Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

**ANNEE 2017**

N°

# EVOLUTION DE LA PRISE EN CHARGE ET DU PRONOSTIC DES CANCERS DE L'ŒSOPHAGE, ETUDE EN POPULATION GENERALE

**THESE**

Présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

Et soutenue publiquement le 27 septembre 2017

Pour obtenir le grade de Docteur en Médecine

Par Marie Napoléon

Né(e) le 22 décembre 1988

A Lyon

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Année Universitaire 2017-2018
au 1er **Septembre 2017**

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# SERMENT D'HIPPOCRATE

*Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois*

*de l'honneur et de la probité.*

*Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.*

*Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.*

*J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.*

*Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.*

*J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.*

*Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.*

*Je donnerai mes soins à l'indigent et à quiconque me les demandera.*

*Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.*

*Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.*

*Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.*

*Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.*

*J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.*

*Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.*

# TABLE DES MATIERES

# PRÉAMBULE

Oesophageal cancer remains the eighth most frequent cancer and the sixth most common cause of death from cancer worldwide. Two main histological subtypes, squamous cell carcinoma and adenocarcinoma, display wide variation in incidence across Europe. The epidemiology has changed over the past 30 years. Although decreasing, squamous cell carcinoma remains the predominant type in France associated with alcohol intake and smoking. The incidence of adenocarcinoma has increased more quickly than any other digestive tract cancer site. Chronic gastro œsophageal reflux, Barrett's oesophagus, obesity and tobacco consumption are considered as risk factors. Oesophageal cancer is often diagnosed at an advanced stage and has a poor prognosis. Several protocols including surgery, radiotherapy, chemotherapy or chemoradiation as sole treatment or as neoadjuvant or adjuvant treatment to surgery were evaluated during the past three decades. However their diffusion at the population level is not known. Data on recent changes in the management of œsophageal cancer are needed as well as recent trends in survival.

# Patterns of care and outcomes for oesophageal cancers in a well-defined population

# 1 ABSTRACT

**Background:** The optimal treatment for oesophageal cancer is still a matter of debate. The aim of this study was to assess patterns of care and survival in a well-defined population of patients with squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the oesophagus.

**Methods:** Data were provided by the population-based Digestive Cancer Registry of Burgundy (France). Excess mortality and net survival over time elapsed since diagnosis were calculated using the Pohar Perme estimator in patients resected for cure and in patients who responded to chemoradiation.

**Findings:** The proportion of oesophageal cancers diagnosed at an advanced stage increased over time. Among non-metastatic patients, the proportion of patients resected for cure in these two periods decreased from 16% to 9% for SCC and from 48% to 22% for AC. The corresponding percentages for chemoradiation were respectively 45 and 53% for SCC and 21 and 30% for AC. In this group, a complete clinical response to chemoradiation was reported in 40% of the patients. Overall, 5-year net survival was 19% and did not vary according to histological types. It was 55% in the selected group of patients resected for cure, 44% in patients treated with chemoradiation with a complete clinical response and 2% in non-responders. In multivariate analysis, the treatment modality was the only criterion associated with survival.

In metastatic patients, 3-year net survival was 14% for those treated with chemoradiation, and almost none of those receiving other treatments survived for 3 years.

**Interpretation:** Survival in oesophageal cancer remained poor. Distant metastases were present in nearly one third of cases at the time of diagnosis, underlining the lateness of diagnosis. Treatment modalities have changed with no significant change in survival. Innovative treatments, in particular more effective chemoradiation regimens or new treatments (immunotherapy ?), are needed.

**Funding:** French Public Health Institute (SpF) and National Cancer Institute (INCa).

# 2 INTRODUCTION

Oesophageal cancer is a major problem in oncology. An estimated 455,000 cases of oesophageal cancer were diagnosed in the world in 2012[1]. In recent decades, the incidence of oesophageal adenocarcinoma (AC) has risen steadily[2], whereas the incidence of squamous cell carcinoma (SCC) has fallen in both sexes. In industrialized countries, the majority of oesophageal SCC are associated with smoking and/or alcohol use whereas chronic gastrooesophageal reflux, Barrett's oesophagus, obesity and tobacco consumption are considered risk factors for oesophageal adenocarcinoma[3,4].

Oesophageal cancer remains a highly fatal disease whose prognosis has improved little over time[5]. Little is known about its management at the population level. Most available reports are provided by specialized centers, and as such cannot be used as a reference because of unavoidable selection bias. Several protocols including surgery, radiotherapy, chemotherapy or the combination of chemoradiation as a neo-adjuvant treatment or as the sole treatment have been evaluated in recent decades[6]. The impact of these changes at the overall population level is not known. In this context, population-based studies which include all cases arising in a well-defined population make it possible to assess the real management and outcomes of oesophageal cancer according to patients' characteristics and treatment modalities. Such studies are rare because they require accurate and detailed data collection, which is seldom possible routinely in cancer registries. Thus the objective of this study was to draw a picture of treatment and survival in patients with SCC and AC of the oesophagus over a recent period of 10 years in a well-defined French population.

## 3.1 POPULATION

The Burgundy population-based digestive cancer registry (France) includes all digestive tract cancers occurring in the resident population of two well-defined areas (counties of Côte-d'Or and Saône-et-Loire). It covers a resident population of 1,052,000. The multiplicity of information sources: public and private pathology laboratories, practitioners in the public and private sectors (gastroenterologists, surgeons, medical oncologists, radiotherapists and general practitioners), the University hospital including the Cancer Center, public and private hospitals, the hospital administrative data base, the regional health service data base, and death certificates ensure the exhaustive collection of the diagnosed cases.

## 3.2 DATA SET

Overall 907 oesophageal cancers were diagnosed between 2004 and 2013. Cases presenting with other morphologies (undifferentiated carcinomas, malignant endocrine tumours, sarcoma and lymphomas) (N=64), cases without a histological diagnosis (N=36) and cases with synchronous cancer (40 head and neck cancers and 45 other cancer sites) were excluded. In total, 483 SCC and 239 AC (n=722) were included in this study. Data relative to clinical features, patients and tumour characteristics, stage at diagnosis, and treatment were routinely recorded. Cancer site and morphology were classified according to the 10th edition of the International Classification of Disease for Oncology[7]. The date of diagnosis was tabulated into two five-year periods: [2004-2008], and [2009-2013] in order to describe recent time trends. Surgical resection included resection for cure (R0 resection) defined as macroscopically complete resection with distal and circumferential margins free of tumor, and palliative resection (R1/R2 resections). Chemotherapy and radiotherapy were considered according to surgical procedures as neoadjuvant or as the sole treatment. A clinical complete response in patients treated with chemoradiation was defined as the absence of visible tumour at endoscopy or other examinations (negative biopsies, endoscopic ultrasonography or PET-Scan). The details of the examinations performed were

not recorded. For patients resected for cure and patients treated with chemoradiation with a clinical complete response, information about recurrence 18 months after treatment was obtained from all of the specialists as well as general practitioners involved in the follow-up of patients. Local recurrence (n=11) and distant metastases (n=27) were defined as any histologic, morphologic or clinical evidence of recurrence. Local recurrence was defined as failure in the tumour bed or on the oesophageal anastomosis.

Cancer extension among resected cases was classified according to the 2012 TNM classification[7] . The Charlson comorbidity score was calculated using the method previously reported by Charlson et al[8], in which each specific comorbid condition is weighted and scored proportionally to the disease-related risk of death irrespective of age. The score was classified according to three comorbid groups: '0', '1', and '2 or more'.

Survival of patients was ascertained through an electronic request to the National directory for the identification of persons or from the register of the place of birth or residence. Both procedures require knowledge of the patient's birth place. Whenever it was missing, registers of the place of residence, medical records or general practitioner were consulted. The life status was known for 674 patients (93.4%) 5 years after diagnosis.

## 3.3 STATISTICS

The association between categorical data was analyzed using the Chi2 test. Recurrence rates after surgical resection or chemoradiation with a complete clinical response were calculated using the Kaplan Meier method. Patients who died recurrence-free were censored at the time of death and patients who developed a recurrence were censored at the time of recurrence. Net survival was defined as the survival that would be observed if cancer was the only possible cause of death. It can be estimated without knowledge of the cause of death using excess mortality rate methodology. The excess mortality rate due to cancer is estimated by subtracting expected mortality in a group of patients from the general population sharing the same demographic characteristics (derived from life-tables according to sex, age and year of death) from overall mortality in the group of patients with cancer. These life-tables were provided by the INSEE (National Institute for Statistic

and Economic Studies). We calculated net survival at the time of diagnosis using the Pohar Perme estimator[9]. The multivariate excess risk model of 5-year relative survival was built using a flexible excess risk model as proposed by Nelson et al [10]. The significance of co-variables was tested with the likelihood test.

STATA, release 14 (STATA, College Station, TX, USA) was used for the analyses and a p value smaller than 0.05 was considered significant.

## 4.1 PATIENT CHARACTERISTICS

Mean age at diagnosis for SCC was 65.5 years (SD: 10.4) in males and 70.0 years in females (SD: 14.2) ($p<0.001$). The corresponding values for AC were 70.4 (SD: 12.4) and 80.7 (SD: 10.4) ($p <0.001$). The characteristics of patients presenting with SCC and AC are presented in Table 1. There was no significant variation overtime in the distribution of SCC and AC according to sex and age group.

The proportion of patients presenting with distant metastatic disease significantly increased over time from 25% to 37% for SCC ($p=0.008$) and from 27% to 40% ($p=0.043$) for AC (annexe 1).

## 4.2 TIME TRENDS IN TREATMENT

Treatment modalities were analyzed separately for non-metastatic patients (M0) and metastatic patients (M1).

M0 patients

Overall, among M0 patients, 20% were surgically resected for cure, 41% received chemoradiation as the initial treatment, 11% radiotherapy, 10% chemotherapy and 18% best supportive care. The proportion of M0 patients treated by surgery with curative intent decreased over the two studied periods from 16% to 9% ($p=0.297$) for SCC and from 48% to 22% for AC ($p=0.016$) (annexe 2). Among SCC resected for cure, surgery was the only treatment in 72% of the cases; it was preceded by chemoradiation in 20%, and by chemotherapy in 8%. The corresponding percentages for AC were 53%, 15% and 32%. Sixteen patients received initial neoadjuvant chemoradiation followed by surgical resection. Among these, six patients (38%) had a pathological complete response on the resection specimen.

The pTNM stage concerned only surgically resected cases. Among SCC resected for cure (N=41), 51% were stage I, 32% stage II and 17% stage III. The corresponding proportions for AC (N=52) were 46%, 19% and 35%. Nearly half (47/96) of the patients resected for cure were T1 or T2. For SCC, the proportion of patients treated with chemoradiation as the

initial treatment did not vary over time: it was 45% during the [2004-2008] and 53% during the [2009-2013] period (p=0.297). For AC, this proportion significantly increased from 21% to 30% (p=0.016) (annexe 2). A complete clinical response was reported in 40% (79/199) of patients treated with chemoradiation. About 10% of patients were treated with radiotherapy as the initial treatment for both SCC and AC. This proportion was stable over time. Chemotherapy as the main treatment was performed mainly for SCC in about 10% of the patients. Among M0 patients, best supportive care was given to 15% of SCC and 24% of AC.

The risk of recurrence was estimated up to 18 months after treatment among patients resected for cure and among clinical responders to chemoradiation. It was 25% in both groups (p=0.857) (Figure 1). Neither sex, nor age nor the period of primary diagnostic was significantly associated with the 18-month recurrence rate.

M1 patients

Among M1 patients, the proportion of patients treated with chemoradiation decreased for both SCC (36% and 32%, p=0.355) and AC (from 36% to 19%, p=0.274), but the difference was not significant (annexe 2). The proportion of patients receiving chemotherapy alone increased for both SCC and AC. Radiotherapy alone was the main treatment for about 10% of patients. The only possibility was best supportive care in 24% of SCC and 18% of AC.

## 4.3 SURVIVAL

Overall 1-, 3- and 5-year net survival for oesophageal cancer was 45%, 20% and 14%, respectively. Net survival according to studied variables is given in Table 3. As survival was similar for SCC and AC, the two histological groups were not analysed separately. For M0 patients, 1-, 3- and 5-year net survival was 52%, 27%, and 20%, respectively. In univariate analysis sex, period of diagnosis, location of cancer and Charlson' score were not significant prognostic factors while advanced age decreased net survival (p<0.001). Regarding treatment modalities, 5-year net survival in the very highly selected population of patients resected for cure was 55%. For patients treated with chemoradiation it was 44%

in those with a complete clinical response and 2% in its absence. One- and 3-year net survival for M1 patients was 30% and 5% (not calculated at 5 years). One-year net survival for patients receiving chemoradiation alone was 64% in M0 patients and 46% in M1 patients. There were no 3-year survivors among M1 patients receiving chemotherapy alone or radiotherapy alone.

Figure 2 presents the dynamics of the excess mortality over time since diagnosis for patients resected for cure and for clinical complete responders to chemoradiation. During the first year after treatment, excess mortality in the group of patients resected for cure was higher than that in patients treated with chemoradiation. Excess mortality for complete responders to chemoradiation was significantly higher during the1.5 to 2.5 years following diagnosis and then levelled off.

This study provides crucial unpublished information on the usual management of oesophageal cancer over the past 10 years. Only one study on time trends and covering a recent period is available for the care of oesophageal cancer in a community-based setting[11]. One of the most striking results reported in this paper is the 9% of M0 SCC and 22% of AC resected for cure over the last study period. In the same period, 53% of patients with SCC and 30% of those with AC received chemoradiation as the initial treatment. This study also provides for the first time data at the population level on the proportion of complete clinical responders in patients treated with chemoradiation and on their survival. The fact that 38% of patients receiving neoadjuvant chemoradiation had a pathological complete response is one of the major results. However, it must be interpreted with caution because of the small size of this group of patients.

There was an increase in the proportion of patients diagnosed with distant metastases. Over the period 2009-2013 distant metastases were present at the time of diagnosis in nearly one third of patients, for both SCC and AC. An increase in the proportion of patients with distant metastasis was also reported in the Netherlands[12]. It is probably related to stage migration associated with improvements in imaging. The use of computed tomography scans, endoscopic ultrasound and 16 F-fluorodesoxyglucose positron emission tomography has been increasing over time to establish a pretherapeutic stage. However, such data were not recorded for the present study. Another difficulty concerning staging for oesophageal cancers is the variation over time in the definition of the metastatic status. In our study, as recommended in the last published TNM recommendations[13], we classified lymph nodes in the oesophageal drainage area, including coeliac axis nodes and paraoesophageal nodes in the neck but not supraclavicular nodes, as regional lymph nodes and thus not metastatic[13]. Variations over time in such definitions may impair comparisons between international publications.

The rarity of comparable data on the management of oesophageal cancer at the population level may be due to the relative rarity of oesophageal cancer and to the complexity of

therapeutic schemes, which make it difficult for general cancer registries, which collect data for a wide variety of cancers, to record data for oesophageal cancer routinely. In this context, it is of interest to compare recorded data with published French and European recommendations. Over the study period, five successive ESMO recommendations concerning the treatment of oesophageal cancer were published[14-18] as well as French recommendations[19]. Everyday practice indicates that these recommendations are only partly followed. Most surgically resected oesophageal cancers were T1/T2. This is in agreement with the recommendations, which advocate surgery alone as the standard treatment. In the guidelines, surgery is often recommended as the standard treatment in patients fit for surgery although it is considered suboptimal for locally advanced disease (uT3/T4 uN0/N+ M0) with 5-year survival not exceeding 20%. The reported data demonstrate a dramatic increase in chemoradiation as the main treatment and a decrease in surgical resection for cure for both SCC and AC. Similar trends were reported in a population-based study in Ireland[11]. The current attitude is probably related to the publication of two phase III trials in 2005[16] and 2007[20] demonstrating that in locally advanced SCC, chemoradiation alone in responders to chemoradiation leads to the same overall survival as as that achieved with surgery. A phase III trial[21] and a Cochrane review[6] published at the same moment add to the confusion. The results of the trial suggest that neoadjuvant chemoradiation followed by surgical resection should be viewed as a standard of care against surgery alone for locally advanced oesophageal cancer. This trial confirmed, with new therapies, the results of previous studies and meta-analyses[22]. The Cochrane review concluded that chemoradiation appeared to be at least equivalent to surgery in terms of survival among responders to chemoradiation, but that the evidence was low because of the small size of the study.

Population-based data available on survival in patients with oesophageal cancer are scarce. The recently published EUROCARE-5 study included cancer registries from 29 countries over the period 2005-2007[5]. The mean 1- and 5-year European survival rate was 40% and 12%, respectively. Similar results are reported in this study. Survival in oesophageal cancers remained poor and there was no improvement over time when comparing the 2004-

2008 period with the 2009-2013 period. The decrease in resected cancers was not associated with a decrease in survival. Observational population-based studies cannot be used to compare survival according to treatment directly. Very often the selection of patients differs from one therapeutic strategy to another. For instance, oesophageal cancer patients resected for cure are a very highly selected group, nearly half of them being T1 or T2 with 5-year net survival of 55%. The group of patients treated with chemoradiation was heterogeneous. It included patients with a complete clinical response to chemoradiation and 5-year net survival of 44%, and patients without a complete clinical response and 5-year net survival of 2%.

As a substantial proportion of patients treated with neoadjuvant chemoradiation followed by surgical resection had a pathological complete response (38%), one might suggest that by extension, patients with a clinical complete response could be managed by a watch-and-wait approach. This could avoid major surgery with no loss of oncological safety. The reported results thus provide strong arguments to guide subsequent management and to randomize patients in the ongoing controlled PRODIGE 32- ESOSTRATE FFCD 1401 trial ("Comparison of systematic surgery versus surveillance and rescue surgery in operable oesophageal cancer with a complete clinical response to radiochemotherapy", ClinicalTrials.gov Identifier: NCT02551458). Such a strategy, although already recommended in the French and ESMO guidelines, must be evaluated.

The strengths of this study include the population-based design, the detailed information on patients and cancer characteristics, treatment modalities and comorbidities. One of the major problems faced by population-based studies is to determine the completeness and reliability of the data. The quality of the data collection is evaluated every 4 years by an audit by the National Institute for Health and Medical Research (INSERM), the French Public Health Institute (SpF) and the National Cancer Institute (INCa).

Net survival reflects disease-specific mortality, and is particularly useful for comparisons between countries and time periods. However this study has some limits. The pretherapeutic work-up and stage, as defined by imaging and endoscopic ultrasound, were not recorded. Another limit was the absence of data on long-term recurrence in the group of

patients with a complete clinical response after chemoradiation and in patients surgically resected for cure. The study also had the limit of being descriptive and retrospective.

In conclusion, survival in patients with oesophageal cancer remained poor and about one third of such patients had distant metastases at diagnosis. Several therapeutic options have been evaluated over the past 10 years, which probably explains why recommendations are not always clear. Surgical resection is no longer the reference treatment and chemoradiation has become the most frequently administered treatment. More effective chemoradiation regimens or innovative treatments such as immunotherapy are needed [23]. More studies reporting patterns of care in oesophageal cancer must be performed.

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**THESE SOUTENUE PAR Mme NAPOLEON Marie**

## CONCLUSIONS

Nous rapportons un travail permettant de décrire l'évolution des pratiques de soins et du pronostic des adénocarcinomes et des cancers épidermoïdes de l'œsophage en France entre 2004 et 2013 dans une population bien définie.

La proportion de patients présentant des métastases à distance au moment du diagnostic a augmenté au cours de la dernière décennie avec environ un tiers des patients métastatiques au diagnostic, quel que soit le type histologique.

Parmi les patients non métastatiques, la proportion de patients réséqués à visée curative était de 13% pour les carcinomes épidermoïdes et 34% pour les adénocarcinomes. Environ la moitié de ces patients étaient classés pT1 ou pT2. Entre 2004 et 2013, la proportion de patients traités par radiochimiothérapie n'a pas significativement varié chez les épidermoïdes alors qu'elle a augmentée chez les adénocarcinomes. Elle était réalisée chez la moitié des patients ayant un cancer épidermoïde et chez un quart des patients ayant un adénocarcinome. Une réponse complète était observée chez 40% des patients. Parmi le petit groupe de patients opérés à visée curative après une radiochimiothérapie néoadjuvante (n=16), la pièce opératoire était stérilisée chez 6 patients.

La survie nette à 5 ans de l'ensemble de la population était de 14% et ne différait pas selon le type histologique. La meilleure survie nette à 5 ans, 55%, était observée pour le petit groupe de patients ayant été réséqués à visée curative. Les patients traités par radiochimiothérapie et ayant une réponse complète avait une survie de 44%. Le risque de récidive à 18 mois était estimé à 25% à la fois chez les patients ayant été réséqué à visée curative et chez les patients ayant eu une réponse complète à la radiochimiothérapie.

Bien que plusieurs essais de phase III aient été publiés depuis une vingtaine d'années, il n'y a pas actuellement de consensus concernant la stratégie thérapeutique en dehors des rares cancers diagnostiqués au stade T1-T2 pour lesquels une exérèse chirurgicale seule est proposée. La question qui se pose dans les cancers localement évolués (T3-T4) après radiochimiothérapie néoadjuvante est celle d'une surveillance ou d'une chirurgie d'exérèse complémentaire. Une étude comparant ces deux

stratégies après réponse complète suite à une radiochimiothérapie est en cours et sera intéressante afin de mieux préciser la conduite à tenir chez ces patients.

Le développement de traitements innovants, en particulier de meilleures associations radio chimiothérapiques et le développement de l'immunothérapie pourraient améliorer le pronostic de ce cancer.

Le Président du jury,

Pr. S. MANFREDI

Vu et permis d'imprimer

Dijon, le 30 Août 2017
Le Doyen, Pr. F.HUET

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**Table 1. Characteristics of patients with oesophageal cancer according to histology**

| | Squamous cell carcinoma N=483 | | Adenocarcinoma N=240 | | p° |
|---|---|---|---|---|---|
| **Period** | | | | | |
| 2004-2008 | 240 | 70% | 104 | 30% | |
| 2009-2013 | 243 | 64% | 136 | 36% | 0.107 |
| **Sex** | | | | | |
| Men | 370 | 63% | 215 | 37% | |
| Women | 113 | 82% | 25 | 18% | <0.001 |
| **Age (years)** | | | | | |
| <65 | 229 | 75% | 77 | 25% | |
| 65-74 | 119 | 68% | 57 | 32% | |
| ≥75 | 135 | 56% | 106 | 44% | <0.001 |
| **Charlson comorbidity score*** | | | | | |
| 0 | 231 | 68% | 111 | 32% | |
| 1 | 115 | 62% | 72 | 39% | |
| ≥2 | 131 | 70% | 55 | 30% | 0.169 |

° *Chi-2 test.*

**Charlson score unknown for 6 cases with SCC and 2 cases with AD.*

**Table 1. Treatment modalities of patients with oesophageal cancer according to metastatic status and histology.**

| | Squamous cell carcinoma | | Adenocarcinoma | |
|---|---|---|---|---|
| **M0** | | | | |
| Resection for cure (R0) | 41 | 13% | 54 | 34% |
| Chemoradiation alone¥ | 158 | 48% | 41 | 26% |
| *Responders* | *63* | *46%* | *16* | *44%* |
| *No responders* | *74* | *54%* | *20* | *56%* |
| Radiotherapy alone | 39 | 12% | 16 | 10% |
| Chemotherapy alone | 39 | 12% | 9 | 6% |
| Best supportive care | 50 | 15% | 37 | 24% |
| **M1** | | | | |
| Chemoradiation alone | 50 | 34% | 20 | 25% |
| Radiotherapy alone | 11 | 7% | 9 | 11% |
| Chemotherapy alone | 52 | 35% | 38 | 46% |
| Best supportive care | 36 | 24% | 15 | 18% |

*Metastatic status unknown for 2 cases with SCC and 1 case with AD.*
*Treatment modality unknown for 5 cases with M0*

*¥ Response to treatment unknown for 21 cases with squamous cell carcinoma and 5 cases with adenocarcinoma.*

**Table 3. Univariate net survival of patients with oesophageal cancer according to metastatic status**

| | M0 | | | | | | | M1 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1-year | | 3-year | | 5-year | | | 1-year | | 3-year | | |
| | % | [95% CI] | % | [95% CI] | % | [95% CI] | p | % | [95% CI] | % | [95% CI] | p |
| **Over all** | 52 | [47-56] | 27 | [23-31] | 20 | [16-24] | | 30 | [24-36] | 5 | [2-8] | |
| **Period** | | | | | | | | | | | | |
| 2004-2008 | 54 | [47-60] | 27 | [21-33] | 20 | [14-25] | 0.727 | 26 | [17-35] | 5 | [0-9] | 0.360 |
| 2009-2013 | 50 | [43-57] | 27 | [21-33] | 21 | [15-27] | | 33 | [25-41] | 6 | [2-9] | |
| **Sex** | | | | | | | | | | | | |
| Men | 53 | [48-58] | 27 | [22-32] | 19 | [15-24] | 0.884 | 32 | [26-39] | 6 | [3-10] | 0.043 |
| Women | 49 | [39-59] | 27 | [19-36] | 23 | [14-32] | | 17 | [4-29] | 0 | [0-0] | |
| **Age (years)** | | | | | | | | | | | | |
| <65 | 61 | [54-68] | 34 | [27-41] | 27 | [2134] | | 35 | [26-44] | 4 | [1-8] | |
| 65-74 | 51 | [42-60] | 31 | [22-40] | 21 | [12-29] | <0.001 | 36 | [24-48] | 11 | [3-18] | 0.010 |
| ≥75 | 42 | [34-50] | 16 | [10-23] | 12 | [6-17] | | 18 | [8-27] | 2 | [0-4] | |
| **Histology** | | | | | | | | | | | | |
| Squamous cell carcinoma | 51 | [46-57] | 25 | [20-30] | 25 | [20-30] | 0.255 | 31 | [24-39] | 7 | [3-11] | 0.583 |
| Adenocarcinoma | 53 | [45-61] | 31 | [24-39] | 31 | [24-39] | | 28 | [18-38] | 3 | [0-6] | |
| **Charlson comorbidity score*** | | | | | | | | | | | | |
| 0 | 53 | [47-59] | 28 | [22-34] | 23 | [17-29] | | 34 | [25-43] | 5 | [1-9] | |
| 1 | 51 | [42-60] | 28 | [20-36] | 28 | [20-36] | 0.251 | 27 | [16-39] | 4 | [0-8] | 0.850 |
| ≥2 | 49 | [40-58] | 23 | [15-31] | 20 | [12-27] | | 25 | [15-36] | 6 | [0-12] | |
| **Treatment modalities#** | | | | | | | | | | | | |
| Resection for cure (R0) | 83 | [76-91] | 66 | [57-76] | 55 | [43-66] | | - | - | | - | |
| Chemoradiation alone | 64 | [57-71] | 27 | [21-34] | 19 | [12-35] | | 46 | [34-58] | 14 | [5-22] | |
| *Responders* | *94* | *[85-100]* | *59* | *[48-71]* | *44* | *[32-57]* | | - | - | | - | |
| *No responders* | *42* | *[32-52]* | *2* | *[0-5]* | *2* | *[0-4]* | | - | - | | - | |
| Radiotherapy alone | 36 | [23-49] | 17 | [6-28] | 8 | [0-15] | | 0 | [0-0] | 0 | [0-0] | |
| Chemotherapy alone | 23 | [12-35] | 9 | [1-17] | 0 | [0-0] | | 41 | [31-51] | 4 | [0-7] | |
| Best supportive care | 17 | [9-25] | 3 | [0-6] | 3 | [0-6] | | 2 | [0-5] | 0 | [0-1] | |

**Charlson score unknown for 5 cases with M0 and 2 cases with M1*

*# Treatment modality unknown for 5 cases with M0*

**Figure 1. Dynamic of the excess mortality rate for patients with M0 oesophageal cancer according to treatment modalities.**

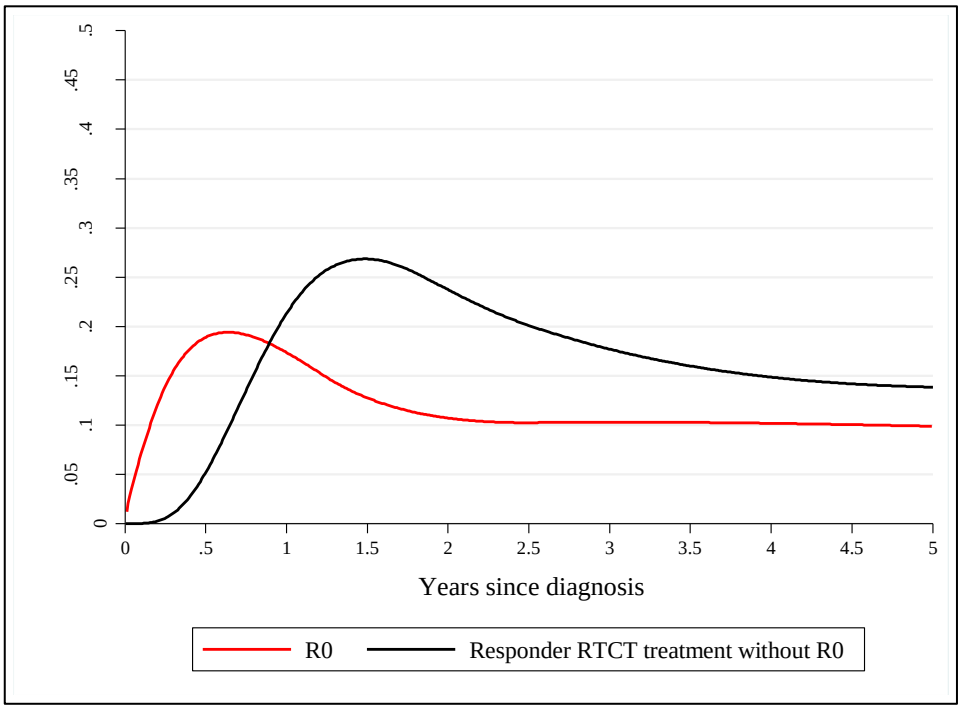
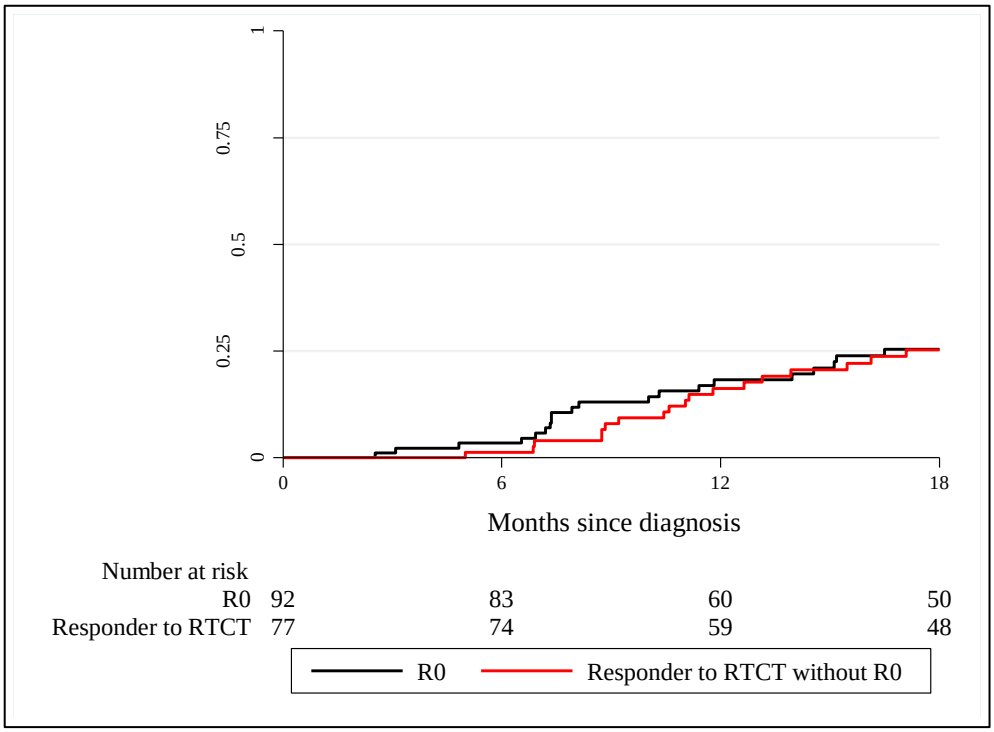


**Figure 2. Recurrence of patients with M0 oesophageal cancer according to treatment modalities.**



**ANNEXE 2. Characteristics of patients with oesophageal cancer according to time period and histology.**

| | Squamous cell carcinoma | | | | | Adenocarcinoma | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N=240 | | N=243 | | | N=104 | | N=136 | | |
| **Sex** | | | | | | | | | | |
| Men | 182 | 76% | 188 | 77% | 0.691 | 97 | 93% | 118 | 87% | 0.102 |
| Women | 58 | 24% | 55 | 23% | | 7 | 7% | 18 | 13% | |
| **Age (years)** | | | | | | | | | | |
| <65 | 113 | 47% | 116 | 48% | | 34 | 33% | 43 | 32% | |
| 65-74 | 54 | 23% | 65 | 27% | 0.380 | 29 | 28% | 28 | 21% | 0.320 |
| ≥75 | 73 | 30% | 62 | 26% | | 41 | 39% | 65 | 48% | |
| **Charlson comorbidity score*** | | | | | | | | | | |
| 0 | 124 | 52% | 107 | 45% | | 51 | 49% | 60 | 45% | |
| 1 | 64 | 27% | 51 | 21% | 0.004 | 32 | 31% | 40 | 30% | 0.630 |
| ≥2 | 49 | 21% | 82 | 34% | | 21 | 20% | 34 | 25% | |
| **Location** [§] | | | | | | | | | | |
| Upper third | 59 | 25% | 76 | 32% | | 1 | 1% | 6 | 5% | |
| Middle third | 108 | 46% | 97 | 41% | 0.213 | 10 | 10% | 17 | 13% | 0.194 |
| Low third | 70 | 30% | 63 | 27% | | 91 | 89% | 108 | 82% | |
| **Metastatic status** [#] | | | | | | | | | | |
| M0 | 179 | 75% | 153 | 63% | 0.008 | 75 | 73% | 82 | 60% | 0.043 |
| M1 | 61 | 25% | 88 | 37% | | 28 | 27% | 54 | 40% | |

*° Chi-2 test.*

**Charlson score unknown for 6 cases with squamous cell carcinoma and 2 cases with adenocarcinoma.*

*§ Location unknown for 10 cases with squamous cell carcinoma and 7 cases with adenocarcinoma.*

*# Metastatic status unknown for 2 cases with squamous cell carcinoma and 1 case with adenocarcinoma.*

**ANNEXE 2. Treatment modalities of patients with oesophageal cancer according to time period, histology and metastatic status.**

| | Squamous cell carcinoma | | | | Adenocarcinoma | | | |
|---|---|---|---|---|---|---|---|---|
| | 2004-2008 | | 2009-2013 | | 2004-2008 | | 2009-2013 | |
| **M0** | *175* | | *152* | | *75* | | *82* | |
| Resection for cure (R0) | 28 | 16% | 13 | 9% | 36 | 48% | 18 | 22% |
| Chemoradiation alone[¥] | 78 | 45% | 80 | 53% | 16 | 21% | 25 | 30% |
| *Responders* | *27* | *39%* | *36* | *54%* | *6* | *43%* | *10* | *45%* |
| *No responders* | *43* | *61%* | *31* | *46%* | *8* | *57%* | *12* | *55%* |
| Radiotherapy alone | 20 | 11% | 19 | 13% | 7 | 9% | 9 | 11% |
| Chemotherapy alone | 22 | 13% | 17 | 11% | 3 | 4% | 6 | 7% |
| Best supportive care | 27 | 15% | 23 | 15% | 13 | 17% | 24 | 29% |
| **M1** | *61* | | *88* | | *28* | | *54* | |
| Chemoradiation alone | 22 | 36% | 28 | 32% | 10 | 36% | 10 | 19% |
| Radiotherapy alone | 5 | 8% | 6 | 7% | 3 | 11% | 6 | 11% |
| Chemotherapy alone | 18 | 30% | 34 | 39% | 10 | 36% | 28 | 52% |
| Best supportive care | 16 | 26% | 20 | 23% | 5 | 18% | 10 | 19% |

*§ Treatment modalities unknown for 4 cases in 2004-2008 and 1 case in 2009-2013 with squamous cell carcinoma.*
** Réponse à la RTCT unknown for 21 cases with squamous cell carcinoma and 5 cases with adenocarcinoma*

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

**TITRE DE LA THESE : EVOLUTION DE LA PRISE EN CHARGE ET DU PRONOSTIC DES CANCERS DE L'ŒSOPHAGE, ETUDE EN POPULATION GENERALE.**

**AUTEUR : NAPOLEON MARIE**

**RESUME :**

**Objectif :** L'objectif de ce travail était de décrire l'évolution des pratiques de soins et du pronostic des adénocarcinomes et des cancers épidermoïdes de l'œsophage en France au cours de la dernière décennie, dans une population bien définie.

**Méthodes :** Tous les cas de cancers diagnostiqués entre 2004 et 2013 et enregistrés par le Registre des cancers digestifs de Bourgogne ont été inclus. Au total 483 cancers épidermoïdes et 289 adénocarcinomes ont été analysés. La survie nette et la survie nette conditionnelle ont été calculées. Des analyses unies et multivariées des facteurs associés à la survie ont été menées.

**Résultats :** La proportion de patients présentant des métastases à distance au moment du diagnostic a augmenté significativement de 25% (2004-2008) à 37% (2009-2013) pour les cancers épidermoïdes et de 27% à 40%, pour les adénocarcinomes, sans doute du fait des progrès de l'imagerie. Parmi les patients non métastatiques (M0), la proportion de patients réséqués à visée curative a diminué de 16% à 9% (p=0.297) pour les épidermoïdes et de 48% à 22%(p=0.016) pour les adénocarcinomes. La radiochimiothérapie est devenue le traitement principal. Elle est réalisée chez la moitié des patients avec cancer épidermoïde et chez un quart des patients avec adénocarcinome. Une réponse clinique complète étant obtenue chez 40% des patients traités.

La survie nette à 5 ans était de 14% et ne variait pas selon le type histologique. Elle était de 55% pour le petit groupe de patients ayant été réséqués à visée curative. Parmi les patients M0 traités par radiochimiothérapie, la survie nette à 5 ans était de 44% pour ceux ayant une réponse complète et de 2% en l'absence de réponse complète. Le taux de récidive à 18 mois étant de 25% dans le groupe des patients traités par résection chirurgicale et 25% dans le groupe des patients répondeurs à la radiochimiothérapie.

**Conclusion :** Le pronostic du cancer de l'œsophage reste très sombre. Environ 1/3 des patients sont diagnostiqués à un stade métastatique, ce qui souligne le caractère tardif du diagnostic. Les modalités thérapeutiques ont profondément changé au cours de la dernière décennie, en faveur des traitements non chirurgicaux, sans effet patent sur la survie.

**MOTS-CLES : CANCER ŒSOPHAGE, PRATIQUE DE SOINS, SURVIE, REGISTRE DES CANCERS**