $P<0.001$). We found no effect of trial center ($P=0.39$) (Fig. S2 in the Supplementary Appendix).

After adjustment for age, sex, American Society of Anesthesiologists risk score, neoadjuvant therapy use, tumor location, histologic subtype, resection-margin status, pathological tumor and node stages, and trial center, we found that minimally invasive surgery was associated with a 77% lower risk of major intraoperative and postoperative complications within 30 days than open surgery (adjusted odds ratio, 0.23; 95% CI, 0.12 to 0.44; $P<0.001$). Secondary end-point analysis showed no differences between the groups in postoperative mortality at 30 days, intraoperative and postoperative overall morbidity (major and minor) at 30 days, and surgical or medical morbidity (Table 2, and Tables S1 and S2 in the Supplementary Appendix). However, hybrid minimally invasive surgery was associated with a lower incidence of major pulmonary complications within 30 days than open surgery (18% vs. 30%). Moreover, the risk of major pulmonary complications within 30 days was 50% lower in the hybrid-procedure group than in the open-procedure group (odds ratio, 0.50; 95% CI, 0.26 to 0.96). Other end points, including operative time and the median length of hospital stay, were similar in the two groups.

PATHOLOGICAL ANALYSIS

No significant differences between the hybrid-procedure group and the open-procedure group were noted with regard to tumor histologic findings, differentiation, pathological tumor or node stage, total number of lymph nodes resected, or the number of positive lymph nodes

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Total Trial Population (N=207)	Hybrid Minimally Invasive Esophagectomy (N=103)	Open Esophagectomy (N=104)
Age — yr			
Median	61	59	62
Range	23–78	23–75	41–78
Sex — no. (%)			
Male	175 (85)	88 (85)	87 (84)
Female	32 (15)	15 (15)	17 (16)
Body-mass index†			
Median	25	26	25
Range	16–37	16–37	18–35
ASA risk score — no. (%)‡			
1	59 (29)	25 (24)	34 (33)
2	119 (57)	61 (59)	58 (56)
3	29 (14)	17 (17)	12 (12)
WHO performance-status score — no. (%)§			
0	120 (58)	67 (65)	53 (51)
1	79 (38)	31 (30)	48 (46)
2	8 (4)	5 (5)	3 (3)
Clinical tumor classification — no./total no. (%)¶			
cT1	37/198 (19)	18/98 (18)	19/100 (19)
cT2	63/198 (32)	30/98 (31)	33/100 (33)
cT3	98/198 (49)	50/98 (51)	48/100 (48)
Clinical node classification — no./total no. (%)¶			
cN0	89/199 (45)	41/98 (42)	48/101 (48)
cN1	102/199 (51)	53/98 (54)	49/101 (49)
cN2	8/199 (4)	4/98 (4)	4/101 (4)
Tumor histologic findings — no. (%)			
Squamous-cell carcinoma	84 (41)	46 (45)	38 (37)
Adenocarcinoma	123 (59)	57 (55)	66 (63)
Location of tumor in esophagus — no. (%)			
Upper third	1 (<1)	0	1 (1)
Middle third	63 (30)	32 (31)	31 (30)
Lower third	143 (69)	71 (69)	72 (69)
Neoadjuvant therapy — no. (%)			
Chemotherapy	86 (42)	41 (40)	45 (43)
Chemoradiotherapy	66 (32)	36 (35)	30 (29)
None	55 (27)	26 (25)	29 (28)

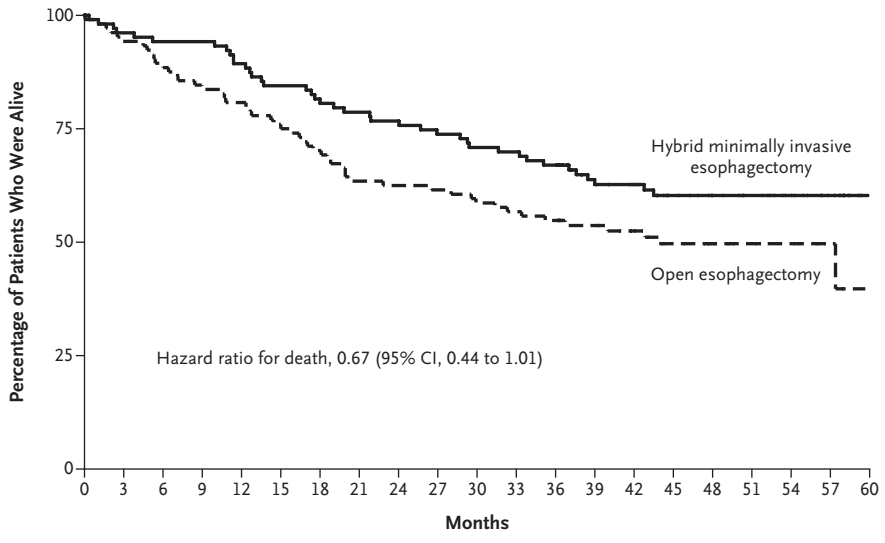
* There were no significant between-group differences at baseline. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The ASA scoring system is used to assess the physical status of patients before surgery; scores range from 1 to 5, with higher numbers indicating a lower likelihood of survival.
§ World Health Organization (WHO) performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability. A score of 0 indicates asymptomatic status, a score of 1 symptomatic but ambulatory and capable of carrying out light work, and a score of 2 symptomatic and in bed less than 50% of the day.
¶ The clinical tumor–node–metastasis (cTNM) classification we used was a combination of the ctTNM classification for carcinoma of the thoracic esophagus (based on Wurtz et al.[17] as modified by Bosset et al.[18]) and of the usTNM classification for carcinoma of the esophagus (based on Tio et al.[19]). The combination of the two, taking into account the most advanced stage, was used in the trial.

Table 2. Primary and Secondary End Points (Intention-to-Treat Population).*

End Points	Total Trial Population (N=207)	Hybrid Minimally Invasive Esophagectomy (N=103)	Open Esophagectomy (N=104)
Primary end point			
Major complication at 30 days — no. (%)	104 (50)	37 (36)	67 (64)
Secondary end points			
Postoperative death — no. (%)			
At 30 days	3 (1)	1 (1)	2 (2)
At 90 days	10 (5)	4 (4)	6 (6)
Major pulmonary complication at 30 days — no./total no. (%)†	49/205 (24)	18/102 (18)	31/103 (30)
Other end points			
Intraoperative complication — no./total no. (%)†	21/205 (10)	10/102 (10)	11/103 (11)
Total operative time — min			
Median	327	327	330
Range	65–583	103–582	65–583
Abdominal operative time — min			
Median	120	127	110
Range	51–350	60–280	51–350
Length of hospital stay — days			
Median	14	14	14
Range	3–218	7–95	3–218
Surgical complication — no./total no. (%)†	72/205 (35)	32/102 (31)	40/103 (39)
Anastomotic leak	18/205 (9)	11/102 (11)	7/103 (7)
Gastric necrosis	5/205 (2)	2/102 (2)	3/103 (3)
Chylothorax	12/205 (6)	5/102 (5)	7/103 (7)
Delayed gastric emptying	12/205 (6)	3/102 (3)	9/103 (9)
Medical complication — no./total no. (%)†	110/205 (54)	50/102 (49)	60/103 (58)
Respiratory failure‡	21/205 (10)	11/102 (11)	10/103 (10)
ARDS‡	15/205 (7)	8/102 (8)	7/103 (7)
Cardiac arrhythmia	26/205 (13)	12/102 (12)	14/103 (14)
Deep-vein thrombosis	3/205 (1)	2/102 (2)	1/103 (1)
Pulmonary embolus	2/205 (1)	1/102 (1)	1/103 (1)
Infectious complication — no./total no. (%)†	53/205 (26)	24/102 (24)	29/103 (28)

* Data on the total operative time were missing for one patient in the hybrid-procedure group, and data on the duration of abdominal operation and length of hospital stay were missing for one patient in the open-procedure group.
† Data on intraoperative and postoperative complications were not recorded for the two patients (one in each group) who did not undergo resection.
‡ Major bronchial sputum, pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS) were included in the classification of major pulmonary complication. Details are provided in Table S1 in the Supplementary Appendix.

resected (Table S3 in the Supplementary Appendix). Perioperative discovery of a hepatic metastasis was noted in one patient in the hybrid-procedure group. No significant between-group differences were noted in the incidence of resection-margin involvement (R1 [microscopic tumor involvement at the resection margin] or R2 [macroscopic tumor involvement at the resection margin]) or vertical or lateral margin involvement.



No. at Risk																					
Hybrid minimally invasive esophagectomy	103	99	97	97	92	87	84	81	79	76	73	72	69	58	54	43	37	33	27	20	7
Open esophagectomy	104	98	93	87	84	79	73	66	65	64	61	59	57	48	40	33	22	17	13	5	1

Figure 2. Overall Survival among Patients Undergoing Hybrid Minimally Invasive Esophagectomy, as Compared with Open Esophagectomy.

The number of patients at risk in each interval is shown in the table at the bottom of the figure.

DISEASE-FREE AND OVERALL SURVIVAL

Among the 207 patients who underwent randomization, 92 (44%) died during follow-up. The median follow-up as assessed by means of the reverse Kaplan–Meier method was 48.8 months (95% CI, 46.9 to 52.2). The median overall survival was 52.2 months (95% CI, 47.7 to 55.2) among the 103 patients in the hybrid-procedure group and 47.6 months (95% CI, 44.2 to 49.1) among the 104 patients in the open-procedure group.

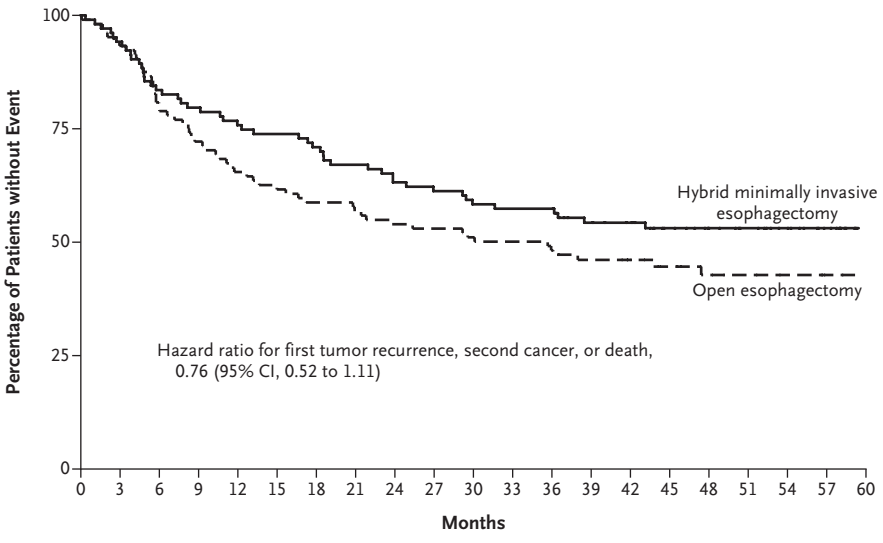
The percentage of patients who lived was higher in the hybrid-procedure group than in the open-procedure group, but the difference was not significant. The overall survival at 3 years was 67% (95% CI, 57 to 75) in the hybrid-procedure group, as compared with 55% (95% CI, 45 to 64) in the open-procedure group; the overall survival at 5 years was 60% (95% CI, 50 to 69) and 40% (95% CI, 21 to 58), respectively (hazard ratio for death, 0.67; 95% CI, 0.44 to 1.01) (Fig. 2).

Disease-free survival did not differ significantly between the two groups. Disease-free survival at 3 years was 57% (95% CI, 47 to 66) in the hybrid-procedure group and 48% (95% CI, 38 to 57) in the open-procedure group; at 5 years, the percentages were 53% (95% CI, 43 to 62) and 43% (95% CI, 33 to 52), respectively (hazard ratio for first tumor recurrence, second cancer, or death, 0.76; 95% CI, 0.52 to 1.11) (Fig. 3).

DISCUSSION

In this multicenter, randomized, controlled trial, we found that hybrid minimally invasive esophagectomy was associated with a 77% lower risk of major intraoperative and postoperative complications than open esophagectomy. Furthermore, minimally invasive surgery was associated with a 50% lower risk of major pulmonary complications than open surgery. Overall survival and disease-free survival were at least as good with minimally invasive surgery as with the open procedure.

In parallel to previous findings regarding colorectal resection and gastrectomy, we found that a minimally invasive approach to the abdominal phase of an Ivor–Lewis two-field abdominal–thoracic esophagectomy was associated with substantially lower major morbidity, specifically



No. at Risk

Hybrid minimally invasive esophagectomy	103	97	86	82	78	76	73	69	65	63	60	59	59	50	47	39	33	29	24	17	6
Open esophagectomy	104	97	83	75	68	64	61	59	56	55	53	52	50	40	34	28	19	15	12	4	1

Figure 3. Disease-free Survival among Patients Undergoing Hybrid Minimally Invasive Esophagectomy, as Compared with Open Esophagectomy.

Disease-free survival was defined as the time from randomization to the first tumor recurrence (local, regional, or distant), second cancer, or death from any cause. The number of patients at risk in each interval is shown in the table at the bottom of the figure.

pulmonary morbidity.[8-10] This result was most probably mediated by the reduction in surgical trauma, with less postoperative pain and a lower incidence of diaphragmatic splinting and thus less basal lung atelectasis and fewer major pulmonary complications. These results also parallel the results of the TIME trial,[11] in which total minimally invasive esophagectomy was associated with a 70% lower incidence of pneumonia at 2 weeks than open esophagectomy. Our trial included approximately twice the number of patients and more than twice the number of participating centers as were in the TIME trial.

In the present trial, we found nonsignificant prolongations of overall survival and disease-free survival with minimally invasive surgery, as compared with open esophagectomy. The long-term prognostic influence of major complications after esophageal-cancer surgery has been established previously, and the observed prolongation of survival with the hybrid minimally invasive approach may be mediated by the lower incidence of major complications described above.[20-22] It is important to note that this trial was not adequately powered to examine survival after esophagectomy, because the sample-size calculation was based on major complications as the primary end point. However, given our findings, a trial design that is based on a survival end point remains an important area for future research.

The strengths of our trial include the robust methods, which involved a well-defined, standardized description of complications that allowed for objective interpretation and limited subjectivity. The standardization and control of intraoperative and postoperative respiratory and cardiovascular variables in the present trial constitute an important strength that reduced the influence of these variables. The incidence of complications in this trial was higher than we expected, given previous published and largely retrospective literature on the subject.[13,23-25] This finding most probably represents the comprehensiveness of data collection and the definition of complications that were used in the trial. The trial also benefited from its large sample size.

This trial had a strong surgical quality-assur-

ance element in the design methods, which has been shown to influence the results of surgical intervention in randomized, controlled trials,[26] and their control within this trial represents a substantial strength that ensured a relatively homogeneous level of surgical performance. However, as is the case with many randomized, controlled trials, the generalizability of these findings to the international population of patients undergoing esophageal-cancer surgery remains undefined. The surgeons who took part in this trial were experienced, which implies that a critical threshold is needed before independent practice. At a national level, surgical performance can be a variable that affects patients' outcomes[27,28]; thus, the credentialing of surgeons before independent practice in a similar manner to their inclusion in randomized, controlled trials remains an important component of surgical quality assurance if results from trials are to be replicated in national outcomes.

In conclusion, this multicenter, randomized, controlled trial showed that hybrid minimally invasive esophagectomy resulted in a lower incidence of major complications (specifically, pulmonary complications) during or after esophagectomy for cancer than did open surgery. The hybrid procedure also resulted in overall survival and disease-free survival that were similar to those observed with open esophagectomy.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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