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THE IMPACT OF NEOADJUVANT ONCOLOGICAL TREATMENT AND SURGICAL OESOPHAGECTOMY FOR OESOPHAGEAL CANCER ON OVERALL SURVIVAL

A SINGLE CENTER SERIES

Student

Gaspar Figueiredo, Sergio

Faculté de biologie et médecine, Lausanne

Tutor

Prof. Markus Schäfer

Dpt of Visceral Surgery, CHUV

Co-tutor

Drs Mantziari, Allemann, Winiker

Dpt of Visceral Surgery, CHUV

Assessor

Prof. Dieter Hahnloser

Dpt of Visceral Surgery, CHUV

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Abstract

Introduction

Despite there are robust data supporting neoadjuvant radiochemotherapy in oesophageal cancer, some doubts subsist concerning the real effect on the different histological subtypes. In this study, we compared long-term overall survival in squamous cell carcinoma (SCC) and adenocarcinoma (AD) depending upon neoadjuvant radiochemotherapy (NAT).

Patients & Methods

Patients were selected from our institutional database from January 2000 until December 2013. The eligibility criteria were: Adenocarcinoma or squamous cell carcinoma, stage I-IVa and patients with and without neoadjuvant treatment.

For the primary endpoint, the overall survival was compared according to the response to neoadjuvant treatment. Then, we subdivided the pathological response in "Down-staging" group for a partial response and in "ypCR" group for the pathological complete response.

Then we compared the effect of down-staging on overall survival same way as mentioned. Finally, we compared patients with NAT and a surgery against patients who only had surgery.

Results

Only primary endpoint - Without subdivision of histological sub-types 32.7% had no response to NAT, 47.3% had a down-staging (without ypCR) and 20% a pathological complete response. They had an overall survival of 45 [2-97], 39[14.4-63.6], 43 months [37.4-48.6] (p=0.78), respectively. The difference of survival were statistically not significant. The overall median survival period was 43 months [33-53 months].

Conclusion

Our retrospective study did not demonstrate any advantage in overall survival period on groups with ypCR against those without. The subtypes analysis did not show a difference either. Finally, we also compared our survival data with the current literature. Our results showed that patients with advanced stage who receive a NAT retrieve similar survival as patients with early stages, which is in line with other studies.

In conclusion, our retrospective study supports the current literature about the interest of multimodal treatment for patients with oesophageal cancer. They are needed to determine the most accurate chemo or radio treatment for each histological subtype and if they should be treated with different regimens.

Keywords: Neoadjuvant treatment; oesophageal cancer; adenocarcinoma; squamous cell carcinoma; overall survival

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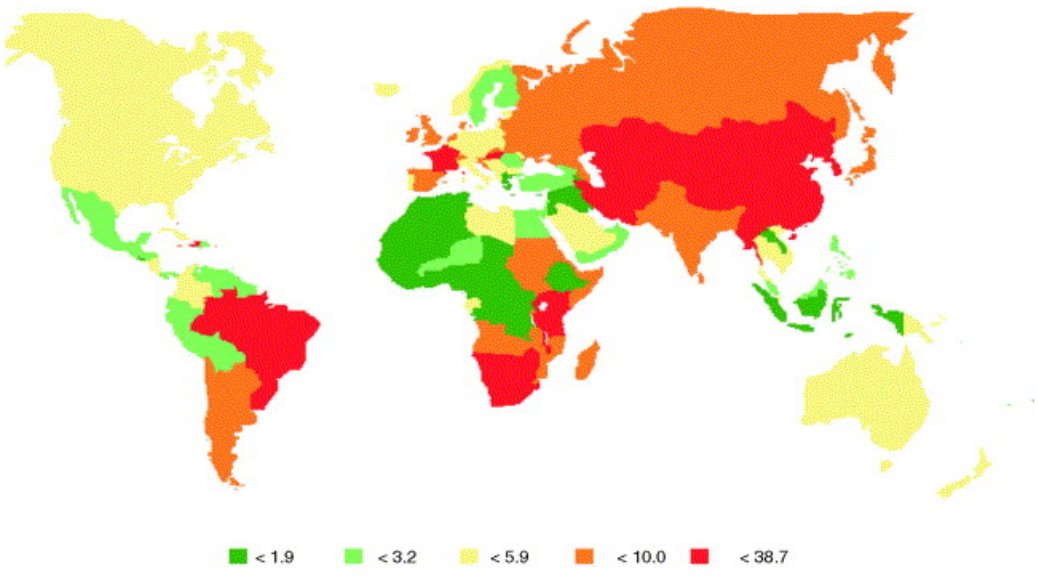
1 Introduction

1.1 Epidemiology of oesophageal cancer

To date, oesophageal cancer is the eighth most widespread and the sixth deadliest cancer worldwide. Each year, 450'000 new patients are diagnosed. The oesophageal cancer has two main forms: adenocarcinoma (AD) and squamous cell carcinoma (SCC). The SCC is the predominant form worldwide, but AD has by now a higher incidence in some European countries, USA and Australia (1,2,3). The most frequent location of the oesophageal cancer is the oesogastric junction and the gastric cardia (4).

The incidence has been increasing during recent years (5,6); e.g. Brown *et al.* (7) reported an increase from 5.76 to 8.34/100'000 for AD from 1975 to 2004 for white Americans. Incidence shows a large range between geographical regions. The most prevalent places are Southern Africa, Eastern Europe and Asia, while incidences are lower in Western and Central Africa but also in Central America. A particular high incidence of SCC is present in Iran, Central Asia and in Northern China. This specific regions are known as "oesophageal cancer belt" (8,9). This type of oesophageal cancer has an extremely bad prognosis with approximately 350'000 deaths/year over the 391'000 that occurs each year (10).



Incidence of oesophagus cancer: age-standardised rate (world)—male (all ages)(10)

In Switzerland, the incidence is 9.4/100'000 and 2/100'000 for men and women, respectively; with a tendency to increase over time. Estimation for Switzerland show an increase from 350 to 771 patients in 2029 (11).

1.2 Risk factors

Both cancer types have different risk factors (12-13). For instance, alcohol is a main risk factor for SCC but not for AD. Smoking affects both, SCC and AD development. Pennathur *et al.* (14)

and other authors (15,16) summarised these risk factors and looked for additional papers to highlight them. They are presented in the following table.

Risk factors for both types of oesophageal cancer

Squamous cell carcinoma	**Adenocarcinoma**
Alcohol (17–20)*:* - Major risk - Smoking increases the alcohol consumption - Risk: amount > type of beverage (21)	*Gastroesophageal reflux disease* - 7.7-fold increased risk of AD for patients with reflux (22) → 5-fold if weekly symptoms (23) → 7-fold if daily symptoms (23) - Barrett's oesophagus (24) → 30-fold above overall population to develop cancer
Smoking: - Major risk in Asia (25) → higher tobacco consumption	*Smoking* - 2-fold risk (26,27)
Mutations in enzymes who metabolise alcohol (28–30) - Mutations in genes involved in ADH (alcohol dehydrogenase) pathway [ADH1B and ADH7]	*Obesity* - *High BMI increases risk of Barrett's oesophagus* (31) → 1.71-fold risk (BMI 25-30) → 2.34-fold risk (BMI ≥30)
Achalasia (32)	*Relaxing drugs of the lower oesophagus*
Caustic injury (33)	Diets low in vegetables and fruits
Gastric atrophy (34)	Age, gender
Poor oral hygiene - Periodontal loss (35, 36)	
Other - nutritional deficiencies: Zinc (37) or vitamin E (38) - low economic status (39)	

When we compare the risk factors of the two histological subtypes, we can see some differences. For example, alcohol is a risk for SCC but not for AD (19) and obesity (40) is one for AD and not for SCC.

1.3 Clinical presentation

About (41) 75% of patients have dysphagia at time of diagnosis, and 17% reported odynodysphagia. However, some patients remain asymptomatic and are only diagnosed during endoscopic surveillance for Barrett's oesophagus. The above presented risk factors are often part of the clinical features as well as weight loss related to dysphagia, changes in diet and anorexia induced by cancer. Malnutrition, defined as a loss of >10 % of the body weight indicates a poor prognosis (42). Cough, hoarseness and retrosternal pain are less frequent, but they are highly suspicious for an oesophageal malignancy. Other symptoms are more typical of metastatic disease, e.g. lymphadenopathy, hepatomegaly, and pleural effusion.

1.4 Treatment plans

Currently, all patients with oesophageal cancer should be discussed at a multidisciplinary tumor board prior to any treatment.

Patients with a cancer diagnosis are grouped into early disease (stage I UICC) or advanced disease (> stage I UICC), respectively. Patients with advanced disease are candidates for a multimodal treatment. Early disease can be treated by interventional endoscopy or, more commonly by surgery. Unfortunately, many patients are diagnosed with metastatic disease. These patients will only receive palliative treatment.

The type of chemotherapy depends on tumour histology and location (14). Usually, patients with advanced disease will receive chemotherapy (5-FU/cisplatin or Taxotere/cisplatin) and radiotherapy (doses 40-50.4 Gy). Time between the end of the neoadjuvant treatment and the surgery is 6-8 weeks (43).

1.4.1 Surgical modalities

Surgical resections are performed by the following procedures (43).

1.4.1.1 Transhiatal oesophagectomy

Lin *et al.*(44) summarized the operative procedure divided in four distinctive stages:

1. *The abdominal phase* consists in opening the abdomen to assess the resectability and metastasis. The stomach is then mobilized and tubulised. The abdominal lymph nodes are removed. The hiatus is enlarged and the mediastinal oesophagus and its adjacent lymph nodes are dissected.
2. The *cervical phase* starts with a cervical incision, followed by the mobilization of the cervical oesophagus.

3. The cervical oesogastric anastomosis is the last stage. We remove the oesophagus en bloc with the thoracic lymph nodes. The gastric tube is pulled up to the neck to perform an anastomosis.

This procedure is indicated for middle and distal third cancer of the oesophagus.

1.4.1.2 Transthoracic approach (Ivor-Lewis-Santy)

The Ivor-Lewis-Santy consists in a twofold approach (43,45). First, an upper median laparotomy is done to prepare the gastric tube and to clear the abdominal lymph nodes. Then a right thoractomy is performed to remove the oesophagus and the adjacent lymph nodes. Finally, the gastric tube is pulled up and the anastomosis is performed on the level of the azygos vein.

Recently, a complete minimal invasive approach has been developed to minimize the perioperative morbidity.

The Lewis-Santy is indicated for cancer in the middle and distal third of the oesophagus

1.4.1.3 McKeown (triple approach)

The McKeown approach is similar to the Lewis-Santy, but we add a cervical incision (46). Contrary to the Lewis-Santy, we begin by performing a right chest incision and then the abdominal incision. The technique for the cervical incision is the same as the transhiatal oesophagectomy. The selected route for the tubulised stomach is the posterior mediastinal one. The McKeown approach is mostly indicated for upper and middle third cancers.

1.4.1.4 Akiyama

A direct thoracotomy is made at first to set the tumour free (43,47). We then mobilize the stomach by laparotomy and finally make an anastomosis via a cervical incision. The selected route is the retrosternal one. The Akiyama approach is mostly indicated for upper and mean third cancers.

1.5 Staging and pathology

All patients are staged before the treatment (cTNM) and after surgery (pTNM). While the precise pre-treatment is important to determine the indication for neoadjuvant treatment, the postsurgical tumor classification allows the risk stratification for recurrence and follow-up. The pre-operatory staging consists of:

- Biopsies via oesogastroduodenoscopy associated with ultrasonography, which is essential for the assessment of the T- and N-stage, respectively.
- CT of the thorax and abdomen and the PET-CT are primarily used to assess distant metastasis. As a second aim, adjacent organ infiltration of the primary tumor and lymph node infiltration can be determined.

1.6 Survival indicators

1.6.1 Resection margins

There are actually two definitions of the circumferential resection margins (CRM). The first one is suggested by the UK Royal College of Pathologists (RCP) and defines it as a "positive margin" when the tumour is involved within the last millimetre before the cut margin (48). On the other side of the Atlantic, the College of American Pathologists (CAP) defines a "positive resection margin" when the tumour reach the cut margin (49). A systematic review made by Chan *et al.* (50) concludes that the positive resection margins predict a poor prognosis. In this systematic review Chan *et al.* analysed the 5-years mortality according to the two definitions. Positive margins have a poor prognosis when compared to high risk margins (tumour between 0.1-1 mm of the margin) and more than 1 mm. Interestingly, in 2010, Khan *et al.* (51) concluded that the CRM as prognostic factor was unclear for patients who only undergo surgery but for patients benefiting from NAT, the CRM appeared to be a long-term survival predictor.

1.6.2 Tumour regression grade

Based on histological observations, Mandard *et al.* (52) proposed a classification is nowadays widely used: the Tumour Regression Grade (TRG). The classification is based on the two main changes hereafter:

1. "[1]Cytology: eosinophilia, cytoplasmic vacuolisation, nuclear pyknosis and necrosis.
2. Stromal changes: fibrosis with or without inflammatory infiltrate including giant cell granuloma."

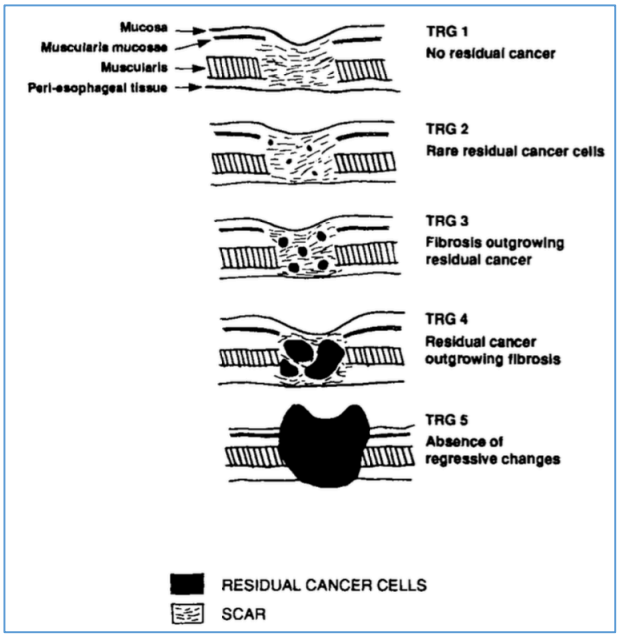


Figure 1 - Tumour regression grade by Mandard et al.[1]

Figure 1 shows the Mandard classification: It goes from TRG 1 (complete regression) to TRG 5 (no histological changes). They assessed then the disease-free-survival according to the TRG and found evidence between TRG 1-2-3 and TRG 4-5.

1.6.3 Pathological complete response

The prognostic value of a pathological complete response (pCR) compared with residual tumour has been largely assessed (53–63); and most authors confirmed that a pCR is a

[1] Mandard *et al.* (52), page 2681-262

favroable prognostic factor. E.g., Van Scheer *et al.* (56) showed that patients with a pCR have a better OS than patients with a partial response. Mariette *et al.* (64) suggested that patients without pCR do not benefit from NAT, but suffer from its toxicity. Toxopeus *et al.* (65) recently developed a nomogram to identify whether patients will have a pCR.

The rate of pCR shows a large variety ranging from (53) <30% to 50% (53–63) (58).

2 Endpoints of the study

The primary endpoint of this study was to evaluate the effect of NAT on patients with oesophageal cancer (both AD and SCC). To this end, we assessed the tumor response according to the Mandard score. We then compared patients with complete response (ypCR) TRG 1 to patients with a partial response (TRG 2-4) and patients with no response (TRG 5). Subgroup analysis were performed to assess differences between AD and SCC.

3 Material and methods

3.1 General eligibility

Patients were selected from our institutional data base that includes all patients undergoing oesophageal cancer surgery at the department of visceral surgery, CHUV, from January 2000 to December 2013. Eligibility criteria are:

- Adenocarcinoma or squamous cell carcinoma
- Stage I-IVa
- Patients with and without neoadjuvant treatment

Each endpoint was analysed 3 times:

- Without stratification (no differentiation between AD and SCC)
- Adenocarcinoma only
- Squamous cell carcinoma only

3.2 Assessment of endpoints

3.2.1 Patients with pathological complete response (ypCR) and their overall survival

For the primary endpoint, the overall survival was compared according to the response to neoadjuvant treatment. Then, we subdivided the pathological response in “Down-staging” group for a partial response and in “ypCR” group for the pathological complete response.

- « Down-staging » → clinical stage higher than pathological stage
- « No response » → clinical stage equal or higher to the pathological stage
- « ypCR » → pathological complete response which means pT0N0

3.2.2 Secondary endpoints

3.2.2.1 Effect of down-staging on overall survival

The method was similar as to assess the primary endpoint.

3.2.2.2 Comparison of overall survival on patients with surgery only versus surgery and neoadjuvant treatment

We compared patients with NAT and a surgery against patients who only had surgery.

3.3 Chemo-radiotherapy protocol

Our study was performed on a heterogeneous population, with different treatments of chemo- and radiotherapy according to the recommendations at the time of the initial disease treatment. Most of them were cisplatin-based (Figure A) and the radiotherapy (Figure B) was mostly with 50.4 Gy.

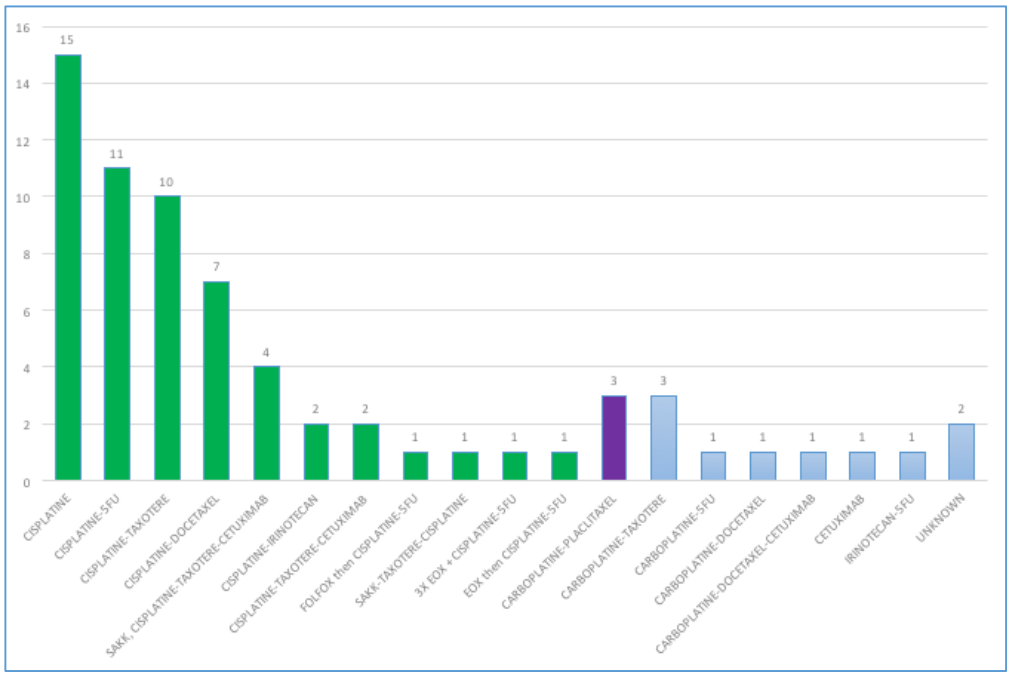


Figure A: Heterogeneity of chemotherapy - Green: cisplatin based treatments; violet: CROSS protocol; blue: other types of chemotherapy

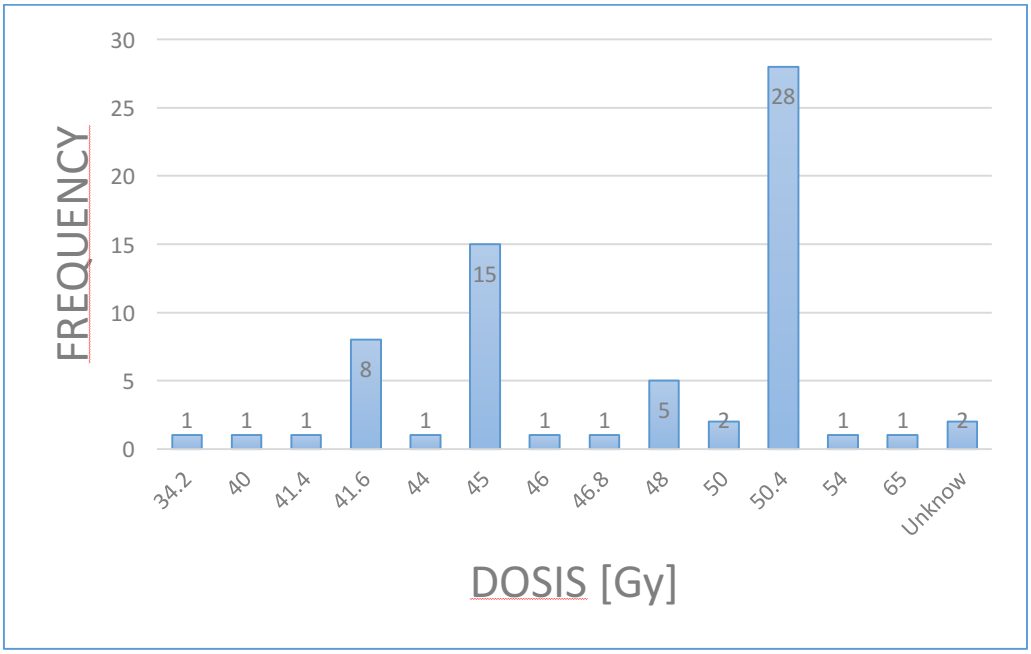


Figure B: Radiotherapy regimen - 41.6 Gy regimen represents the CROSS protocol; 45 Gy regimen represents the SAKK protocol; 50.4 Gy regimen represents the protocols based on cisplatin

3.4 Data analysis and statistical methods

The following data were extracted from the database: Age, sex, type of cancer, NAT details (drugs, doses for radiotherapy, date of beginning, date of ending, time between the end and the surgery), cTNM, pTNM, date of surgery, date of death, time of follow-up, length of survival.

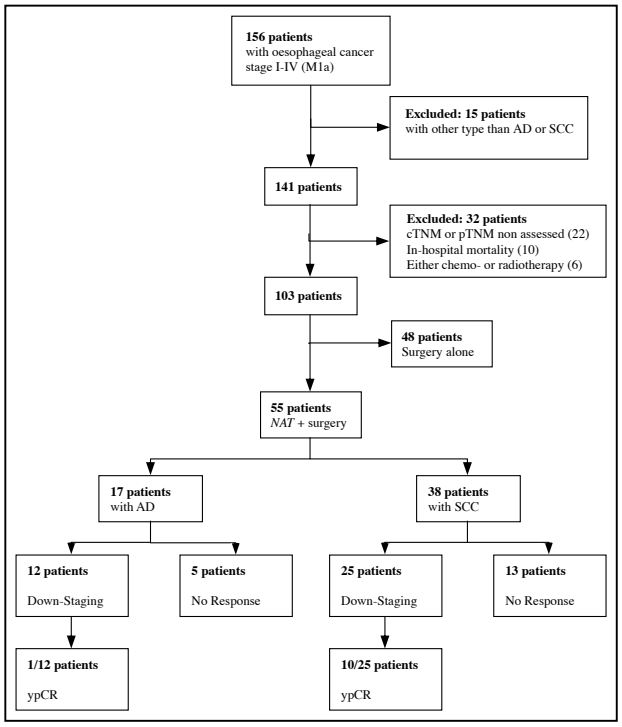
Statistical analysis were performed with SPSS V.23 and STATA. We used the Kaplan-Meier method to test the overall survival and the log-rank test for inter-group comparisons ($p<0.05$ for statistical significance). Adequate statistical test were used for categorical and continuous data.

4 Results

4.1 *Primary endpoint - Rate & overall survival of the pathological complete response (ypCR)*

There were 156 patients initially selected, 15 patients were excluded because of their histological tumor type group. Another 22 patients were excluded because of incomplete data. Ten (6.4%) patients died during the 30 days after surgery and 6 patients did not receive a full neoadjuvant treatment. Forty-eight patients had no neoadjuvant treatment.

The final patient group was divided into different subgroups. A group with a down-staging (subdivided in ypCR and non-complete response) and another group without response to the NAT. 82% of patients were males and 18% females. The median age was 63 years [45-77]. The rate of R0 was 95% and 5% for R1. The median follow-up was 29 months [2-160].



Flowchart 1 - Primary endpoint - Selection of patients according their response to neoadjuvant treatment

4.1.1 Effect of NAT without stratification

Without subdivision of histological sub-types (55 patients), 18 (32.7%) had no response to NAT, 26 (47.3%) had a down-staging (without ypCR) and 11 (20%) a pathological complete response. They respectively had an overall survival of 45 [2-97], 39[14.4-63.6], 43 months [37.4-48.6] (p=0.78). Therefore, patients with ypCR had 72% mortality, patients with down-staging without ypCR had 65% mortality and patients without response had 94% mortality. The survival curves were statistically not significant. The overall median survival period was estimated at 43 months [33-53]. (Figure 2)

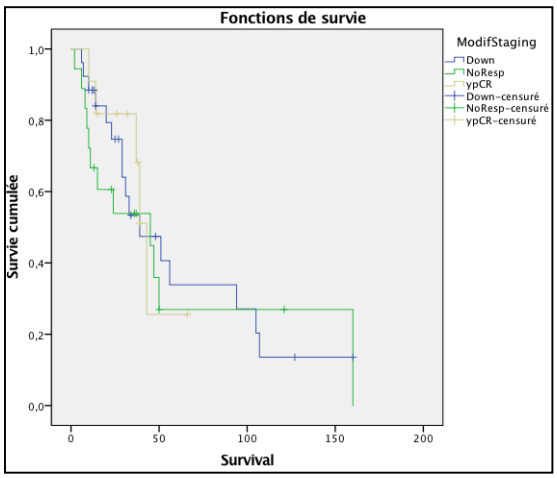


Figure 2 - Effect of neoadjuvant treatment on patients with oesophageal cancer without subgroup stratification. "Down": patients with downstaging after NAT; "NoResp": patients without response to NAT; "ypCR": patients with complete response to NAT.

Moyennes et médianes pour la durée de survie

Modification of staging	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
Down-Staging	61,998	11,674	39,118	84,879	39,000	12,560	14,383	63,617
No Response	60,928	17,459	26,708	95,148	45,000	24,856	,000	93,717
ypCR	41,744	6,584	28,841	54,648	43,000	2,873	37,369	48,631
Global	61,175	9,052	43,432	78,918	43,000	5,058	33,087	52,913

4.1.2 Effect of NAT on adenocarcinomas

For the 17 patients with AD, 5 (29.4%) had no response, 11 (64.7%) a down-staging (without ypCR) and 1 (5.9%) a pathological complete response. Patients with a down-staging had a median overall survival of 31 months. The patient with ypCR is still alive and patients without response to NAT don't have enough follow-up to calculate a median overall survival. Difference was not significantly demonstrated(P=0.663). (Figure 3)

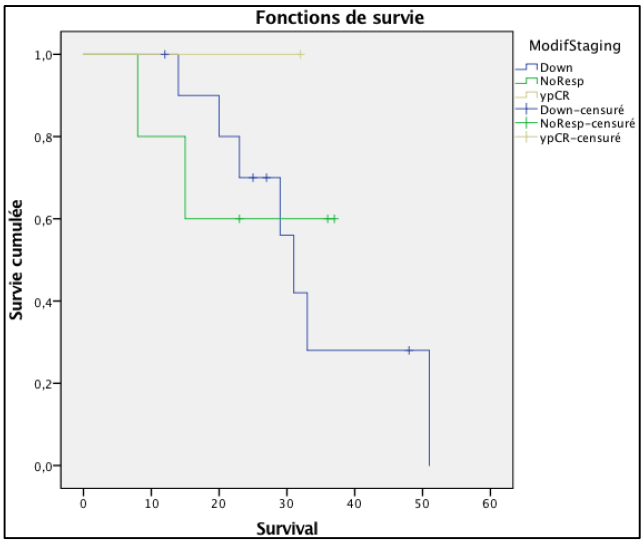


Figure 3 - Effect of neoadjuvant treatment on patients with oesophageal adenocarcinoma. "Down": patients with downstaging after NAT; "NoResp": patients without response to NAT; "ypCR": patients with complete response to NAT.

Moyennes et médianes pour la durée de survie

Modification of staging	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
Down	33,000	4,631	23,923	42,077	31,000	2,519	26,064	35,936
NoResp	26,800	5,674	15,679	37,921	.	.	.	.
Global	33,733	4,373	25,163	42,304	31,000	2,998	25,124	36,876

4.1.3 Effect of NAT on squamous cell carcinoma

For the 38 patients with SCC, 13 (34.2 %) patients had no response, 15 (39.5 %) a down-staging (without ypCR) and 10 (26.3%) a pathological complete response. They respectively have an overall survival period of 45 [0-99], 94 [14-174], 39 [34-44] months (p=0.66). Difference was not significantly demonstrated. (Figure 4)

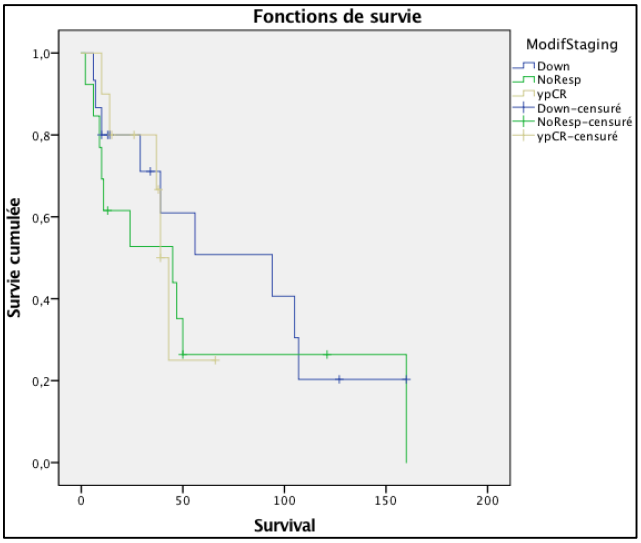


Figure 4 - Effect of neoadjuvant treatment on patients with oesophageal squamous cell carcinoma. "Down": patients with downstaging after NAT; "NoResp": patients without response to NAT; "ypCR": patients with complete response to NAT.

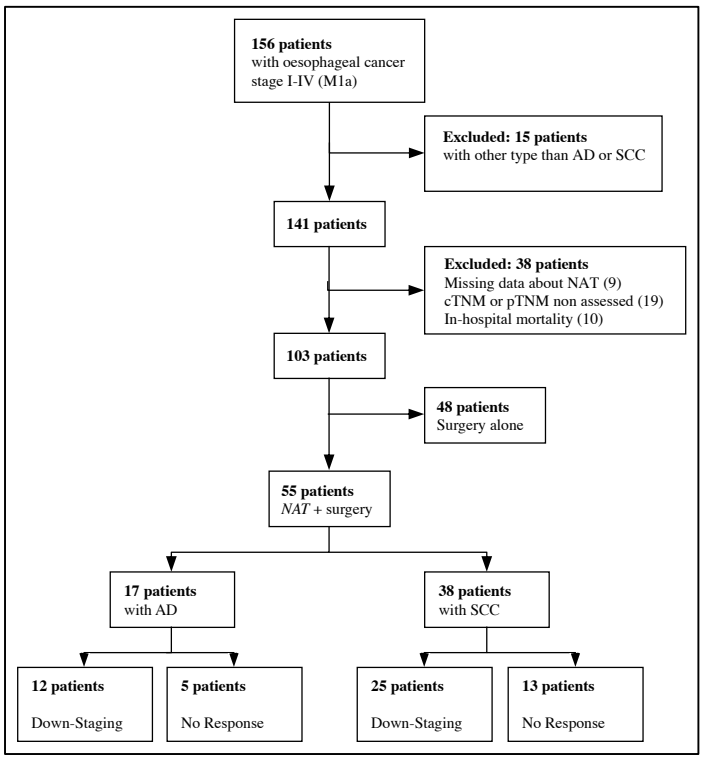
Moyennes et médianes pour la durée de survie

Modification of staging	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
Down-Staging	77,356	15,894	46,204	108,507	94,000	40,819	13,996	174,004
No Response	59,714	18,862	22,745	96,683	45,000	27,572	,000	99,041
ypCR	41,083	6,746	27,861	54,306	39,000	2,710	33,688	44,312
Global	65,970	10,718	44,962	86,978	45,000	6,140	32,965	57,035

4.2 Secondary endpoints

4.2.1 Effect of a down-staging on overall survival

Same selection as the primary endpoint. These patients have been separated in different groups. The group with down-staging (without ypCR) and the group without response to the NAT. (flowchart 2)



Flowchart 2 - Selection of patients according their response to neoadjuvant treatment - No subdivision of the "Down-staging" group

4.2.1.1 *Effect of NAT without subdivision*

Without any stratification of histological subtypes, patients with a response to the NAT had lower median survival periods in comparison with the group without response. The median survival period was 39 months [30.74-47.26] for the "Down"-staging group and 45 months [0-93.72] for the group without response to the neoadjuvant treatment. No significance was found between the two groups (p=0.495). (Figure 5)

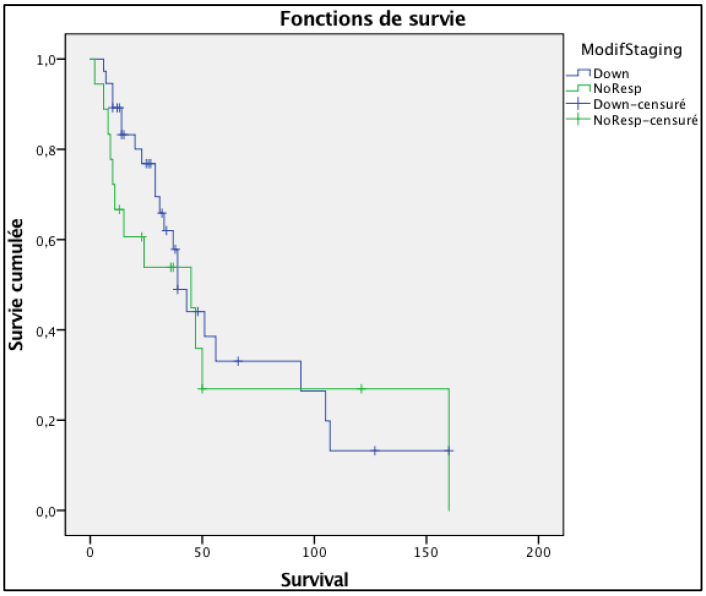


Figure 5 - Effect of neoadjuvant treatment on patients with oesophageal cancer without subtype division. "Down": patients with downstaging after NAT; "NoResp": patients without response to NAT.

Moyennes et médianes pour la durée de survie

Modification of Staging	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
Down-staging	62,006	10,167	42,078	81,934	39,000	4,217	30,736	47,264
No response	60,928	17,459	26,708	95,148	45,000	24,856	,000	93,717
Global	61,175	9,052	43,432	78,918	43,000	5,058	33,087	52,913

4.2.1.2 *Effect of NAT on adenocarcinomas*

17 patients over 55 had adenocarcinoma. 12 out of 17 (71%) had a down-staging (ypCR included) and the remaining 5 (29%) didn't. Patients with a down-staging had a median survival period of 31 months [26-36] but we didn't have enough follow-up to adequately estimate an overall survival period for the group without response. No significance was found between the two groups (p=0.835). (Figure 6)

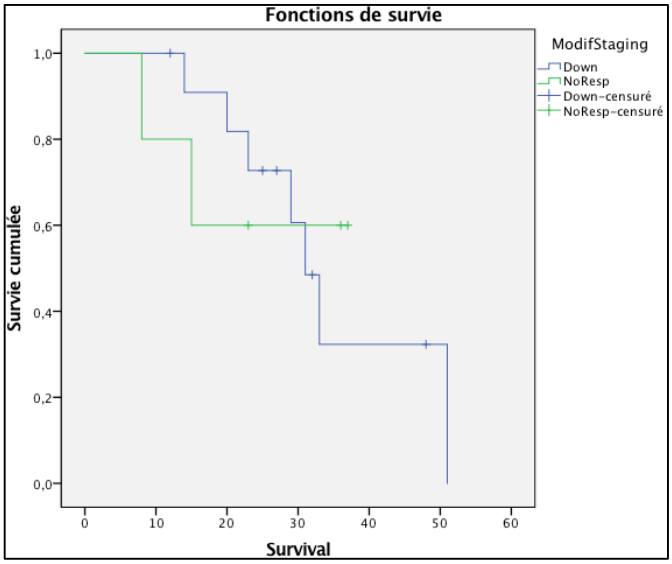


Figure 6 - Effect of neoadjuvant treatment on patients with oesophageal adenocarcinoma.. "Down": patients with downstaging after NAT; "NoResp": patients without response to NAT.

Moyennes et médianes pour la durée de survie

Modification of Staging	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
Down-staging	34,273	4,630	25,197	43,348	31,000	2,350	26,394	35,606
No response	26,800	5,674	15,679	37,921	.	.	.	.
Global	34,701	4,276	26,320	43,082	33,000	3,018	27,085	38,915

4.2.1.3 Effect of NAT on squamous cell carcinoma

38 patients over 55 had squamous cell carcinoma. 25 out of 38 (66%) had a down-staging and the remaining 13 (34%) didn't. Patients having a response to the NAT ("Down"-group) obtained a median survival period of 43 months [14.49-71.512]. However, the group without response to NAT ("NoResp"-group) obtained a median survival of 45 months [0-99.04]. No statistical difference was found between the two survival curves (p=0.415).

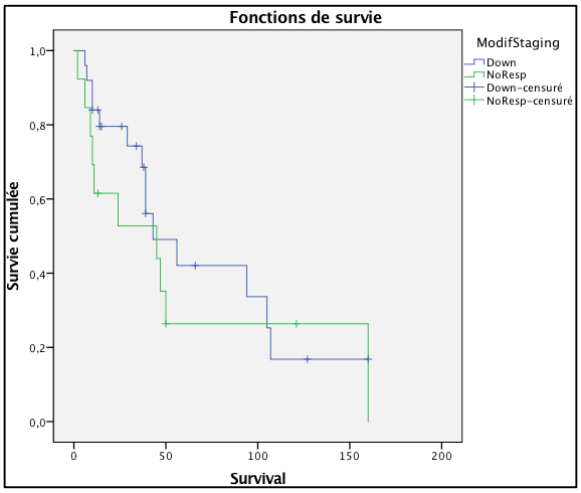


Figure 7 - Effect of neoadjuvant treatment on patients with oesophageal squamous cell carcinoma. "Down": patients with downstaging after NAT; "NoResp": patients without response to NAT.

Moyennes et médianes pour la durée de survie

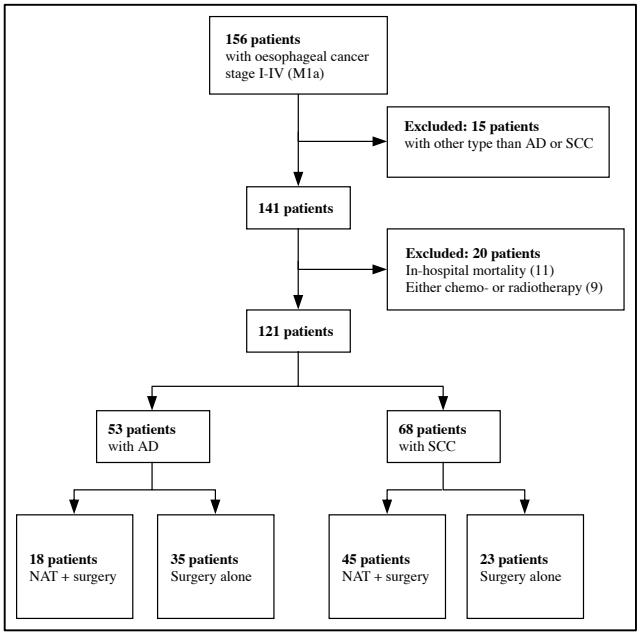
Modification of staging	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
Down-staging	70,068	12,603	45,367	94,769	43,000	14,547	14,488	71,512
No Response	59,714	18,862	22,745	96,683	45,000	27,572	,000	99,041
Global	65,970	10,718	44,962	86,978	45,000	6,140	32,965	57,035

4.2.2 Comparison of overall survival on patients with surgery only VS surgery plus neoadjuvant treatment

The selection initially included 156 patients from which 15 patients were excluded because of histological group was neither adenocarcinoma nor squamous cell carcinoma. 11 patients died during the 30st days after surgery and 9 patients didn't receive a full treatment of radio- and chemo-therapy.

121 patients were sampled for statistical analysis.

77 % of patients are males and 23% females. The median age is 63 years ± 8.7. The rate of R0 was 88 % and 12 % for R1. (Flowchart 3)



Flowchart 3 - Subdivision of patients according their modality of treatment

4.2.2.1 *Effect of NAT without subdivision*

We first compared groups without histological subtypes division. 121 patients were selected, 58 with surgery only and 63 with surgery and neoadjuvant treatment. The median overall survival period of patients with surgery alone was 62 months [36.2-87.751] and for patients with neoadjuvant treatment and NAT 39 months [25.3-52.7]. No significance was found in log rank comparisons but a small trend was observable (**p=0.065**). (Figure 8)

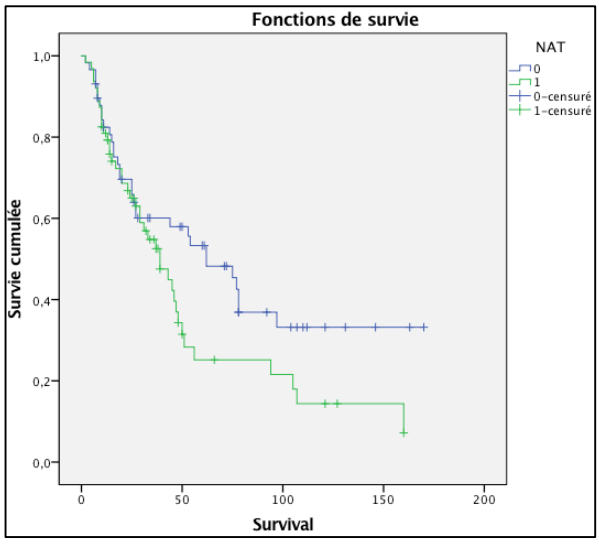


Figure 8 - Overall survival of patients with oesophageal cancer according to the modality of treatment. ***"0" = surgery only; "1" = neoadjuvant treatment followed by surgery.***

Moyennes et médianes pour la durée de survie

Neoadjuvant treatment	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
0 = surgery only	81,271	9,778	62,105	100,436	62,000	13,138	36,249	87,751
1 = NAT + surgery	55,001	7,862	39,592	70,410	39,000	6,997	25,287	52,713
Global	68,673	6,470	55,992	81,353	46,000	5,830	34,574	57,426

4.2.2.2 *Effect of NAT on adenocarcinomas*

53 patients were included in the adenocarcinoma group. 35 (66%) in the surgery alone group and 18 (34%) in the group with surgery and NAT. The median overall survival period was 75 [39.9-110.1] months in the surgery only group and 31 [25.1-36.9] months in the group with surgery and NAT. **The p=0.355** in the log rank test didn't result in statistical significance. (Figure 9)

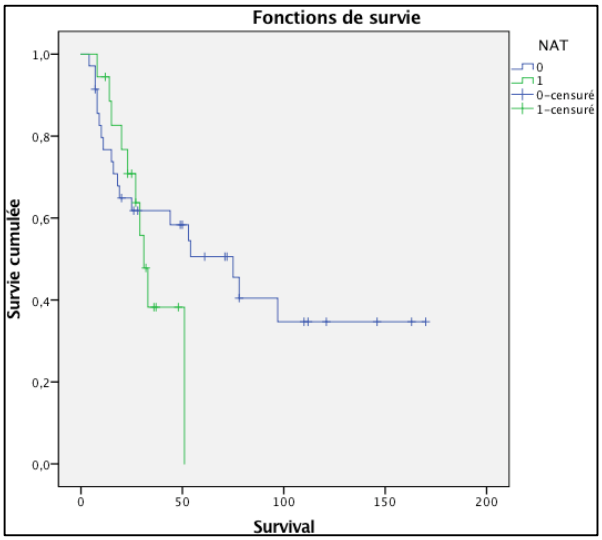


Figure 9 - Overall survival of patients with oesophageal adenocarcinoma according to the modality of treatment. ***"0" = surgery only; "1" = neoadjuvant treatment followed by surgery.***

Moyennes et médianes pour la durée de survie

Neoadjuvant treatment	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
0 = surgery only	82,631	12,798	57,547	107,715	75,000	17,910	39,897	110,103
1 = NAT + surgery	34,051	4,025	26,162	41,941	31,000	3,025	25,071	36,929
Global	74,979	10,695	54,017	95,942	51,000	12,662	26,182	75,818

4.2.2.3 *Effect of NAT on squamous cell carcinoma*

68 patients were included in the group with squamous cell carcinoma. 23 were in the surgery only group and 45 in the group with surgery and NAT. The overall survival period was 62 months [0-124.1] in the group with surgery alone and 43 months [32.7-53.3] in the group with surgery and NAT. We obtained a **p=0.269** in log rank test. (Figure 10)

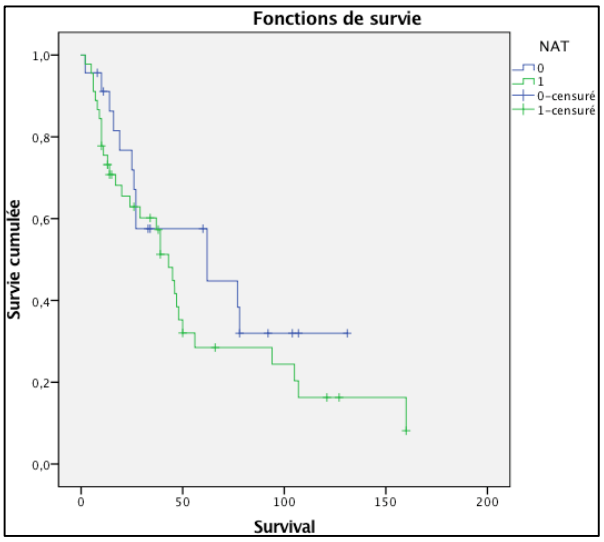


Figure 10 - Overall survival of patients with oesophageal squamous cell carcinoma according to the modality of treatment. ***"0" = surgery only; "1" = neoadjuvant treatment followed by surgery.***

Moyennes et médianes pour la durée de survie

Neoadjuvant treatment	Moyenne				Médiane			
			Intervalle de confiance à 95 %				Intervalle de confiance à 95 %	
	Estimation	Erreur standard	Borne inférieure	Borne supérieure	Estimation	Erreur standard	Borne inférieure	Borne supérieure
0 = surgery only	67,635	10,953	46,167	89,102	62,000	31,662	,000	124,058
1 = NAT + surgery	57,743	9,190	39,731	75,754	43,000	5,235	32,740	53,260
Global	63,064	7,758	47,858	78,271	45,000	5,450	34,317	55,683

5 Discussion

5.1 Primary endpoint

This study did not show an advantage in overall survival in patients who had a pCR after neoadjuvant treatment. Nevertheless, the overall survival of all patients who underwent a NAT and surgery is comparable with most of the recent studies. The rate of pCR also meets values found in the literature (See table 1 – page 20). The greatest difference between our study and other studies is the fact that despite similar overall survival period and a similar pCR rate, we do not have an extended median overall survival.

Some factors might explain the differences. Our university hospital takes patients with oesophageal cancer from all the western Switzerland (Romandie) and from Ticino. These patients have often already received a neoadjuvant treatment implying some difficulties to compare with other single-center studies who received a standardised chemo- or radiotherapy. The toxicity of these drugs is different and the efficiency of these treatment regimens varies largely. The size of the patient group is an important bias. We only have 55 patients who had a NAT and surgery who were included in the study between 2000 and 2013, which represents a small group.

Pasini et al. (53) made in 2013 a similar study with 74 patients. They had exactly 37 patients with AD and 37 with SCC. The study was based on the fact that a pCR, according to some other studies (54,59,62,66,67), improves the overall survival up to 50% in 5 years. They tried a treatment to improve the pCR and see if the OS is effectively improved. While they obtained a pCR in 52% of the operated patients (32 of 67 patients), we had merely a 20% pCR. Their median survival period was 16 months for patients in ResT (no response to NAT) group, 53 months in npCR (near pathological complete response) and not reached for the pCR group.

Our ypCR rate is in line with some studies (59,62,67–70) already published [range 10-33%]. The Pasini protocol would be interesting to test in the future to see if we have similar results with the rate of ypCR and if, according with the current literature, we have a better OS for these patients.

Concerning sub-types analysis, the group of patients with adenocarcinoma was too small to have consistent statistical analysis. The results were also presented, but the group is too small to make any interpretation.

The group of patients with squamous cell carcinoma was a little larger. Despite the fact that de OS is different between the groups, no significance was found on the survival curves and the confidence intervals are large enough to also point out the direction that there is no difference.

The ypCR rate seems also different between the two histological groups (5.9% for AD vs. 26.3% for SCC) being comparable with other studies proving that SCC seems to have a better

response to NAT in comparison to AD (60). However, there is no significance between these groups clearly demonstrated until nowadays.

5.2 Secondary endpoints

5.2.1 Effect of a down-staging on overall survival

Recently, Siddiqui *et al.* (71) (2014) published a similar study of 106 patients. The main purpose was to compare the OS of patients who received NAT according to their response. Despite the fact that they had a larger cohort, the statistical analysis and endpoints were similar to those encountered in our research (this endpoint). They concluded in a retrospective observation over 15 years, 59% patients of the patients with a NAT got a down-staging and their OS was improved as follows 42 months when down-staged vs. 13-17% without modification or with an upstaging The median survival period of all their patients was 35.2 months. These specific patients offered a greater chance of having a R0 resection (92.5%) and improving OS. They also noticed that patients with SCC had a better response to NAT compared to patients with AD.

67 % of our patients got a down-staging. The median overall survival period was 43 [33-53] months. The median survival period was 39 months [31-47] for the "Down"-staging group and 45 [0-94] months for the group without response to the neoadjuvant treatment. Our R0 rate with patients having a down-staging was 100% and 84% for patients without response to NAT.

We had a similar OS for all patients, specifically, a good OS for the down staging group and a similar one for group without response when we were expecting to have a better overall survival for the group with a down staging. It can be explained by the fact that we only had 55 patients, which can decrease the power of the statistical analysis.

Interestingly, we were expecting to have a better rate of patients with down-staging in SCC in comparison with patients with adenocarcinoma. Our results showed that rates were nearly the same (70 % vs. 66 %).

5.2.2 Comparison of overall survival on patients with surgery only VS surgery plus neoadjuvant treatment

The aim of this second endpoint was to compare our results with the one's obtained by Van Hagen *et al*. (60) in the CROSS trial. This randomised controlled study has shown the advantage of the radio-chemotherapy followed by oesophagectomy above surgery alone (49.4 months vs. 24 months). Both subtypes are benefiting from NAT, besides SCC seems to have a better response but without evidence actually.

Our study, for this last endpoint, tried to reproduce the same analysis as the CROSS to verify if, globally, we get the same results. The overall median survival of our patients was similar (46 months vs 49 months in the CROSS). The difference of overall survival between patients who benefit from surgery alone and patients with NAT followed by surgery was not shown in our study, probably for the same reasons developed in the two previous endpoints.

Patients with surgery alone have a better OS than patients with multimodal treatment (62 vs 39 months) with a statistical trend (p=0.065) to show difference. The confidence interval is wider in the surgery group what could demonstrate that we do not have enough patients in this group. This information seems to be in contradiction with the current papers but we must keep in mind, that patients were not randomized. That means patients with more advanced stage received a neoadjuvant treatment and those with early did not and they have statistically the same OS. In the histological subgroup analysis, the survival curves were statistically the same. This means that patients with a more advanced stage retrieve in a comparable overall survival period as patients in early stages. We can only suppose that with a greater number of patients, randomised groups and standardised treatments, we could have had a better survival for patients with multimodal treatment.

In conclusion, with these results we can situate ourselves within recent randomised studies. Our study shows a similar overall survival period, a trend to a benefit of the NAT for both subtypes without knowing which neoadjuvant protocol exactly.

Studies who tested survival after neoadjuvant treatment; RS: retrospective; RCT: randomised controlled study; AD: adenocarcinoma; SCC squamous cell carcinoma; ys: year-survival

Author	year	Type of study	Number of patients	Median follow up	Type of cancer	Protocol	Overall survival (months)	Global survival	30 days mortality	ypCR %	Overall survival after ypCR
Urba(72)	2001	RCT	47	98	all	45 Gy; cisplatin, 5-FU & vinblastine	16.9	30% 3ys	2%	28%	60% 3ys
Burmeister(73)	2005	RCT	128	65	all	35 Gy; cisplatin, 5-FU	22.2	28% 3ys	1.90%	15%	49% 3ys
Lee(74)	2004	RCT	51	25	SCC	45,6 Gy; 5-FU & platin	28.2	55% 2ys	2%	43%%	
Mariette(64)	2010	RCT	97	60	all: stage I & II	45 Gy; 5-FU & platin	31.8		7.30%		
Tepper(75)	2008	RCT	30	60	SCC & AD	50.4 Gy; 5-FU & platin	48	39% 5ys	0%	33%	
Schneider(76)	2005	RS	74	20.3	AD & SCC	40-45 Gy; 5-FU & platin	23	31% 3ys	4%	15%	
Rizk(77)	2007	RS	266		AD	50.4 Gy; 5-FU & platin/taxol/irinotecan				19%	70% 3ys
Donahue(67)	2008	RS	162	24	AD >> SCC	50.4 Gy; 5-FU & platin	25.2	33% 5ys	4.9	26%	34% 5ys
Pasini(53)	2013	RCT	74	55	AD & SCC	50 Gy; 5-FU, docetaxel & platin	55			47%%	83 % 3ys; 77% 5ys
Siddiqui(71)	2011	RS	106	80.4	AD & SCC	36-63 Gy; platin, 5-FU or capecitabin	31.2			29%	52 months
Brücher(78)	2006	RS	311	48	SCC	40-45 Gy; 5-FU & platin	26.4	35.7 5ys	3.5	48%	55% 5ys
Berger(59)	2005	RS	131	14	AD & SCC	45 Gy; 5-FU & platin	33	33% 5ys	5%	32%	48% 5ys
Van Hagen(60)	2012	RCT	168	45.4	AD & SCC	41.4 Gy; taxol & platin	49.4	47% 5ys	6%	29%	
Ruffier-Loubière(55)	2015	RS	102	22.4	AD & SCC	40-44 Gy; 5-FU & platin	27	27% 5ys	4%	17.50%	33% 5ys
Our Study	**2015**	**RS**	**55**	**29**	**AD & SCC**	**see point 3.3 & 3.4**	**43**	**30 % 4ys**	**6.7%**	**20%**	**26% 2ys**

5.3 Nota bene

One of the main objectives was to assess the efficiency of the NAT with the TRG and the resection margins. Unfortunately, during the construction of the database we could not gather sufficient data. Hence, we redirect the paper on more common survival indicators.

5.4 Strengths and weaknesses

As mentioned in the discussion, our study has some weaknesses:

- Heterogeneous treatments of radio-chemotherapy. This bias is because our hospital receives patients for surgery from all Latin based regions of Switzerland but they already had received a NAT. There are no clear recommendations, so each hospital has different protocols.
- A small sized group of patients implies that for some of our statistical analysis, some interpretations were impossible.
- The appropriate determination of the clinical TNM. Patients could have been over or under staged.
- All bias found in a retrospective study: loss of data, variation in treatments, patients incorrectly selected, changes in treatments protocols, changes in staging protocols, etc

6 Conclusion

Ultimately, our retrospective study did not demonstrate any advantage in overall survival period on groups with ypCR against those without. The limited number of patients, the fact that patients were not randomly assigned in groups and the heterogeneity of chemo and radio treatments are probably the best explanation of the lack of significance. The subtypes analysis didn't show any difference either.

We also tried to see if there was a difference overall survival on patients with a down-staging against those without. Our results were not sufficient to show any significant difference for the same reasons as mentioned above.

Finally, we also wanted to compare our survival data with the current literature and see if in our center there was an advantage in multimodal treatment. Our results showed that patients with advanced stage who receive a NAT retrieve similar survival as patients with early stages.

In conclusion, our retrospective study supports the current literature about the interest of multimodal treatment for patients with oesophageal cancer. They are needed to determine the most accurate chemo or radio treatment for each histological subtype and if they should be treated with different regimens.

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