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Impact du tabagisme sur le pronostic des patients atteints de carcinome épidermoïde de l'œsophage : étude d'une cohorte prospective de 718 patients.

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Abréviations

CEE : carcinome épidermoïde de l'œsophage
F : fumeur
NF : non-fumeur
SG : survie globale
SSR : survie sans récidive
RCT : radiochimiothérapie
ORL : oto-rhino-laryngé

ESCC : esophageal squamous cell carcinoma
S : smoker
NS : non-smoker
OS : overall survival
RFS : recurrence free survival
CRT : chemoradiotherapy
AJCC : American Joint Committee on Cancer
CT-scan : computerized tomography
EUS : ultrasonography
PET-scan : positron emission tomography
TRG : tumor regression grade (Mandard)
pCR : pathological complete response
POM30 : 30-day postoperative mortality
POM90 : 90-day postoperative mortality
ECCG : Esophageal Complications Consensus Group
ASA : American Society of Anesthesiologists
HR(a) : Hazard ratio (adjusted)
CI95% : 95% confidence interval
LOS : length of stay
cCR : clinical complete response
AUC : Areas Under Receiver Operator Characteristic Curve
COPD : chronic obstructive pulmonary disease
OPL : œso-pharyngolaryngectomy
LN: Lymph-node
R0: Complete resection
R1: Microscopically incomplete resection
R2: Macroscopically incomplete resection

TABLE DES MATIÈRES

RESUME

Contexte: Le principal facteur de risque du carcinome épidermoïde de l'œsophage (CEE) est le tabagisme. Cependant, une proportion croissante de patients atteints de CEE est constituée de non-fumeurs. Les non-fumeurs atteints de cancers associés au tabagisme, comme les cancers de la sphère oto-rhino-laryngée ou le cancer bronchique, présentent un meilleur pronostic à long terme que les fumeurs mais peu de données existent en ce qui concerne le CEE.

Objectif: Décrire le pronostic de la population de non-fumeurs atteinte de CEE.

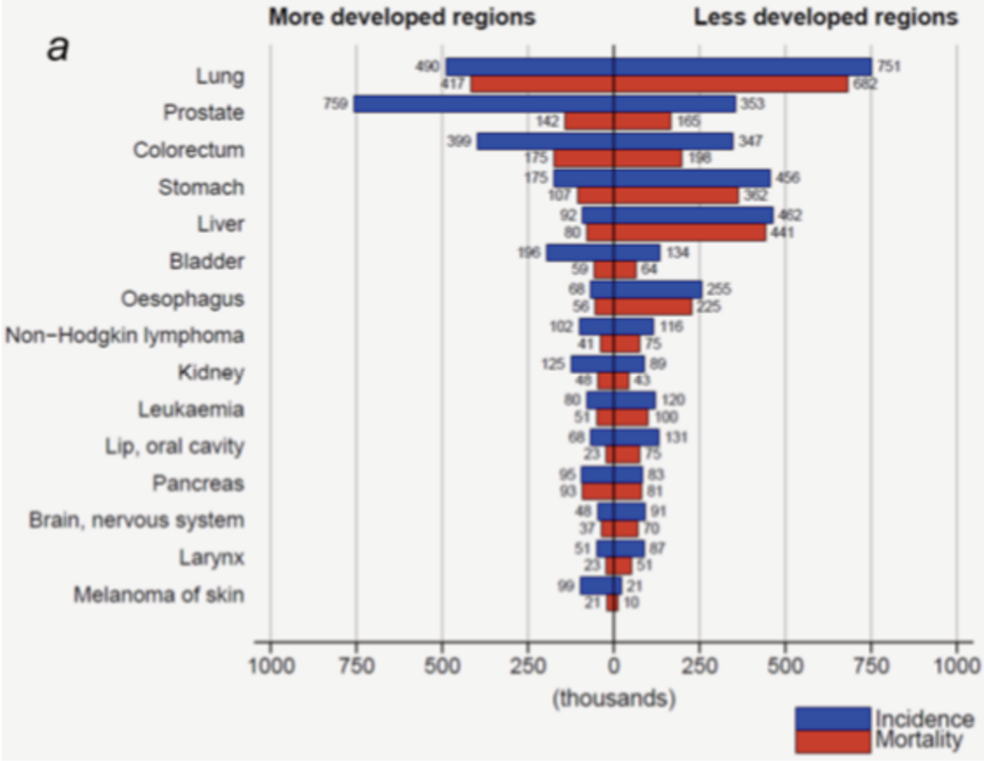
Méthodes: Les patients opérés d'un CEE dans notre centre entre le 1996 et le 2019 ont été rétrospectivement inclus à partir d'une base de données prospective. Les patients étaient classés fumeurs (F) ou non-fumeurs (NF) lors du diagnostic de la maladie. Le critère de jugement principal était la Survie Globale (SG). Les critères de jugement secondaires étaient la Survie Sans Récidive (SSR), les suites post-opératoires, les réponses clinique et histologique à la radiochimiothérapie (RCT) préopératoire.

Résultats: Parmi les 718 patients inclus, 103 (14.3%) et 615 (85.7%) étaient classés NF et F, respectivement. Le groupe NF comportait des patients plus âgés, plus souvent de sexe féminin, avec moins de comorbidités que les patients du groupe F. Les caractéristiques tumorales (localisation, stade, différenciation, radicalité) étaient similaires entre les groupes. Après un suivi médian de 63.9 mois, la SG était plus longue dans le groupe NF (médiane, mois : 57.4 vs 33.3, p=0.046), mais pas la SSR (médiane; mois : 36.0 vs 21.9, p=0.053). Les suites post-opératoires, les réponses clinique et histologique étaient similaires entre les groupes. Après analyse multivariée, le tabagisme n'était pas associé à la SG (Hazard Ratio ajusté: 1.10 (0.77-1.57, p=0.608)). Après RCT, les patients montraient des résultats comparables en termes de SG, de SSR, de réponses clinique et histologique. Le sevrage tabagique était associé à moins de complications respiratoires, moins de mortalité post-opératoire et une SG augmentée, quelle que soit la durée de sevrage.

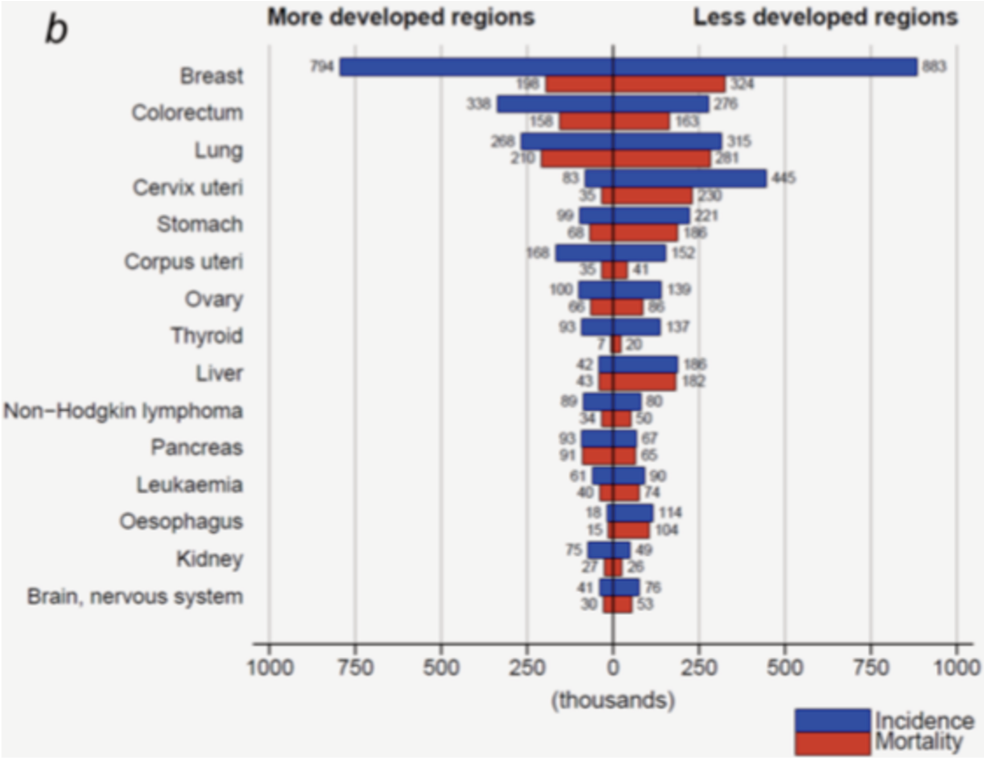
Conclusion: Le pronostic à long terme des patients atteints de CEE est meilleur en l'absence de tabagisme, mais cette différence apparaît plus liée au terrain du patient qu'à l'effet du tabagisme sur l'agressivité tumorale ou sa sensibilité au traitement par RCT. Le sevrage tabagique améliore le pronostic à court terme et à long terme et devrait être encouragé dès le début de la prise en charge du patient.

INTRODUCTION

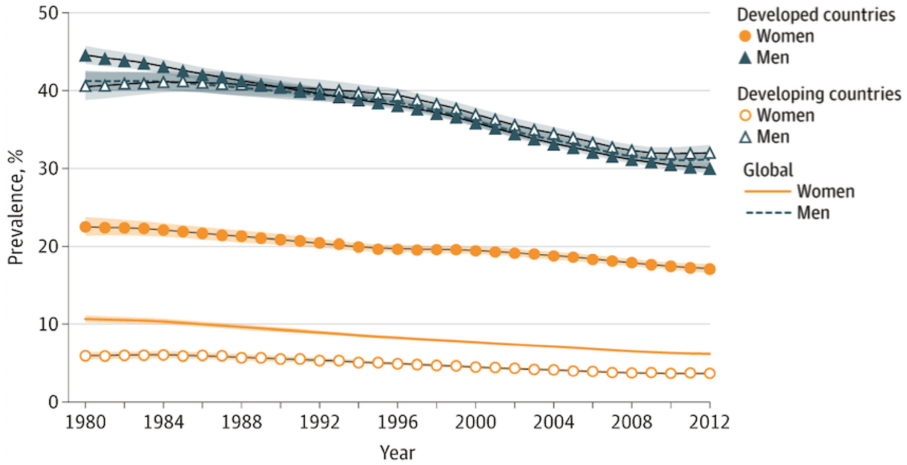
Le cancer de l'œsophage se situe au 8e rang des plus fréquents et au 6e rang des plus léthaux[1], avec une survie à 5 ans estimée à 14%[2]. En Europe, le carcinome épidermoïde de l'œsophage (CEE), représente 45 à 87% de l'ensemble des cancers de l'œsophage. Le tabagisme multiplie par 3 à 5 le risque de CEE et en représente le facteur de risque principal[3].



Estimations (en milliers d'habitants) de l'incidence (en bleu) et de la mortalité (en rouge) des cancers par organe dans les régions développées (vers la gauche) et moins développées (vers la droite), chez les hommes en 2012. De haut en bas : pourmons, prostate, colon & rectum, estomac, foie, vessie, œsophage, lymphome, reins, leucémie, cavité orale, pancréas, systène nerveux, larynx, mélanome. Extrait de Ferlay et al.[1]



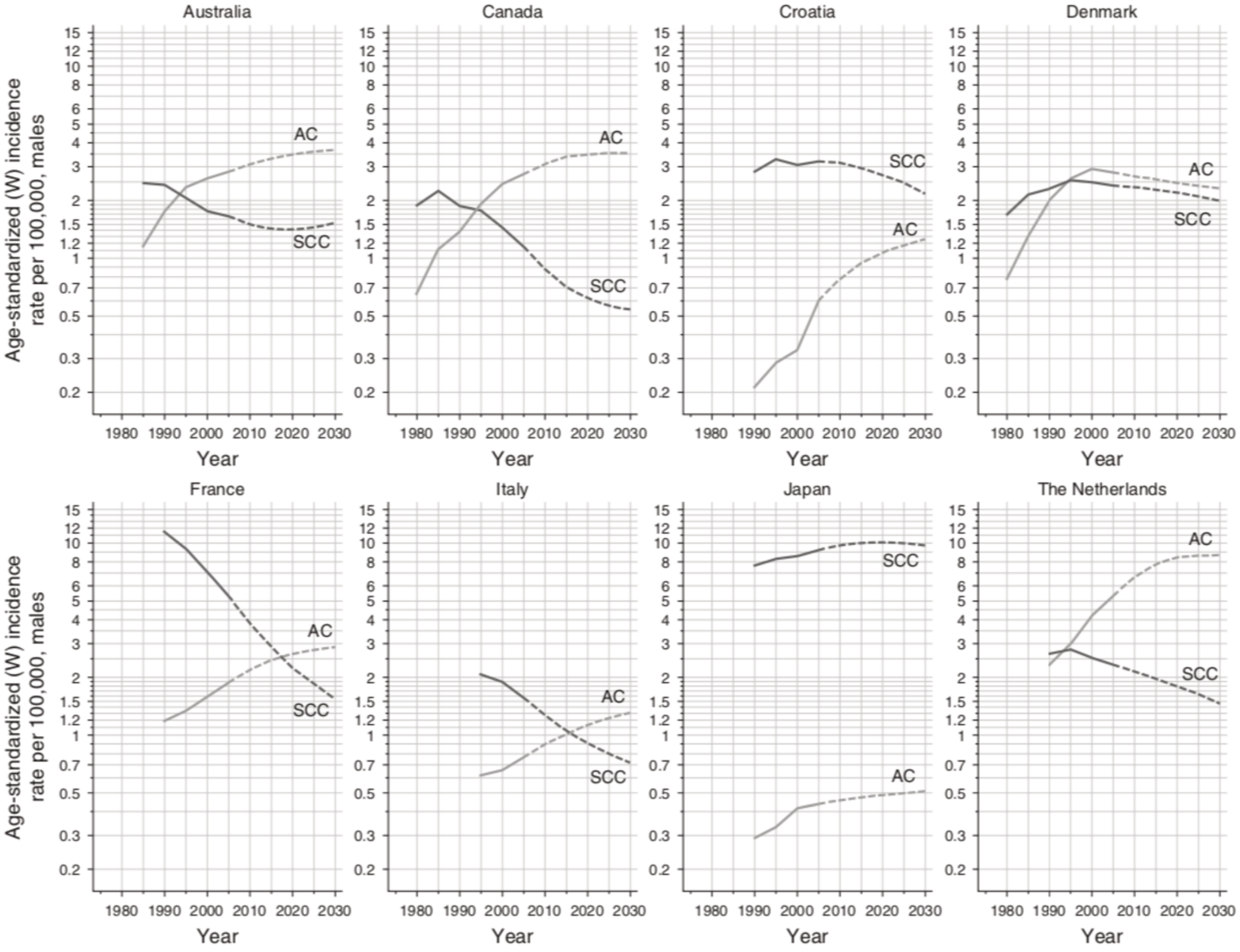
Estimations (en milliers d'habitants) de l'incidence (en bleu) et de la mortalité (en rouge) des cancers par organe dans les régions développées (vers la gauche) et moins développées (vers la droite), chez les femmes en 2012. De haut en bas : seins, colon & rectum, poumons, col utérin, estomac, corps utérin, ovaires, thyroïde, foie, lymphome, pancréas, leucémie, œsophage, reins, systène nerveux. Extrait de Ferlay et al.[1]



Prévalence du tabagisme dans les pays développés et en développement depuis 1980, standardisés sur l'âge et par sexe (en bleu les hommes, en jaune les femmes). Extrait de Ng et al.[4]

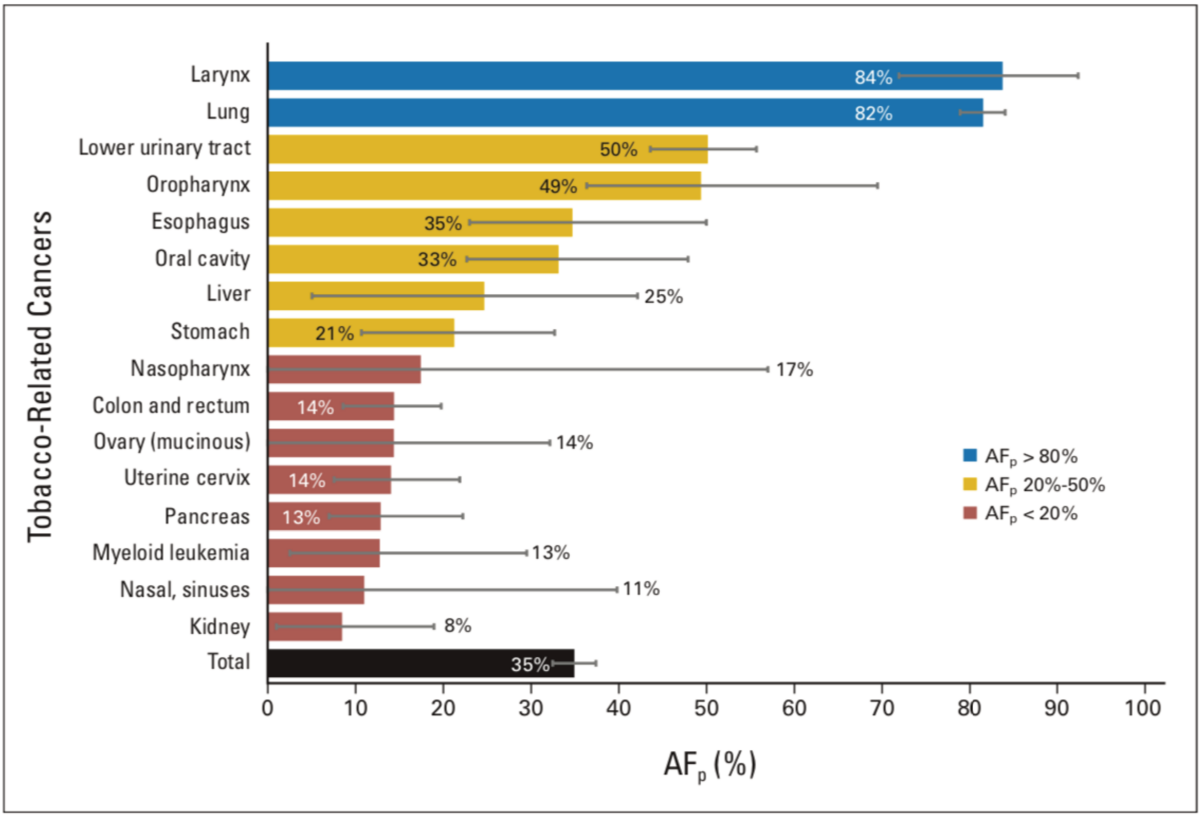
De ce fait, l'épidémiologie du CEE change dans la plupart des pays européens : sa prévalence est en déclin par rapport à celle de l'adénocarcinome, qui constitue l'autre type histologique principal de cancer de l'œsophage[5]. Cependant, le carcinome épidermoïde reste un type histologique

fréquemment observé en France, d'autant qu'une proportion croissante de non-fumeurs en est atteinte, en particuliers des femmes[6]. Le pronostic de cette population de non-fumeurs, majoritairement féminine, atteinte de CEE est à ce jour peu étudié.



Tendances (standardisées sur l'âge, pour 100 000 hommes) de l'incidence du cancer de l'œsophage selon le type histologique pour certains pays du monde, observées (lignes pleins) et prédites (lignes pointillées). AC = adénocarcinome; SCC = carcinome épidermoïde. Extrait de Arnold et al.[5]

Le rôle du tabagisme dans la cancérogenèse est inégal selon les cancers : dans le cancer bronchique, 82% des cas peuvent être attribués au tabagisme tandis que seuls un tiers des cas de CEE lui sont attribuables[7].



Fraction attribuable au tabac (AFp) dans la cohorte EPIC (European Prospective Investigation into Cancer and Nutrition), par cancer. Estimations ajustées sur l'âge, le sexe, le niveau socio-économique, l'indice de masse corporelle, l'activité physique, la consommation d'alcool, l'apport énergétique total et la consommation de fruits et légumes, en supposant une population également répartie répartie entre les sexes. Les IC de 95% (lignes grises) pour chaque estimation incluse dans la figure sont les suivants : larynx 72-92% ; poumon 79-84% ; bas-appareil urinaire 44-56% ; oropharynx 36-69% ; œsophage 23-50% ; cavité buccale 23-48% ; foie 5-42% ; estomac 11-33% ; nasopharynx 0.001-57% ; colorectal 9-20% ; ovaire (mucineux) 0-32% ; col utérin 8-22% ; pancréas 7-22% ; leucémie myéloïde 3-30% ; nasopharynx 0,0001-40% ; reins 1-19% ; tous cancers confondus 32-37%. Extrait de Agudo et al. [7]

Son influence sur le pronostic à long terme est aussi inégal, puisqu'il diminue la survie globale (SG) de patients atteints de cancers liés au tabagisme comme les cancers de la sphère ORL (oto-rhino-laryngée)[8,9] ou le cancer bronchique[10,11], alors que les données concernant le CEE sont plus rares et contradictoires.[12–14] Le pronostic à long terme des patients atteints de CEE est intimement lié à la prise en charge proposée, qui reste débattue dans certaines situations. Alors que la chirurgie est le traitement standard des maladies localisées (stades II-III)[15,16], les maladies localement avancées (stade III) peuvent être traitées soit par radiochimiothérapie (RCT) *exclusive* (à haute dose) sans chirurgie soit par RCT *néoadjuvante* (à plus faible dose) suivie d'une résection chirurgicale systématique, avec des résultats similaires sur la SG[17,18]. Puisque la résistance à la radiothérapie des fumeurs atteints de CEE a déjà été rapportée[19], le traitement chirurgical des formes localement avancées pourrait être plus efficace que la radiothérapie chez les fumeurs. Alors que des données existent sur l'intérêt du sevrage tabagique sur la diminution des complications post-opératoires après œsophagectomie[20], il n'existe aucun argument pour un bénéfice à plus long terme. Cette

étude a donc pour but de décrire le pronostic de la population de non-fumeurs atteinte de CEE. De plus, elle a pour objectifs secondaires de décrire l'efficacité de la RCT en fonction du tabagisme et l'influence du sevrage tabagique sur le pronostic.

ARTICLE

TITLE: ESOPHAGEAL SQUAMOUS CELL CARCINOMA IN NON-SMOKERS IS ASSOCIATED WITH BETTER OUTCOMES: RESULTS OF A PROSPECTIVE COHORT OF 718 PATIENTS.

ABSTRACT

Background: The main risk factor for esophageal squamous cell carcinoma (ESCC) is tobacco smoking. However, a growing proportion of patients with ESCC are non-smokers. Non-smokers affected by otherwise smoking-related cancers, like head and neck or lung cancers, have a better long-term prognosis than smokers but this data remains unknown in patients with ESCC.

Objectives: To describe outcomes of the non-smoking population affected with ESCC.

Methods: Patients surgically treated for ESCC in a single center between 1996 and 2019 were retrospectively included from a prospectively maintained database. Smoking (S) and non-smoking (NS) groups were defined at diagnosis. The primary outcome was Overall Survival (OS). Secondary outcomes were Recurrence Free Survival (RFS), postoperative outcomes, and pathological response to preoperative chemoradiotherapy (CRT).

Results: Among 718 patients included, 103 (14.3%) and 615 (85.7%) were NS and S, respectively. Patients in the NS group were older, mostly female and had less comorbidities than S patients. Tumor characteristics (location, stage, differentiation, complete resection (R0) rate) were similar between the groups. After a median follow-up of 63.9 months, OS was longer in the NS group (median in months: 57.4 vs 33.3, p=0.046), but not RFS (median in months: 36.0 vs 21.9, p=0.053). Postoperative outcomes, clinical and pathological response were similar between groups. After multivariate analysis, smoking was not associated with OS (adjusted Hazard Ratio: 1.10 (0.77-1.57, p=0.608)). After CRT, NS and S patients showed similar OS, RFS, clinical and pathological responses. Smoking cessation was associated with less respiratory complications, reduced postoperative mortality and prolonged OS, regardless of cessation time span.

Conclusion: Long-term prognosis of patients diagnosed with ESCC is better if they are non-smokers, but this difference appears to be more associated with patient's terrain than the effect of smoking on tumor aggressiveness or it's sensitivity to radiation therapy. Smoking cessation improves short-term and long-term outcomes and should therefore be encouraged as soon as possible in the patient's care.

INTRODUCTION

Esophageal cancer is the 8th most common cancer worldwide and the 6th deadliest cancer[1] with a 5-year survival rate as low as 14%[2]. In Europe, esophageal squamous cell carcinoma (ESCC) represents 45 to 87% of all esophageal cancers[21]. Tobacco smoking, with a 3- to 5-fold increased risk, is the main risk factor for ESCC[3]. Other risk factors include male gender and alcohol consumption. Smoking prevalence is declining in Europe since the 1980's[4]. Therefore ESCC epidemiology is shifting in most European countries: ESCC prevalence is declining in respect of adenocarcinoma, the other main esophageal cancer histological subtype[5]. However, ESCC remains widely encountered in France, with a growing proportion of non-smokers being affected, especially females[6]. The prognosis of this non-smoking population, mainly women, affected with ESCC remains unknown. In lung cancer, 82% of all cases are attributed to smoking but only a third of ESCC cases can be attributed to smoking[7]. It's influence on long-term prognosis is also uneven, with existing evidence on decreasing overall survival (OS) in smoking-related cancers like head and neck[8,9] and lung cancer patients[10,11], but scarce and conflicting data about ESCC patients[12–14]. Long-term prognosis of ESCC patients is closely related to its curative management, which remains controversial in some settings. Although the standard treatment for limited disease (stages I-II) is upfront surgery[15,16], treatment of locally advanced disease (stage III) can either constitute of *exclusive* (higher dose of) chemoradiation (CRT) without surgery or *neoadjuvant* (lower dose of) CRT followed by systematic surgery with similar results on OS[17,18]. Since resistance to radiation therapy in smokers with ESCC has been reported[19], surgical treatment of locally advanced could reveal more beneficial to smokers in comparison to radiotherapy. Although evidence of decreased post-operative complication rates after esophagectomy for cancer following smoking cessation exists[20], there is no evidence of improved long-term survival. This study aims to describe outcomes of the non-smoking population affected with ESCC. As secondary objectives, it aims to describe CRT effectiveness with respect to smoking status and influence of smoking cessation on patient outcomes.

PATIENTS AND METHODS

Patients

From a prospectively maintained database in our institution, all patients operated for ESCC between January 01, 1996 and December 31, 2019 were retrospectively analyzed. Medical records were reviewed for medical history, surgical, radiological, and pathological reports. Patient characteristics,

including age, gender, nutritional status, smoking, and alcohol consumption were collected at diagnosis. Patients were categorized into two groups depending on their smoking status: patients who declared to have ever smoked (S group) and patients who never smoked (NS group). Initial workup, treatment strategy, postoperative monitoring, and oncological follow-up were conducted according to the French guidelines[22]. All tumors were categorized according to the American Joint Committee on Cancer (AJCC) 7th classification[23] after a standard initial workup including a clinical assessment with nutritional status evaluation, CT-scan, upper endoscopy with endoscopic ultrasonography (EUS), bronchial fibroscopy, and upper aerodigestive tract panendoscopy. Explorative laparoscopy and/or PET-scan were also realized in suspected metastatic cases if doubt persisted after the standard workup. Patients with clinical stage III ESCC were operated after neoadjuvant CRT[24] or exclusive CRT in the salvage surgery setting[25] whereas those with clinical stages I-II ESCC were operated without neoadjuvant treatment[15]. In ESCC developed in previously radiated field (e.g. patients previously treated with radiation for lymphoma, breast cancer or previous squamous cell carcinoma), radiation dose was reduced to the maximal dose allowed by the previous radiotherapy. Surgical and anesthetic protocols were standardized. The pathological AJCC stage was based on the pathological reports. Pathological response to preoperative CRT was assessed by Mandard's Tumor Regression Grade (TRG) in esophageal tumor, where TRG1 corresponds to complete pathological response[26] and by pathological complete response (pCR) rates (i.e. absence of residual tumor cells in surgical specimen, including lymph nodes). Patient consent for data utilization was collected at the initial consultation.

Outcomes

The primary outcome was Overall Survival (OS), defined by the interval between surgery and death by any cause. Secondary outcomes were Recurrence Free Survival (RFS), postoperative outcomes (complications, reinterventions, deaths), clinical response (evaluated by EUS and CT-scan at minimum, and PET-scan if done preoperatively) and pathological response to preoperative CRT (assessed by TRG and pCR on surgical specimen). RFS was defined by the interval between surgery and pathologically or radiologically proven recurrence of ESCC or death by any cause. Postoperative complications were defined according to Esophageal Complications Consensus Group (ECCG)[27] definitions and graded according to the Clavien-Dindo classification[28]. Minor pulmonary complications encompassed dyspnea and bronchial congestion without need for orotracheal intubation. Major pulmonary complications encompassed atelectasis, pneumonia, respiratory failure and acute respiratory distress syndrome. Postoperative mortality was assessed at day 30 (POM30) and at day 90 (POM90) as recommended by the ECCG. Oncological follow-up

consisted in clinical evaluation, standard biological markers and a CT-scan at one month postoperatively, every 6 months for 2 years and every year for 5 years thereafter. A complete endoscopic workup was systematically done at least every 2 years.

Statistical analysis

Statistical analysis was performed with R version 4.0.2 (2020-06-22). The survival data were last updated on May 20, 2020. Patients alive on that date or lost to follow-up were censored. Median follow-up time was estimated using the Schemper's method[29]. OS and RFS were estimated using the Kaplan-Meier method and intergroup comparisons of OS and RFS were performed with the log-rank test. Chi-squared (or Fisher) and Student (or Mann-Whitney) tests were used to compare categorical and continuous variables, respectively. Univariate and multivariate Cox proportional hazards regression analysis were performed to identify factors independently associated with OS. Known factors associated with OS after esophagectomy were selected for univariate analysis: age > 60, American Society of Anesthesiologists (ASA) score, malnutrition (defined by weight loss > 10% in the past 6 months), AJCC tumor stage, tumor location, preoperative chemo- or radiation therapy, and surgical technique (thoracotomy, intrathoracic anastomosis)[30,31]. Additionally, every factor unevenly distributed between groups at baseline were included in univariate analysis. For multivariate analysis, all factors associated with OS with a p-value ≤ 0.10 in univariate analysis were included in the Cox proportional-hazards model. A multiple imputation algorithm was used in case of missing variables. Hazard Ratios (HR) and adjusted HR (HRa) are displayed with 95% confidence intervals (CI95%). A p-value ≤ 5 was considered as significant.

Subgroup analysis

A subgroup analysis of patients treated with preoperative radiotherapy was performed to evaluate whether smoking had a different effect in clinical and pathological outcomes in this subgroup. Variables evaluated were postoperative morbidity, mortality, reinterventions, median length of stay (LOS), complete clinical response (cCR), pathological outcomes (TRG, pCR), and long-term outcomes (OS, RFS).

Analysis of smoking cessation

Comparison of former and current smokers were performed within the S group to evaluate whether smoking cessation influenced the outcomes aforementioned. Outcomes differing between former and current smokers with statistical significance were then tested against cessation time span as an explanatory continuous variable to distinguish the early and the late quitters. Areas Under Receiver Operator Characteristic Curves (AUC) were used to determine if cessation time span

could predict categorical variables (short term outcomes). For survival analysis, multiple log-rank tests with every time span as threshold were done to find the maximum statistical significance.

RESULTS

Baseline characteristics (Table 1)

Among 718 patients included, 103 (14.3%) and 615 (85.7%) were NS and S, respectively. There were more females (65.0% vs 12.7%, p<0.001) and older patients (median age: 67.0 vs 59.0, p<0.001) in the NS group. Alcohol consumption was less frequent in the NS group (26.5% vs 77.9%, p<0.001). Smoking-related comorbidities were less frequent in the NS group. However, patients had similar ASA scores and malnutrition rates. NS had a higher rate of radiotherapy history (14.6% vs 3.9%, p<0.001). Tumors in NS patients were less frequently located in the upper third (12.7% vs 19.8%, p=0.049). There was no statistical difference in terms of preoperative chemotherapy, preoperative radiotherapy, cCR or adjuvant treatment. Surgical techniques were similar between groups, except for the laparoscopic abdominal approach, more often performed in the NS group (43.7% vs 29.4%, p=0.006).

Overall Survival (Figure 1)

After a median follow-up of 63.9 months, OS was significantly better in the NS group (median in months: 57.4 vs 33.3, p=0.046).

Recurrence Free Survival (Figure 2)

RFS was not significantly different between the NS and S groups (median in months: 36.0 vs 21.9, p=0.053).

Postoperative outcomes (Table 2)

Overall morbidity was comparable between the two groups (68.9% vs 68.3%, p=0.988), but major complications (Clavien-Dindo grades III-IV-IV) were significantly lower in the NS group (21.4% vs 37.6%, p<0.001). Anastomotic leak (7.8% vs 15.4%, p=0.057 and pneumonia (7.8% vs 15.9%, p=0.044) rates were also lower in the NS group. There were no statistical difference in reinterventions rates, POM30 or POM90 between groups.

Pathological findings (Table 3)

There was no statistical difference in pathological findings between groups, especially in rates of tumor classified TRG1 (35.7% vs 31.7%, p=0.921) or pCR rate (16.5% vs 16.1%, p=1.000).

Multivariate analysis of factors associated with Overall Survival (Table 4)

In univariate analysis, factors associated with OS were gender, ASA score, smoking, alcohol consumption, malnutrition, arteriopathy, chronic obstructive pulmonary disease, radiotherapy history, tumor localization, preoperative chemo- and radiotherapy, adjuvant chemo- and radiotherapy, type of abdominal approach, anastomotic location, pathological AJCC stage, tumor differenciation, incomplete resection and pCR. After multivariate analysis, factors independently associated with decreased OS were ASA score (HRa=1.31 (1.03-1.67, p=0.026), preoperative chemotherapy (HRa=1.64 (1.02-2.66, p=0.042)), radiotherapy history (HRa=1.79 (1.12-2.88, p=0.016), pathological AJCC stages III-IV (HRa=2.46 (1.91-3.17, p<0.001) and HRa=2.75 (1.93-3.91, p<0.001), respectively) and incomplete resection (HRa=2.32 (1.66-3.24, p<0.001)). The laparoscopic abdominal approach was independently associated with increased OS (HRa=0.73 (0.56-0.94, p=0.016)). Smoking was not associated with OS after adjusting for confounding variables in multivariate analysis (HRa=1.10 (0.77-1.57, p=0.608)).

Subgroup analysis: patients treated with RT (Table 5)

In the subgroup analysis of 406 patients treated with preoperative radiotherapy, 50 (12.3%) were non-smokers. There were less major complications in the NS group (24.0% vs 39.4%, p<0.001) but no statistical difference regarding other outcomes, especially regarding cCR, TGR1 or pCR rates, OS and RFS.

Effect of smoking cessation on postoperative outcomes

A majority of smokers (60.0%) were former smokers, all cessation time spans included. Comparison of former and current smokers showed that the former experience less major respiratory complications (25.5% vs 38.3%, p=0.002), less acute respiratory distress syndrome (5.1% vs 10.4%, p=0.035) and less POM30 (1.4% vs 5.6%, p=0.010). Long-term prognosis was also better for former smokers (5-year OS: 40.4% vs 32.3%, p=0.023), but not RFS (5-year RFS: 34.4% vs 30.9%, p=0.256). The AUC were 0.44 for respiratory complications, 0.38 for acute respiratory distress syndrome and 0.45 for POM30, which indicates no predictive value of cessation time span for these variables. The cut-off of 5 months maximized the significance assessed by the log-rank test between early and late cessation, but OS differences between late and early quitters remained statistically not significant with this cut-off (p=0.263).

DISCUSSION

This study suggests that the long-term prognosis of patients diagnosed with ESCC is better if they are non-smokers, but this difference appears to be more associated with patient's terrain than the effect of smoking on tumor aggressiveness or it's sensitivity to radiation therapy.

Unlike the independent negative effect found in lung cancer[10,11] or head and neck cancer patients[8], data regarding the impact of smoking on ESCC patients' survival are contradictory. Cohorts from Asian[14,32–38], American[39] or Australian[40] populations are already published with two meta-analyses summarizing their results[12,13]. Fahey et al.[12] published a pooled analysis of 6 articles and reported worst OS in smokers with a HR= 1.19 (CI95% 1.04-1.36), although with a marked heterogeneity between studies (I2= 47%). In the study published by Kuang et al.[13], pooled analysis of 5 studies, including 4 of the 6 aforementioned studies, also revealed that smoking decreased OS, with a HR= 1.41 (IC95% 1.22-1.64) and no heterogeneity between studies (I2= 0%). However, these are univariate analyses and the HR are not adjusted for potential confounding variables. There is only one prospective study addressing this topic: Okada et al.[14] evaluated demographic and lifestyle factors in 365 ESCC patients. Factors independently associated with decreased survival after multivariate analysis were age > 80 years (HR= 2.79 CI95% 1.34-5.80) and alcohol consumption (HR= 2.37 CI95% 1.24-4.53) whereas no significant association was observed for smoking history (HR= 0.97 CI95% 0.62-1.50). In the present study, smoking was associated with decreased OS in univariate analysis, but this association became non-significant after multivariate analysis, suggesting that the negative impact of smoking could stem from the negative impact of confounding factors, inherently associated with tobacco use. For example, smokers in this study presented with more alcohol consumption, respiratory disease history, chronic obstructive pulmonary disease and head and neck cancer history, which convey worse overall prognosis.

In terms of treatment, patients in both groups were comparable in terms of surgical approach, preoperative or adjuvant therapies. Nearly all patients in this study had an open thoracic approach. The only notable difference was a significantly higher proportion of laparoscopic abdominal approach in the NS group. This is certainly explained by the decrease in smoking prevalence with time and the fact that laparoscopy was introduced during the study period in our center (from 2005). Two aspects support the idea that part of the better prognosis observed in the NS group is due to the higher proportion of laparoscopic abdominal approach. Firstly, the laparoscopic approach was independently associated with better OS with a HRa=0.73 (0.56-0.94, p=0.016) in this population. Secondly, data on it's beneficial effect on long-term prognosis already exists, as shown in the results

of a multicentric prospective phase III trial published by Mariette and al.[41], which showed better OS with a HR=0.67 (CI95% 0.44-1.01) in favor of a hybrid minimally invasive esophagectomy (thoracotomy and laparoscopy) versus a totally open esophagectomy (thoracotomy and laparotomy).

In line with previously published data, this study showed that the long-term outcomes of ESCC patients is significantly impacted by ASA score[30], tumor stage[43] and incomplete resection[45]. Since both groups were comparable regarding those factors at baseline, it is unlikely that they constitute confounding factors.

The higher postoperative morbidity in smokers could also explain their worst long-term survival. Postoperative morbidity is undoubtedly increased in smokers after esophagectomy[47–49], especially regarding respiratory complications[50–52] and anastomotic leak[30]. The negative effect of postoperative pneumonia on long-term prognosis is debated in some studies: some are in favor[53–55], others against[56,57]. In this study, smokers experienced more major complications, and particularly more major respiratory complications, which is almost exclusively explained by the higher pneumonia and anastomotic leak rates in this group. This certainly contributes to the poorer prognosis of smokers in this study.

Interestingly, despite these complications, reintervention rates, POM30 and POM90 remained equivalent between groups. This could be explained by the proactive and standardized postoperative management of our high-volume center. High-volume activity in esogastric surgery has indeed been associated with less POM30 and POM90 in a multicentric study[58]. Nonetheless, high postoperative morbidity, if not fatal, could reduce the accessibility to adjuvant treatment for patients who need it. In this study, even though radicality and neoadjuvant therapy, which dictates most of the indications for adjuvant therapy, were similar in both groups, smokers were less treated with adjuvant therapy, although this difference was not statistically significant (5.6% vs 11.5%, p=0.053). This suggests that some patients may not have had access to otherwise indicated adjuvant therapy. Indeed, when focusing on patients with theoretical indication of adjuvant therapy, only 11.1% (4/38) were treated with adjuvant treatment in the S group versus 40.0% (4/13) in the NS group, p=0.055. This may contribute but only marginally to long-term outcome since adjuvant therapy was not independently associated with OS in this study (HRa=1.14 (0.67-1.95, p=0.623) and HRa=1.07 (0.71-1.62, p=0.732) for adjuvant radio- and chemotherapy, respectively).

It is challenging to understand why the negative effect of smoking is not as striking in ESCC as it is in other smoking-related cancers. In head and neck cancer, long-term prognosis is directly

correlated to external radiotherapy efficacy, which depends on tumor oxygenation[59,60]. Smokers with head and neck cancers therefore show significant resistance to radiotherapy, due to lower tumor oxygenation, as demonstrated in retrospective and prospective studies[61,62]. In this study, the subgroup analysis of patients treated with preoperative CRT showed similar results between smokers and non-smokers in terms of pathological (TRG, pCR) and long-term clinical (OS, RFS) outcomes, suggesting a weaker relation between tumor oxygenation and radio-sensitivity in ESCC. This is also supported by the statistically non-significant effect of preoperative radiotherapy on OS in multivariate analysis (HRa=0.73 (0.56-0.94, p=0.016)).

The retrospective nature of this study dictates caution in it interpretation. The cohort comprised only operated patients which can lead to under-representation of specific subgroups. This is notably the case for endoscopically resected superficial ESCC or for inoperable and cervical ESCC treated with exclusive CRT. Besides, some patients with cCR after neoadjuvant CRT could have been selected for non-operative management and would have been absent of this cohort. In contrast, recurring ESCC after exclusive CRT would be over-represented since non-recurring ESCC after exclusive CRT are absent of this cohort. Higher prevalence of non-smokers in any of these subgroups could indicate a better prognosis for non-smokers but would not appear in this study. For example, one could be alerted by the under-representation of upper third localization of tumors in non-smokers (12.7% vs 19.8%, p=0.049), which could be explained by the absence of non-recurring CRT-treated patients not addressed to surgery and would suggest better CRT efficiency in non-smokers. To this date, the optimal curative strategy of stage III (locally advanced) ESCC is still debated. Although there is no doubt that CRT is essential in curative intent of stage III ESCC, surgery can be avoided if radiation doses are augmented (exclusive CRT)[17,18]. In case of incomplete clinical response or relapse after CRT however, surgery is the only curative choice (salvage surgery) but it is burdened with enhanced postoperative complications in comparison to surgery after lower doses of CRT (neoadjuvant CRT)[25]. However, pathological complete response (pCR) to CRT correlates imperfectly with clinical complete response (cCR), with residual cancer cells remaining in one quarter of complete clinical responders[63]. Therefore, there is still debate about the management of cCR after CRT with planned surgery, some authors advocating systematic surgery to avoid under-treating patients with residuals tumors, and others advocating a “watch-and-wait and salvage surgery at recurrence” strategy to avoid exposing patients to the 5% mortality risk of esophagectomy. Retrospective data suggest a benefit of systematic surgery after cCR in terms of OS (median: 83 vs 31 months, p=0.001), PFS (median: 7.8 vs 19.0 months, p=0.002), and locoregional recurrence rate (16.2% vs 46.7%, p=0.007), with 34.6% of specimens harbouring

microscopic residual tumor[64]. There are currently two randomized trials ongoing to address this question: the SANO[65] and ESOTRATE (NCT02551458) trials. Predicting sensitivity to radiation therapy could help to personalize treatment options for ESCC patients. There is currently no evidence that smoking alters this radiosensitivity. Evidence of enhanced pCR rates after neoadjuvant CRT has been reported by Huang et al.[19], with smoking status independently associated with pCR rates after multivariate analysis, but no data exists on long-term clinical outcomes. In this retrospective study, smoking does not appear to affect short- or long-term outcomes except for major complications rates, but with comparable postoperative mortality. Pathological findings in particular were not statistically different. Therefore, smoking status should not interfere in treatment orientation, especially regarding the choice between CRT and surgery.

Smoking history can widely differ between patients, thus one major factor to take into account is smoking cessation. Numerous studies confirmed the beneficial effect of smoking cessation on long-term survival in head and neck cancer patients[66–68] and lung cancer patients[69–71] treated with standard care, but a majority of smokers continue to smoke after diagnosis[72]. This may be due to patient's readiness to quit in the cancer setting, around one third of patients feeling ready to quit[73], and to the doctors propensity to advise and help patients to quit, which is less likely in the cancer setting, compared to other smoking-related illenesses[74]. Since smoking cessation provides only 2.0 to 3.7 years of supplementary life expectancy at age 65[75], which is the age of diagnosis for most ESCC patients, it can be challenging to convince patients with less than 15% 5-year OS to quit a long lasting habit. However, smoking cessation before surgery has been associated with reduced postoperative morbidity after esophagectomy. In a study[20] of 246 patients undergoing elective esophagectomy for cancer showed that postoperative complications, especially severe and respiratory complications, decreased with early (< 30 days) and late (< 90 days) smoking cessation. Pneumonia rates were significantly lower ($p=0.014$) in late (11.8%) but also in early quitters (17.9%) than in current smoker (40.0%). Severe morbidity (Clavien-Dindo > IIIb) was significantly lower ($p<0.001$) in late (8.8%) but also in early (14.3%) than in current smoker (46.7%). In the present study, comparison of former and current smokers showed that former smokers experience better postoperative outcomes, especially for major respiratory complications and 30-day mortality rates and even have better long-term prognosis (5-year OS: 40.4% vs 32.3%, $p=0.023$), regardless of cessation time span. This suggest that smoking cessation should be advised as soon as possible in the patient's care to reduce postoperative mortality.

CONCLUSION

This cohort of 718 patients is the largest European cohort of ESCC patients evaluating long-term prognosis after esophagectomy regarding smoking status. Long-term prognosis of ESCC patients is better if they are non-smokers, but this difference appears to be correlated to confounding variables such as comorbidities and postoperative complications. Smoking status does not predict tumor response to CRT and should probably not be used as an argument in favor of exclusive CRT in stage III ESCC. Smoking cessation should be encouraged to improve short-term and long-term outcomes after esophagectomy. Smoking cessation improves short-term and long-term outcomes regardless of cessation time span and should therefore be encouraged as soon as possible in the patient's care.

TABLES AND FIGURES

Table 1 Baseline characteristics

	Overall population				Smokers by cessation status		
	Overall *N=718*	**NS group** *N=103*	**S group** *N=615*	**p-value**	**Former** *N=369*	**Current** *N=183*	**p-value**
Gender:				**<0.001**			0.150
Female	145 (20.2%)	67 (65.0%)	78 (12.7%)		41 (11.1%)	29 (15.8%)	
Male	573 (79.8%)	36 (35.0%)	537 (87.3%)		328 (88.9%)	154 (84.2%)	
Age	60.0 [53.0;66.0]	67.0 [61.0;69.5]	59.0 [53.0;65.0]	**<0.001**	60.0 [55.0;66.0]	56.0 [51.0;61.5]	**<0.001**
Year of surgery	2008 [2000;2013]	2010 [2006;2015]	2007 [2000;2013]	**<0.001**	2009 [2000;2014]	2004 [1999;2012]	**0.005**
ASA:				0.532			0.128
1	83 (11.6%)	14 (13.6%)	69 (11.3%)		45 (12.3%)	13 (7.14%)	
2	471 (66.1%)	70 (68.0%)	401 (65.7%)		241 (65.8%)	121 (66.5%)	
3	159 (22.3%)	19 (18.4%)	140 (23.0%)		80 (21.9%)	48 (26.4%)	
Malnutrition	264 (36.8%)	35 (34.0%)	229 (37.3%)	0.592	148 (40.1%)	66 (36.3%)	0.437
Alcohol consumption	463 (69.9%)	27 (26.5%)	436 (77.9%)	**<0.001**	246 (74.1%)	147 (86.5%)	**0.002**
Hypertension history	230 (32.3%)	41 (40.2%)	189 (30.9%)	0.082	126 (34.2%)	47 (25.8%)	0.057
Ischemic cardiopathy history	119 (16.7%)	22 (21.4%)	97 (15.9%)	0.216	64 (17.4%)	26 (14.2%)	0.399
Arteriopathy history	70 (9.93%)	4 (3.96%)	66 (10.9%)	**0.047**	38 (10.5%)	25 (13.7%)	0.331
Diabetes history	58 (8.17%)	14 (13.6%)	44 (7.25%)	**0.048**	36 (9.86%)	4 (2.19%)	**0.002**
Dyspnea history	123 (17.6%)	10 (9.71%)	113 (19.0%)	**0.032**	68 (18.8%)	32 (18.3%)	0.972
Respiratory disease history	167 (23.8%)	10 (9.80%)	157 (26.2%)	**0.001**	79 (22.1%)	60 (33.0%)	**0.009**
Asthma history	18 (2.59%)	5 (4.95%)	13 (2.19%)	0.163	7 (1.99%)	3 (1.66%)	1.000
COPD history	131 (18.9%)	3 (2.97%)	128 (21.6%)	**<0.001**	59 (16.8%)	56 (30.9%)	**<0.001**
Emphysema history	28 (4.03%)	2 (1.98%)	26 (4.38%)	0.410	16 (4.55%)	7 (3.87%)	0.889
Sleep apnea history	9 (1.30%)	0 (0.00%)	9 (1.52%)	0.371	8 (2.27%)	1 (0.55%)	0.285
Cancer history:				**<0.001**			0.217
Head & Neck cancer	103 (14.3%)	3 (2.91%)	100 (16.3%)		68 (18.4%)	24 (13.1%)	
Other cancers	63 (8.77%)	21 (20.4%)	42 (6.83%)		29 (7.86%)	12 (6.56%)	
No cancer history	552 (76.9%)	79 (76.7%)	473 (76.9%)		272 (73.7%)	147 (80.3%)	
Radiotherapy history	39 (5.43%)	15 (14.6%)	24 (3.90%)	**<0.001**	17 (4.61%)	6 (3.28%)	0.611
Clinical AJCC stage at baseline:				0.917			0.481
I	126 (17.5%)	18 (17.5%)	108 (17.6%)		61 (16.5%)	32 (17.5%)	
II	270 (37.6%)	37 (35.9%)	233 (37.9%)		133 (36.0%)	74 (40.4%)	

	Overall population				Smokers by cessation status		
	Overall ***N=718***	**NS group** ***N=103***	**S group** ***N=615***	**p-value**	**Former** ***N=369***	**Current** ***N=183***	**p-value**
III	322 (44.8%)	48 (46.6%)	274 (44.6%)		175 (47.4%)	77 (42.1%)	
Tumour localization:				**0.049**			**0.014**
Upper third	134 (18.8%)	13 (12.7%)	121 (19.8%)		79 (21.5%)	28 (15.3%)	
Middle	379 (53.1%)	51 (50.0%)	328 (53.6%)		181 (49.2%)	114 (62.3%)	
Lower third	201 (28.2%)	38 (37.3%)	163 (26.6%)		108 (29.3%)	41 (22.4%)	
Surgical technique:				0.159			0.080
Ivor Lewis	541 (75.3%)	85 (82.5%)	456 (74.1%)		267 (72.4%)	142 (77.6%)	
Akiyama	52 (7.24%)	5 (4.85%)	47 (7.64%)		24 (6.50%)	17 (9.29%)	
Transhiatal	34 (4.74%)	1 (0.97%)	33 (5.37%)		23 (6.23%)	8 (4.37%)	
3-stage	82 (11.4%)	12 (11.7%)	70 (11.4%)		47 (12.7%)	16 (8.74%)	
OPL	9 (1.25%)	0 (0.00%)	9 (1.46%)		8 (2.17%)	0 (0.00%)	
Abdominal approach:				**0.006**			0.917
Laparotomy	490 (68.5%)	58 (56.3%)	432 (70.6%)		255 (69.5%)	128 (70.3%)	
Laparoscopy	225 (31.5%)	45 (43.7%)	180 (29.4%)		112 (30.5%)	54 (29.7%)	
Thoracotomy	660 (93.9%)	100 (97.1%)	560 (93.3%)	0.213	332 (91.7%)	169 (95.5%)	0.154
Neoadjuvant radiotherapy	406 (56.7%)	50 (48.5%)	356 (58.1%)	0.089	230 (62.3%)	90 (49.7%)	**0.006**
Neoadjuvant chemotherapy	441 (61.5%)	57 (55.3%)	384 (62.5%)	0.200	246 (66.7%)	101 (55.5%)	**0.014**
Clinical complete response:				0.480			0.817
Complete	112 (25.9%)	11 (20.4%)	101 (26.7%)		66 (27.3%)	23 (23.2%)	
Partial	235 (54.4%)	30 (55.6%)	205 (54.2%)		134 (55.4%)	56 (56.6%)	
Stable	69 (16.0%)	12 (22.2%)	57 (15.1%)		32 (13.2%)	16 (16.2%)	
Progression	16 (3.70%)	1 (1.85%)	15 (3.97%)		10 (4.13%)	4 (4.04%)	
Adjuvant radio and/or chemotheray	44 (6.44%)	11 (11.5%)	33 (5.62%)	0.053	20 (5.63%)	5 (2.86%)	0.230

NS: non-smokers | S: smokers | ASA: American Society of Anesthesiologist score | COPD: Chronic obstructive pulmonary disease | AJCC: American Joint Committee on Cancer | OPL: œso-pharyngolaryngectomy

Table 2 Post operative outcomes

	Overall population				Smokers by cessation status		
	Overall *N=718*	NS group *N=103*	S group *N=615*	p-value	Former *N=369*	Current *N=183*	p-value
Overall morbidity:				0.988			0.583
Any complication	491 (68.4%)	71 (68.9%)	420 (68.3%)		258 (69.9%)	123 (67.2%)	
No complication	227 (31.6%)	32 (31.1%)	195 (31.7%)		111 (30.1%)	60 (32.8%)	
Dindo-Clavien:				**0.001**			0.264
I-II - minor complication	238 (33.1%)	49 (47.6%)	189 (30.7%)		124 (33.6%)	49 (26.8%)	
III-V - major complication	253 (35.2%)	22 (21.4%)	231 (37.6%)		134 (36.3%)	74 (40.4%)	
Anastomotic leak	103 (14.3%)	8 (7.77%)	95 (15.4%)	0.057	64 (17.3%)	25 (13.7%)	0.325
Conduit necrosis	13 (1.81%)	0 (0.00%)	13 (2.11%)	0.233	7 (1.90%)	5 (2.73%)	0.544
Chylothorax	30 (4.18%)	5 (4.85%)	25 (4.07%)	0.605	12 (3.25%)	7 (3.83%)	0.921
Respiratory morbidity:				0.075			**0.002**
Major resp. complication	209 (29.1%)	22 (21.4%)	187 (30.4%)		94 (25.5%)	70 (38.3%)	
Minor resp. complication	83 (11.6%)	17 (16.5%)	66 (10.7%)		50 (13.6%)	12 (6.56%)	
No resp. complication	426 (59.3%)	64 (62.1%)	362 (58.9%)		225 (61.0%)	101 (55.2%)	
Bronchic congestion	68 (9.47%)	13 (12.6%)	55 (8.94%)	0.318	40 (10.8%)	11 (6.01%)	0.091
Respiratory impairment	19 (2.65%)	3 (2.91%)	16 (2.60%)	0.745	14 (3.79%)	2 (1.09%)	0.131
Other minor respiratory complications	4 (0.56%)	1 (0.97%)	3 (0.49%)	0.462	1 (0.27%)	2 (1.09%)	0.256
Atelectasia	40 (5.57%)	4 (3.88%)	36 (5.85%)	0.565	19 (5.15%)	10 (5.46%)	1.000
Pneumonia	106 (14.8%)	8 (7.77%)	98 (15.9%)	**0.044**	50 (13.6%)	35 (19.1%)	0.113
Respiratory failure	56 (7.80%)	7 (6.80%)	49 (7.97%)	0.832	23 (6.23%)	20 (10.9%)	0.077
Acute respiratory distress syndrome	48 (6.69%)	5 (4.85%)	43 (6.99%)	0.555	19 (5.15%)	19 (10.4%)	**0.035**
Other major respiratory complications	12 (1.67%)	2 (1.94%)	10 (1.63%)	0.686	9 (2.44%)	1 (0.55%)	0.177
Conversion to laparotomy	21 (4.02%)	5 (5.43%)	16 (3.72%)	0.394	12 (4.43%)	3 (2.78%)	0.570
Reintervention	103 (14.6%)	8 (7.92%)	95 (15.8%)	0.056	55 (15.3%)	29 (16.0%)	0.921
Length of stay	14.0 [11.0;21.0]	13.0 [10.0;17.8]	14.0 [11.0;21.0]	0.076	14.0 [11.0;20.0]	14.0 [11.0;25.0]	0.443
30-day mortality	16 (2.28%)	0 (0.00%)	16 (2.64%)	0.147	5 (1.38%)	10 (5.56%)	**0.010**
90-day mortality	50 (7.11%)	5 (5.10%)	45 (7.44%)	0.533	25 (6.91%)	17 (9.44%)	0.384
5-year OS	38.1%	48.5%	36.4%	**0.046**	40.4%	32.3%	**0.023**
5-year RFS	34.3%	45.5%	32.5%	0.053	34.4%	30.9%	0.256
Recurrence localization:				0.452			0.506
Locoregional	182 (25.3%)	21 (20.4%)	161 (26.2%)		100 (27.1%)	46 (25.1%)	
Distant	108 (15.0%)	16 (15.5%)	92 (15.0%)		57 (15.4%)	23 (12.6%)	
No recurrence	428 (59.6%)	66 (64.1%)	362 (58.9%)		212 (57.5%)	114 (62.3%)	

NS: non-smokers | S: smokers | OS: Overall survival | RFS: Recurrence-free survival

Table 3 Pathological outcomes

	Overall population				Smokers by cessation status		
	Overall *N=718*	NS group *N=103*	S group *N=615*	p-value	Former *N=369*	Current *N=183*	p-value
pT:				0.749			0.864
T0	147 (20.6%)	20 (19.6%)	127 (20.8%)		78 (21.3%)	34 (18.7%)	
T1a	188 (26.3%)	27 (26.5%)	161 (26.3%)		99 (27.0%)	44 (24.2%)	
T1b	38 (5.32%)	8 (7.84%)	30 (4.90%)		19 (5.18%)	11 (6.04%)	
T2	91 (12.7%)	11 (10.8%)	80 (13.1%)		47 (12.8%)	27 (14.8%)	
T3	219 (30.7%)	34 (33.3%)	185 (30.2%)		105 (28.6%)	58 (31.9%)	
T4a	29 (4.06%)	2 (1.96%)	27 (4.41%)		18 (4.90%)	7 (3.85%)	
T4b	2 (0.28%)	0 (0.00%)	2 (0.33%)		1 (0.27%)	1 (0.55%)	
pN:				0.720			0.798
N0	447 (62.4%)	62 (60.2%)	385 (62.8%)		236 (64.1%)	110 (60.4%)	
N1	173 (24.2%)	26 (25.2%)	147 (24.0%)		85 (23.1%)	49 (26.9%)	
N2	66 (9.22%)	12 (11.7%)	54 (8.81%)		32 (8.70%)	16 (8.79%)	
N3	30 (4.19%)	3 (2.91%)	27 (4.40%)		15 (4.08%)	7 (3.85%)	
pM:				0.741			1.000
M0	627 (97.1%)	88 (96.7%)	539 (97.1%)		329 (97.1%)	163 (97.0%)	
M+	19 (2.94%)	3 (3.30%)	16 (2.88%)		10 (2.95%)	5 (2.98%)	
Pathological AJCC stage:				0.937			0.634
0	116 (16.2%)	17 (16.5%)	99 (16.1%)		60 (16.3%)	26 (14.2%)	
I	240 (33.4%)	34 (33.0%)	206 (33.5%)		129 (35.0%)	58 (31.7%)	
II	161 (22.4%)	24 (23.3%)	137 (22.3%)		84 (22.8%)	43 (23.5%)	
III	129 (18.0%)	20 (19.4%)	109 (17.7%)		58 (15.7%)	38 (20.8%)	
IV	72 (10.0%)	8 (7.77%)	64 (10.4%)		38 (10.3%)	18 (9.84%)	
Differenciation:				0.970			**0.014**
Well diff.	309 (52.6%)	41 (51.9%)	268 (52.8%)		151 (50.2%)	96 (60.0%)	
Moderatly diff.	216 (36.8%)	30 (38.0%)	186 (36.6%)		108 (35.9%)	55 (34.4%)	
Poorly diff.	62 (10.6%)	8 (10.1%)	54 (10.6%)		42 (14.0%)	9 (5.62%)	
Mandard:				0.921			0.178
TRG1	136 (32.2%)	20 (35.7%)	116 (31.7%)		70 (29.9%)	32 (33.0%)	
TRG2	73 (17.3%)	10 (17.9%)	63 (17.2%)		51 (21.8%)	10 (10.3%)	
TRG3	70 (16.6%)	7 (12.5%)	63 (17.2%)		41 (17.5%)	18 (18.6%)	
TRG4	96 (22.7%)	13 (23.2%)	83 (22.7%)		49 (20.9%)	25 (25.8%)	
TRG5	47 (11.1%)	6 (10.7%)	41 (11.2%)		23 (9.83%)	12 (12.4%)	
Nb retrived LN	19.5 [13.0;27.0]	22.0 [15.5;26.0]	19.0 [13.0;27.0]	0.133	18.0 [12.0;27.0]	21.0 [13.0;27.0]	0.190
Nb positive LN	0.00 [0.00;1.00]	0.00 [0.00;2.00]	0.00 [0.00;1.00]	0.350	0.00 [0.00;1.00]	0.00 [0.00;1.00]	0.666
Resection status:				0.899			0.289
R0	634 (89.3%)	94 (91.3%)	540 (89.0%)		326 (89.3%)	160 (88.9%)	
R1	43 (6.06%)	5 (4.85%)	38 (6.26%)		19 (5.21%)	14 (7.78%)	
R2	33 (4.65%)	4 (3.88%)	29 (4.78%)		20 (5.48%)	6 (3.33%)	

	Overall population				Smokers by cessation status		
	Overall ***N=718***	**NS group** ***N=103***	**S group** ***N=615***	**p-value**	**Former** ***N=369***	**Current** ***N=183***	**p-value**
Pathological complete response	116 (16.2%)	17 (16.5%)	99 (16.1%)	1.000	60 (16.3%)	26 (14.2%)	0.616

NS: non-smokers | S: smokers | diff.: differenciated | TRG: Tumor regression grade | LN: Lymph-node | R0: Complete resection | R1: Microscopically incomplete resection | R2: Macroscopically incomplete resection

Table 4 Uni- and multivariate analysis of OS

		HR (univariable)	HR (multivariable)
Gender	Male	1.25 (0.97-1.63, p=0.090)	0.94 (0.69-1.29, p=0.710)
Age	+60y	1.10 (0.90-1.33, p=0.354)	-
ASA	3	1.53 (1.22-1.90, p<0.001)	**1.31 (1.03-1.67, p=0.026)**
Smoking		1.36 (1.00-1.84, p=0.047)	1.10 (0.77-1.57, p=0.608)
Alcohol consumption		1.27 (1.02-1.58, p=0.034)	1.17 (0.91-1.51, p=0.212)
Malnutrition		1.43 (1.17-1.74, p=0.001)	1.16 (0.93-1.45, p=0.176)
Hypertension history		1.04 (0.84-1.28, p=0.723)	-
Ischemic cardiopathy history		1.03 (0.79-1.33, p=0.848)	-
Arteriopathy history		1.47 (1.09-1.99, p=0.012)	1.24 (0.90-1.72, p=0.190)
Diabetes history		1.10 (0.77-1.56, p=0.609)	-
Dyspnea history		1.10 (0.86-1.40, p=0.447)	-
Respiratory disease history		1.17 (0.94-1.47, p=0.164)	-
COPD history		1.34 (1.05-1.69, p=0.017)	1.22 (0.94-1.57, p=0.131)
Radiotherapy history		1.46 (0.95-2.24, p=0.086)	**1.79 (1.12-2.88, p=0.016)**
Tumour localization	Upper third	1.23 (0.97-1.56, p=0.090)	0.92 (0.62-1.35, p=0.666)
Neoadjuvant radiotherapy		1.35 (1.11-1.64, p=0.003)	0.96 (0.60-1.54, p=0.856)
Neoadjuvant chemotherapy		1.37 (1.12-1.68, p=0.002)	**1.64 (1.02-2.66, p=0.042)**
Abdominal approach	Laparoscopy	0.75 (0.60-0.95, p=0.015)	**0.73 (0.56-0.94, p=0.016)**
Anastomotic site	Thoracic	0.81 (0.65-1.00, p=0.052)	0.81 (0.56-1.18, p=0.272)
Pathological AJCC stage	0-I-II	-	-
	III	2.54 (2.02-3.20, p<0.001)	**2.46 (1.91-3.17, p<0.001)**
	IV	4.43 (3.34-5.89, p<0.001)	**2.75 (1.93-3.91, p<0.001)**
Differenciation	Poorly diff.	0.78 (0.57-1.06, p=0.118)	0.99 (0.72-1.36, p=0.929)
Resection status	R1/2	3.65 (2.80-4.76, p<0.001)	**2.32 (1.66-3.24, p<0.001)**
Pathological complete response		0.67 (0.50-0.90, p=0.008)	0.80 (0.57-1.12, p=0.185)
Adjuvant radiotherapy		2.54 (1.56-4.14, p<0.001)	1.14 (0.67-1.95, p=0.623)
Adjuvant chemotherapy		1.53 (1.04-2.26, p=0.033)	1.07 (0.71-1.62, p=0.732)

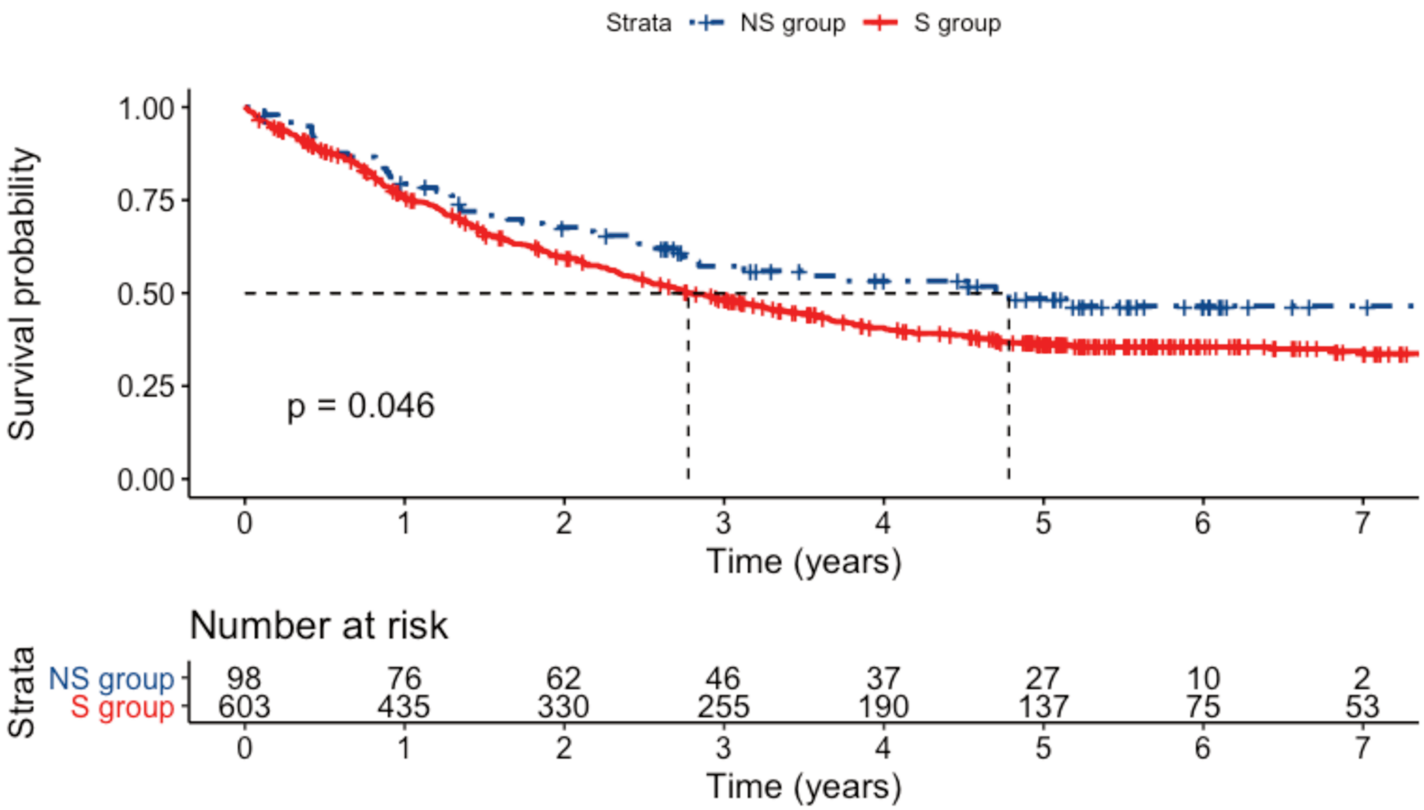
HR: Hazard Ratio | ASA: American Society of Anesthesiologist score | COPD: Chronic obstructive pulmonary disease | AJCC: American Joint Committee on Cancer | S: smokers | diff.: differenciated | R1: Microscopically incomplete resection | R2: Macroscopically incomplete resection

Table 5 Post operative and pathologic outcomes in the population treated with CRT

	Overall *N=403*	NS group *N=50*	S group *N=353*	p-value
Overall morbidity:				0.528
Any complication	287 (71.2%)	38 (76.0%)	249 (70.5%)	
No complication	116 (28.8%)	12 (24.0%)	104 (29.5%)	
Dindo-Clavien:				**0.012**
I-II - minor complication	136 (33.7%)	26 (52.0%)	110 (31.2%)	
III-V - major complication	151 (37.5%)	12 (24.0%)	139 (39.4%)	
Reintervention	62 (15.6%)	5 (10.2%)	57 (16.3%)	0.370
30-day mortality	12 (3.01%)	0 (0.00%)	12 (3.43%)	0.375
90-day mortality	37 (9.27%)	3 (6.12%)	34 (9.71%)	0.600
Respiratory morbidity:				0.214
Major resp. complication	129 (32.0%)	11 (22.0%)	118 (33.4%)	
Minor resp. complication	53 (13.2%)	9 (18.0%)	44 (12.5%)	
No resp. complication	221 (54.8%)	30 (60.0%)	191 (54.1%)	
Anastomotic leak	57 (14.1%)	3 (6.00%)	54 (15.3%)	0.121
Conduit necrosis	5 (1.24%)	0 (0.00%)	5 (1.42%)	1.000
Length of stay	14.0 [11.0;22.0]	14.0 [10.0;17.5]	14.0 [11.0;22.0]	0.214
Clinical complete response:				0.535
Complete	108 (27.6%)	11 (22.9%)	97 (28.2%)	
Partial	216 (55.1%)	26 (54.2%)	190 (55.2%)	
Stable	56 (14.3%)	10 (20.8%)	46 (13.4%)	
Progression	12 (3.06%)	1 (2.08%)	11 (3.20%)	
TRG1	130 (34.6%)	19 (38.8%)	111 (33.9%)	0.616
Pathological complete response	106 (26.3%)	16 (32.0%)	90 (25.5%)	0.420
5-year OS	43.1%	34.2%	44.3%	0.281
5-year RFS	47.0%	33.4%	48.9%	0.312
Recurrence localization:				0.881
Locoregional	90 (22.3%)	10 (20.0%)	80 (22.7%)	
Distant	73 (18.1%)	10 (20.0%)	63 (17.8%)	
No recurrence	240 (59.6%)	30 (60.0%)	210 (59.5%)	

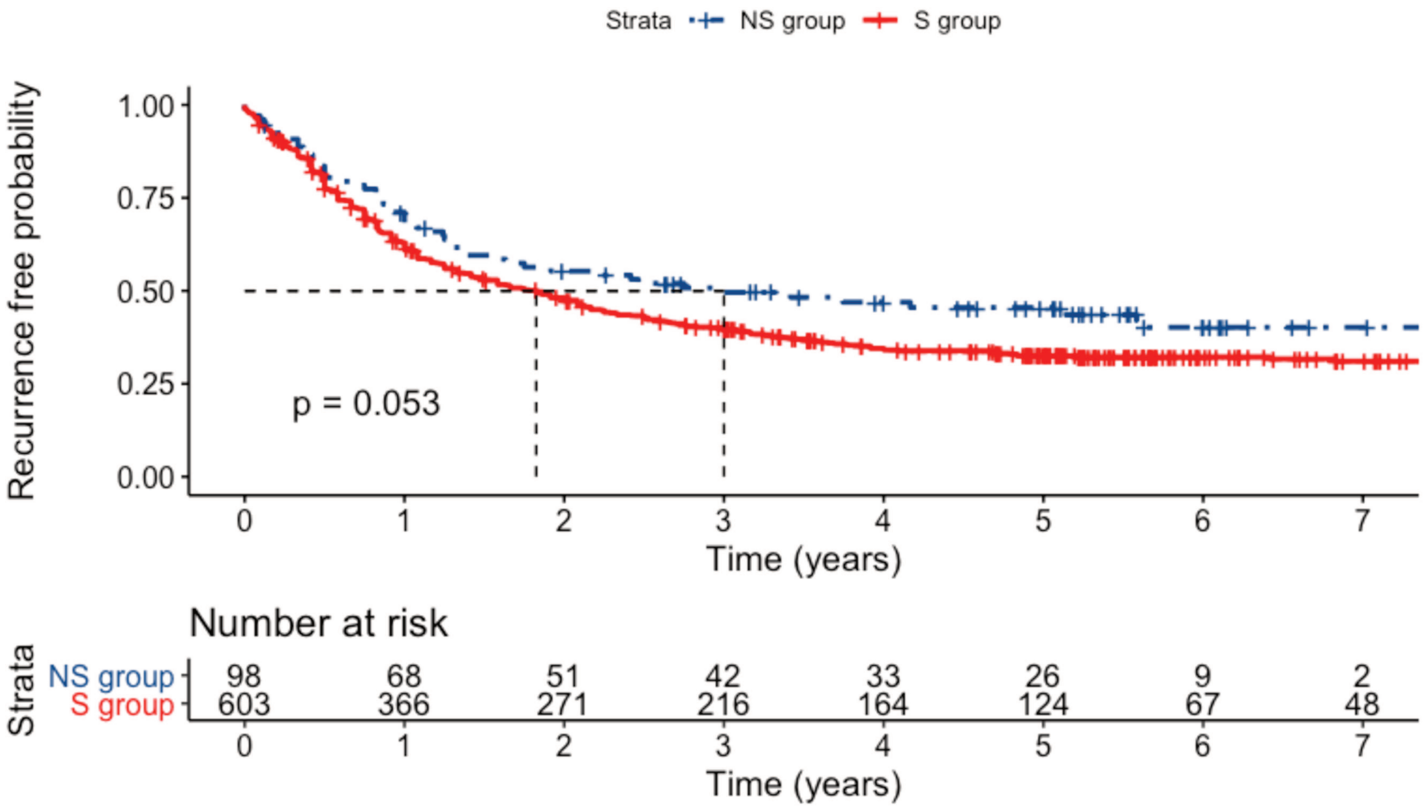
NS: non-smokers | S: smokers | OS: Overall survival | RFS: Recurrence-free survival | TRG: Tumor regression grade

Figure 1



Overall survival in NS (non-smokers) and S (smokers), compared with log-rank test

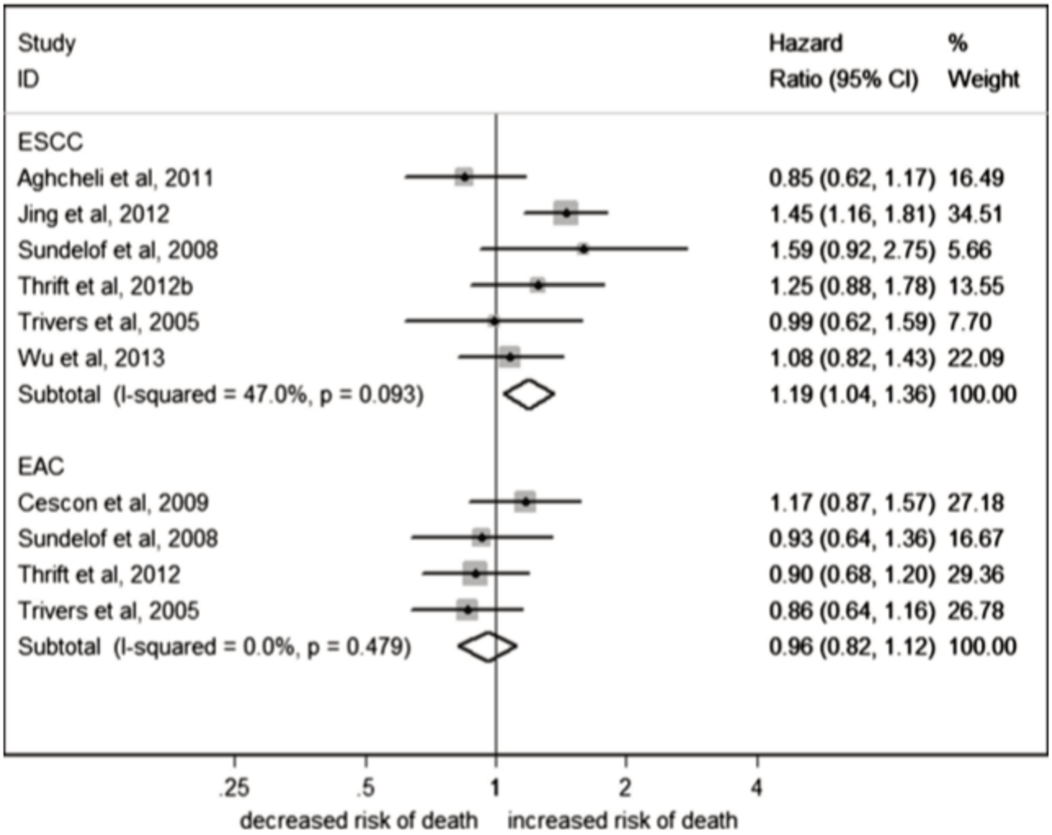
Figure 2 Recurrence free survival in NS and S groups with log-rank test



DISCUSSION

Cette étude suggère que le pronostic à long terme des patients atteints de CEE est meilleur en l'absence de tabagisme, mais cette différence apparaît plus liée au terrain du patient qu'à l'effet du tabagisme sur l'agressivité tumorale ou sa sensibilité au traitement par RCT.

Contrairement à l'effet négatif indépendant retrouvé pour le cancer bronchqiue[10,11] ou ceux de la sphère ORL[8], les données concernant la survie des patients atteints de CEE sont contradictoires. Des cohortes asiatiques[14,32–38], américaine[39] ou australienne[40] ont déjà été publiées et deux méta-analyses en réalisent la synthèse[12,13]. Fahey et al.[12] ont publié une analyse combinée de 6 articles et ont rapporté une moins bonne SG des fumeurs avec un HR= 1.19 (CI95% 1.04-1.36), avec cependant une hétérogénéité des études inclues marquée (I2%= 47%).



Forest plot du risque de décès en fonction du tabagisme selon le type de cancer. Extrait de Fahey et al.[12]

Dans l'étude publiée par Kuang et al.[13], l'analyse combinée de 5 études, incluant 4 des 6 études susmentionnées, a également révélé que le tabagisme diminuait la SG, avec un HR= 1.41 (IC95% 1.22-1.64) et sans hétérogénéité entre les études (I2= 0%). Cependant, ces analyses sont univariées et les HR ne sont pas ajustés sur de potentiels facteurs de confusion. Il n'existe qu'une seule étude prospective à ce sujet : Okada et al.[14] ont évalué des caractéristiques démographiques

et de mode de vie de 365 patients atteints de CEE. Les facteurs indépendamment associés avec une diminution de la SG étaient l'âge > 80 ans (HR= 2.79 CI95% 1.34-5.80) et la consommation d'alcool (HR= 2.37 CI95% 1.24-4.53) tandis qu'aucune association significative n'était observée en ce qui concerne le tabagisme (HR= 0.97 CI95% 0.62-1.50). Dans notre étude, le tabagisme était associé avec une SG diminuée en analyse univariée mais cette association n'était plus significative après analyse multivariée, suggérant donc que l'impact négatif du tabagisme pourrait provenir de l'impact négatif de facteurs de confusion associés au tabagisme. Par exemple, les fumeurs de cette étude présentaient plus de consommation alcoolique, plus que pathologies respiratoires, plus de bronchopneumopathie chronique obstructive et plus d'antécédents de cancers de la sphère ORL, eux-mêmes associés à un moins bon prognostic global.

En ce qui concerne la prise en charge, celle-ci était comparable entre les deux groupes, que ce soit en termes de technique chirurgicale, de traitements préopératoires ou adjuvants. Quasiment tous les patients de cette études ont eu une thoracotomie. La seule différence notable était une proportion significativement plus importante d'abord cœlioscopique dans le groupe non-fumeur. Ceci est certainement expliqué par la diminution de la prévalence du tabagisme avec le temps et le fait que la cœlioscopie ait été introduite durant la période d'étude dans notre centre (à partir de 2005).

Evolution de la prévalence du tabagisme et de l'utilisation de la cœlioscopie parmi les patients atteints de CEE dans notre centre pendant la période de l'étude

Deux aspects soutiennent l'idée qu'une partie du meilleur pronostic observé dans le groupe NS est due à la proportion plus élevée d'approche abdominale par cœlioscopie. Premièrement, l'approche cœlioscopique a été indépendamment associée à une meilleure SG (HRa=0.73 (0.56-0.94, p=0.016)) dans cette population. Deuxièmement, des données sur son effet bénéfique sur le pronostic à long terme existent déjà, comme le montrent les résultats d'un essai multicentrique prospectif de phase III publié par Mariette et al.[41], qui ont montré une meilleure SG avec un HR=0,67 (CI95% 0,44-1,01) en faveur d'une oesophagectomie hybride mini-invasive (thoracotomie et cœlioscopie) par rapport à une oesophagectomie classique (thoracotomie et laparotomie).

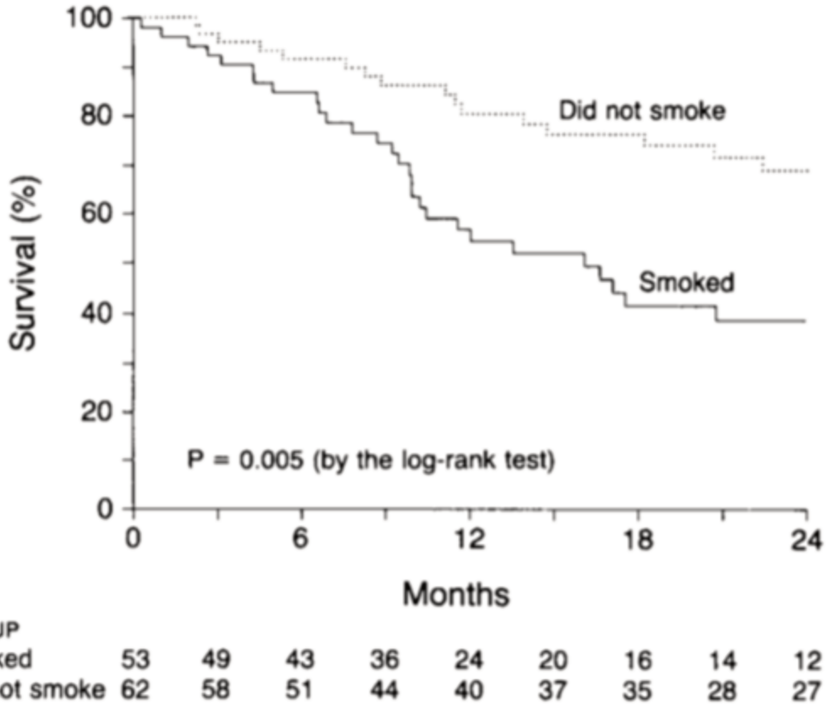
Conformément à des données précédemment publiées, cette étude a montré que les résultats à long terme des patients atteints de CEE sont significativement influencés par le score ASA[30,42], le stade tumoral[30,42–44] et la résection incomplète[45,46]. Comme les deux groupes étaient comparables en ce qui concerne ces variables, il est peu probable qu'elles constituent des facteurs de confusion.

La morbidité postopératoire plus élevée chez les fumeurs pourrait également expliquer la diminution de leur survie à long terme. La morbidité postopératoire après œsophagectoie est plus élevée chez les fumeurs[47–49], notamment en ce qui concerne les complications respiratoires[50–52] et la fistule anastomotique.[30] L'effet négatif des complications respiratoires postopératoires sur le pronostic à long terme est débattu dans certaines études : certaines sont en faveur[53–55], d'autres sont contre.[56,57] Dans cette étude, les fumeurs déploraient plus de complications majeures, et notamment plus de complications respiratoires majeures, ce qui s'explique presque exclusivement par les taux plus élevés de pneumopathie et de fistule anastomotique dans ce groupe. Cela contribue certainement au mauvais pronostic des fumeurs dans cette étude.

Il est intéressant de noter que malgré ces complications, les taux de réintervention et la mortalité postopératoire sont restés équivalents entre les groupes. Cela pourrait s'expliquer par la gestion postopératoire proactive et standardisée de notre centre à haut volume. Une étude multicentrique[58] a en effet montré que la mortalité postopératoire diminuait avec le volume opératorie en chirurgie oesogastrique. Néanmoins, une morbidité postopératoire élevée, même si elle n'est pas fatale, pourrait réduire l'accessibilité à un traitement adjuvant pour les patients qui en ont besoin. Dans cette étude, même si la radicalité et le traitement néoadjuvant, qui dictent la plupart des indications du traitement adjuvant, étaient similaires dans les deux groupes, les fumeurs ont été moins traités par un traitement adjuvant, bien que cette différence ne soit pas statistiquement significative (5.6% vs 11.5%, p=0.053). Ceci laisse suggérer que certains patients n'ont peut-être pas eu accès à un traitement adjuvant qui aurait été indiqué. En effet, en se concentrant sur les patients ayant une

indication théorique à un traitement adjuvant, seulement 11,1% (4/38) ont été traités dans le groupe S contre 40,0% (4/13) dans le groupe NS, p=0,055. Cela peut contribuer, mais de façon marginale seulement, au résultat à long terme, car le traitement adjuvant n'a pas été associé de façon indépendante à la SG dans cette étude (HRa=0.73 (0.56-0.94, p=0.016) et HRa=1.07 (0.71-1.62, p=0.732) pour la radio- et la chimiothérapie adjuvantes, respectivement).

Il est difficile de comprendre pourquoi l'effet négatif du tabagisme n'est pas aussi évident pour les CEE que d'autres cancers liés au tabagisme. Dans les cancers de sphère ORL, le pronostic à long terme est directement corrélé à l'efficacité de la radiothérapie externe, qui dépend de l'oxygénation de la tumeur.[59,60] Les fumeurs atteints de cancers de la tête et du cou présentent donc une résistance significative à la radiothérapie, en raison d'une moindre oxygénation tumorale, comme le démontrent des études rétrospectives et prospectives.[61,62]



Survie des patients atteints d'un cancer de la sphère ORL et traités par radiothérapie exclusive, selon l'abstinence ou la poursuite du tabagisme pendant la radiothérapie, extrait de Browman et al.[61]

Dans cette étude, l'analyse du sous-groupe de patients traités par RCT préopératoire a montré des résultats similaires entre fumeurs et non-fumeurs en termes de résultats histologiques (TRG, pCR) et cliniques à long terme (OS, RFS), suggérant une relation plus faible entre l'oxygénation de la tumeur et la radiosensibilité dans le CEE. Ceci est également confirmé par l'effet statistiquement non significatif de la radiothérapie préopératoire sur la SG dans une analyse multivariée (HRa=0.73 (0.56-0.94, p=0.016)).

La nature rétrospective de cette étude impose la prudence dans son interprétation. La cohorte ne comprenait que des patients opérés, ce qui peut entraîner une sous-représentation de certains sous-groupes. C'est notamment le cas des CEE superficiels réséqués par endoscopie ou des CEE inopérables et cervicaux traités par RCT exclusive. En outre, certains patients présentant un CEE après RCT néoadjuvante auraient pu être sélectionnés pour une prise en charge non opératoire et auraient été absents de cette cohorte. En revanche, les cas de CEE en récidive après RCT exclusive peuvent être surreprésentés, car les cas de CEE en rémission après un RCT exclusive sont absents de cette cohorte. Une prévalence plus élevée de non-fumeurs dans l'un de ces sous-groupes pourrait indiquer un meilleur pronostic pour les non-fumeurs qui n'apparaitrait pas dans cette étude. A titre d'exemple, on peut remarquer que les CEE du tiers supérieur de l'œsophage sont sous-représentés chez les non fumeurs (12.7% vs 19.8%, p=0.049), ce qui pourrait s'expliquer par l'absence de patients traités par RCT en rémission et non adressés en chirurgie et suggérerait une meilleure efficacité de la RCT chez les non-fumeurs. À ce jour, la stratégie curative optimale du stade III (localement avancé) du CEE est toujours débattue. Bien qu'il ne fasse aucun doute que la RCT est essentielle dans le traitement du CEE de stade III, la chirurgie peut être évitée si les doses de radiation sont augmentées (RCT exclusive).[17,18] Toutefois, en cas de réponse clinique incomplète ou de récidive après RCT, la chirurgie est la seule option potentiellement curative (chirurgie de rattrapage), mais celle-ci se grève de complications postopératoires accrues par rapport à la chirurgie succédant à des doses plus faibles de RCT (RCT néoadjuvante).[25] Cependant, la réponse histologique complète (pCR) à la RCT est mal corrélée à la réponse complète clinique (cCR), des cellules cancéreuses résiduelles étant observées dans un quart des cCR.[63] Par conséquent, le débat sur la gestion de la cCR après RCT néoadjuvante reste ouvert, certains auteurs préconisant une chirurgie systématique pour éviter de sous-traiter les patients présentant des tumeurs résiduelles, et d'autres préconisant une stratégie de "surveillance armée et chirurgie de rattrapage uniquement en cas de récidive" pour éviter d'exposer les patients au risque de 5% de mortalité de l'œsophagectomie. Des données rétrospectives suggèrent un bénéfice de la chirurgie systématique après une cCR en termes de SG (médiane : 83 vs 31 mois, p=0,001), de SSR (médiane : 7,8 vs 19,0 mois, p=0,002), et de taux de récidive locorégionale (16,2% vs 46,7%, p=0,007), 34,6% des spécimens abritant une tumeur résiduelle microscopique.[64] Deux essais randomisés sont actuellement en cours pour répondre à cette question : les essais SANO[65] et ESOTRATE (NCT02551458). La prédiction de la sensibilité à la radiothérapie pourrait aider à personnaliser les options de traitement pour les patients atteints de CEE. Il n'existe à l'heure actuelle aucune preuve que le tabagisme modifie cette radiosensibilité. Des taux de pCR accrus après RCT néoadjuvante ont été rapportées par Huang et al. [19], le statut tabagique étant

indépendamment associé aux taux de pCR après une analyse multivariée, mais il n'existe aucune donnée sur les résultats cliniques à long terme. Dans cette étude rétrospective, le tabagisme ne semble pas affecter les résultats à court ou à long terme, sauf pour les taux de complications majeures, mais avec une mortalité postopératoire comparable. Les résultats histologiques, en particulier, ne sont pas statistiquement différents. Par conséquent, le statut tabagique ne devrait pas interférer dans l'orientation du traitement, notamment en ce qui concerne le choix entre RCT et la chirurgie.

Les antécédents de tabagisme peuvent être très différents d'un patient à l'autre, c'est pourquoi l'un des principaux facteurs à prendre en compte est le sevrage tabagique. De nombreuses études ont confirmé l'effet bénéfique du sevrage tabagique sur la survie à long terme des patients atteints d'un cancer de la sphère ORL[66–68] ou bronchique[69–71] pris en charge de manière standard, mais une majorité de fumeurs continuent de fumer après le diagnostic.[72] Cela peut s'expliquer par une faible envie d'arrêter de fumer dans le contexte du cancer, environ un tiers des patients se sentant prêts à arrêter[73] et par une moindre tendance des médecins à conseiller et à aider les patients à arrêter dans le contexte du cancer, par rapport à d'autres maladies liées au tabagisme.[74] Étant donné que le sevrage tabagique ne procure qu'une espérance de vie supplémentaire de 2,0 à 3,7 ans à l'âge de 65 ans,[75] qui est l'âge au diagnostic de la plupart des patients atteints de CEE, il peut être difficile de convaincre les patients ayant une espérance de vie à 5 ans inférieure à 15 % d'abandonner une habitude bien ancrée. Cependant, le sevrage tabagique préopératoire a été associé à une réduction de la morbidité postopératoire après œsophagectomie. Dans une étude[20] portant sur 246 patients subissant une œsophagectomie pour cancer, il a été démontré que les complications postopératoires, en particulier les complications graves et respiratoires, diminuaient avec l'arrêt précoce (< 30 jours) et tardif (< 90 jours) du tabac. Les taux de pneumopathie étaient significativement plus faibles (p=0,014) en cas de sevrage ancien (11,8 %) mais aussi récent (17,9 %) comparés aux fumeurs actifs (40,0 %). La morbidité grave (Clavien-Dindo > IIIb) était significativement plus faible (p<0,001) en cas de sevrage ancien (8,8 %) mais aussi récent (14,3 %) comparés aux fumeurs actifs (46,7 %). Dans la présente étude, la comparaison entre fumeurs actifs et sevrés a montré un avantage en faveur de ces derniers en ce qui concerne les résultats postopératoires, en particulier pour les complications respiratoires majeures et les taux de mortalité à 30 jours mais aussi le pronostic à long terme (SG à 5 ans : 40.4% vs 32.3%, p=0.023), et ce quelle que soit l'ancienneté du sevrage. Cela suggère que le sevrage tabagique doit être conseillé le plus tôt possible dans la prise en charge afin de réduire la mortalité postopératoire.

CONCLUSION

Cette cohorte de 718 patients est la plus grande cohorte européenne de patients atteints de CEE évaluant le pronostic à long terme après œsophagectomie en fonction du tabagisme. Le pronostic à long terme des patients atteints de CEE est meilleur en l'absence de tabagisme, mais cette différence apparaît plus liée au terrain du patient qu'à l'effet du tabagisme sur l'agressivité tumorale ou sa sensibilité au traitement par RCT. Le tabagisme ne prédit pas la réponse tumorale à la RCT et ne devrait probablement pas être utilisé comme un argument en faveur du choix de la RCT exclusive dans le CEE de stade III. Le sevrage tabagique améliore le pronostic à court terme et à long terme et devrait être encouragé dès le début de la prise en charge du patient

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Titre de la thèse :
Impact du tabagisme sur le pronostic des patients atteints de carcinome épidermoïde de l'œsophage : étude d'une cohorte prospective de 718 patients.

Thèse — Médecine — Lille — 2020
Cadre de classement : Oncologie digestive
DES + spécialité : DES Chirurgie Générale — DESC Chirurgie Viscérale
Mots-clés : cancer de l'œsophage, carcinome épidermoïde, tabagisme, sevrage tabagique, radiothérapie

Résumé :
Contexte: Le principal facteur de risque du carcinome épidermoïde de l'œsophage (CEE) est le tabagisme. Cependant, une proportion croissante de patients atteints de CEE est constituée de non-fumeurs. Les non-fumeurs atteints de cancers associés au tabagisme, comme les cancers de la sphère oto-rhino-laryngée ou le cancer bronchique, présentent un meilleur pronostic à long terme que les fumeurs mais peu de données existent en ce qui concerne le CEE.
Objectif: Décrire le pronostic de la population de non-fumeurs atteinte de CEE.
Méthodes: Les patients opérés d'un CEE dans notre centre entre le 1996 et le 2019 ont été rétrospectivement inclus à partir d'une base de données prospective. Les patients étaient classés fumeurs (F) ou non-fumeurs (NF) lors du diagnostic de la maladie. Le critère de jugement principal était la Survie Globale (SG). Les critères de jugement secondaires étaient la Survie Sans Récidive (SSR), les suites post-opératoires, les réponses clinique et histologique à la radiochimiothérapie (RCT) préopératoire.
Résultats: Parmi les 718 patients inclus, 103 (14.3%) et 615 (85.7%) étaient classés NF et F, respectivement. Le groupe NF comportait des patients plus âgés, plus souvent de sexe féminin, avec moins de comorbidités que les patients du groupe F. Les caractéristiques tumorales (localisation, stade, différenciation, radicalité) étaient similaires entre les groupes. Après un suivi médian de 63.9 mois, la SG était plus longue dans le groupe NF (médiane, mois : 57.4 vs 33.3, p=0.046), mais pas la SSR (médiane; mois : 36.0 vs 21.9, p=0.053). Les suites post-opératoires, les réponses clinique et histologique étaient similaires entre les groupes. Après analyse multivariée, le tabagisme n'était pas associé à la SG (Hazard Ratio ajusté: 1.10 (0.77-1.57, p=0.608)). Après RCT, les patients montraient des résultats comparables en termes de SG, de SSR, de réponses clinique et histologique. Le sevrage tabagique était associé à moins de complications respiratoires, moins de mortalité post-opératoire et une SG augmentée, quelle que soit la durée de sevrage.
Conclusion: Le pronostic à long terme des patients atteints de CEE est meilleur en l'absence de tabagisme, mais cette différence apparaît plus liée au terrain du patient qu'à l'effet du tabagisme sur l'agressivité tumorale ou sa sensibilité au traitement par RCT. Le sevrage tabagique améliore le pronostic à court terme et à long terme et devrait être encouragé dès le début de la prise en charge du patient.

Composition du Jury :

Président : ……	**Monsieur le Professeur Guillaume PIESSEN**
Assesseurs : ……	**Monsieur le Professeur Dominique CHEVALIER**
	Monsieur le Professeur Olivier GLEHEN
	Monsieur le Professeur Alexis CORTOT
	Monsieur le Docteur Xavier MIRABEL
Directeur de thèse : ……	**Monsieur le Docteur Thibault VORON**