Title : Comparison of involved field radiotherapy and elective nodal irradiation in combination with concurrent chemotherapy for T1bN0M0 esophageal cancer

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Abstract

Background

The optimal radiation field of chemoradiation therapy (CRT) for stage I esophageal squamous cell carcinoma (ESCC) is unknown. This retrospective study compared efficacy and safety of two CRT modalities, involved field irradiation (IFI) and elective nodal irradiation (ENI), when treating patients with clinical stage I (T1bN0M0) ESCC.

Methods

Patients had received 60 Gy CRT concurrently with 5-FU and cisplatin between January 2000 and December 2012. The clinical target volume of IFI was limited to the primary tumor plus a 2-cm craniocaudal margin; that of ENI covered the primary tumor plus the field of regional lymph nodes.

Results

One hundred and ninety-five patients were selected (IFI group, 78; ENI group, 117). The 5-year overall, cause-specific and progression-free survival rates were 90.5%, 91.6% and 77.6% in the IFI group, and 72.5%, 88.3%, 57.9% in the ENI group, respectively. Of recurrent patients (n=16 in the IF and n=33 in the ENI groups) after achieving complete remission, 12 (75%) in the IFI group

received definitive salvage therapy, 11 (33%) patients did in the ENI group. More patients died of diseases other than esophageal cancer in the ENI group (n=29, 25%) than in the IFI group (n=3, 3.8%). Multivariate analysis identified ENI (HR 3.63 [1.78–7.38], p<0.001), age ≥70 (HR 2.65 [1.53–4.58], p<0.001) and PS = 1 (HR 2.36 [1.33–4.18], p=0.003) as poor prognostic factors for OS.

Conclusions

IF irradiation would be better than ENI for the patients with stage I ESCC who received definitive chemoradiotherapy.

Key words

chemoradiotherapy, esophageal cancer, involved field irradiation, involved field irradiation, Late toxicity

Introduction

According to the Japan Esophageal Cancer Treatment Guideline [1], esophagectomy with three-field lymph node dissection is the standard therapy for clinical T1bN0M0 esophageal squamous cell carcinoma (ESCC). In contrast, chemoradiotherapy (CRT) is recognized as an option for patients who are unfit for surgical resection. From the phase II study of definitive CRT for stage I ESCC, the complete response and 5-year overall survival rates were about 90% and 75%, respectively [2].

Although CRT is considered to be less invasive than esophagectomy [3] further work is required in order to ameliorate the late toxicities associated with the treatment. Although the irradiation field is very important for both the therapeutic effect and radiative toxicity [4,5], there is no consensus about the optimal clinical target volume (CTV), especially in cases where the disease is less advanced. Among 211 patients with cT1bN0M0 who underwent esophagectomy in the JCOG0502 trial, 57 (27%) patients had pathologic lymph node metastasis that had spread widely from abdominal to cervical lymph nodes [6]. So far, the National Comprehensive Cancer Network (NCCN) guidelines (version 2.2018) recommend that the CTV should include the areas at risk for microscopic disease

and elective nodal regions: namely elective nodal irradiation (ENI). This is postulated to eradicate cancer cells not only in the primary tumor but also in “occult” LN metastasis [7]. However, extending the irradiation field may increase acute and late toxicities such as cardiopulmonary complications.

On the other hand, some physicians prefer involved field irradiation (IFI), in which radiation therapy is used only for primary tumor and positive lymph nodes, in order to reduce treatment-related toxicities. Because few studies have compared the effects of two different radiation fields for the treatment of clinical T1bN0M0 esophageal cancer, we conducted a retrospective study, which compared the safety and efficacy of IFI and ENI for CRT modalities in patients with clinical stage I (cT1bN0M0) ESCC in order to determine the most suitable radiation field.

Materials and methods

This study was approved by the institutional review board, and written informed consent was waived because of the retrospective design.

Patient population

From January 2000 to December 2012, 242 patients at our hospital were

diagnosed with cT1bN0M0 ESCC, according to the UICC-TNM 7th system and were received definitive chemoradiotherapy. For staging, all patients received upper gastrointestinal endoscopy and a computed tomographic (CT) scan that covered from the neck to the abdomen. Nodal metastasis was diagnosed if spherical lymph nodes > 8 mm along the short axis, or lymph nodes >10 mm in the long axis were detected. In some cases, endoscopic ultrasonography (EUS) and positron emission tomography (PET) were also used if a small lymph node was suspected to have the metastasis. Depth of the tumor (T stage) and N stage were determined following a multidisciplinary evaluation by endoscopists, radiologists, surgeons and gastrointestinal oncologists. Patients satisfying the following criteria were selected as subjects of this study: (1) newly diagnosed with squamous cell cancer of the thoracic esophagus, (2) no prior treatment, (3) Eastern Cooperative Oncology Group performance status of 0 or 1, (4) receiving chemotherapy comprised 5-FU and cisplatin (700 mg/m^2, days 1–4, 29–32, and 70 mg/m^2, day 1, 29), (5) radiotherapy with a total dose of 60 Gy with IFI or ENI, and (6) no other malignancy.

Among 242 patients, 47 were excluded from this study because of treatment with another chemotherapy regimen containing nedaplatin (n = 4),

other radiation procedure (n = 2) or the presence of double cancer (n = 41). The final study population therefore included 195 esophageal cancer patients with cT1bN0M0 who underwent definitive CRT.

Prior to simulation for determining the radiation field, an endoscope was used to place metal clip markers at the oral and anal ends of the primary tumor. Chronologically, IFI was performed for stage I patients mainly from 2000 to 2004 in a clinical trial [6] and from 2007 to 2012 in clinical practice after obtaining the results of the JCOG9708 trial. ENI was performed mainly from 2000 to 2007 in clinical practice.

Involved field irradiation (IFI)

Between 2000 and 2004, patients in the IFI group received 40 Gy of radiotherapy via anterior-posterior two opposing portals, followed by 20 Gy delivered using a bilateral oblique portals to spare the spinal cord. Thereafter, between 2007 and 2012, three-dimensional (3D) treatment planning was applied to all patients, and a 3- or 4-portal technique was used. Among the patients who received IFI, the clinical target volume (CTV) included the primary tumor plus a 2-cm craniocaudal margin. The planning target volume (PTV) was defined as CTV plus a 1 to 1.5-cm margin in the craniocaudal direction and 1-cm margin in

the lateral direction. Total dose was set at 60 Gy in 30 fractions at the isocenter.

Elective nodal irradiation (ENI)

In most cases, 2D-treatment planning was performed. Anterior-posterior opposing portal radiation was used up to 40 Gy including the primary tumor and the regional nodes. Using bilateral oblique portals to spare the spinal cord, a boost dose of 20 Gy was given to the primary tumor, yielding a total dose of 60 Gy. The CTV was designed to cover mediastinal and upper perigastric lymph nodes for all cases, and additionally include bilateral supraclavicular fossae for the upper thoracic primary tumor and celiac axis lymph nodes for the lower thoracic primary tumor.

Evaluation of clinical outcomes

Tumor response was evaluated by CT scan and endoscopy one month after the end of radiotherapy, and then repeated every 3 months for the first year, every 4 months for the second year, and every 6 months thereafter. Tumor response was evaluated according to the criteria of the Japanese Classification for Esophageal Cancer (2017) 11th edition [8]. Definitions of complete response are

as follows: disappearance of the tumor lesion, no endoscopic findings of active esophagitis under endoscopic observation and pathological confirmation. All of the above criteria had to be satisfied at a subsequent time point (at least 4 weeks later).

Statistical analysis

Overall survival (OS) was defined as the period from the initiation of treatment and death due to any cause, and surviving patients were censored at the last contact. Cause-specific survival was defined as the time from the initiation of treatment to death due to esophageal cancer, and patients who died from causes other than esophageal cancer were regarded as censored. Progression-free survival (PFS) was defined as the time from the initiation of treatment to disease progression or death from any cause. Survival data was analyzed using the Kaplan-Meier method. Multivariate analyses were performed using a Cox proportional hazard model by forward selection including all baseline factors. All p-values were two-sided, and 95% confidence intervals were calculated. Results were considered significant if the p-value was < 0.05. All statistical analyses were performed using SPSS v.25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

One hundred and ninety-five ESCC patients (78 in the IFI group and 117 in the ENI group) were included in this study (Table 1). There were no significant differences in gender, age, ECOG performance status (PS) between the two groups. There was a certain trend toward significance in tumor location (p value = 0.1). All patients completed radiation with a total dose of 60 Gy. None of the patients required a break from radiation therapy due to acute complications. However, 10 patients received radiotherapy with a planned 1-week treatment break in the middle, because they enrolled in the clinical trial, JCOG9708. Average relative dose intensities (RDI) of 5-FU and CDDP were 0.976 and 0.973 in the IFI group, and 0.983 and 0.976 in the ENI group, respectively. The median follow-up period (62 months) in the IFI group was significantly shorter than that (112 months) of ENI group.

Efficacy

The complete response rates were 98.7% in the IFI group and 92.3% in the ENI group (p = 0.12). The 3- and 5-year survival rates were 97.4% and 90.5% in

the IFI group and 78.0% and 72.5% in the ENI group, respectively (Figure 1). The IFI group demonstrated significantly better survival than the ENI group (HR 2.99 [1.51–5.93], p = 0.002). The 3- and 5-year PFS rates were 80.8% and 77.6% in the IFI group and 70.6% and 57.9% in the ENI group, respectively (Figure 2). The IFI group demonstrated significantly better PFS than the ENI group (HR 2.03 [1.22–3.36], p = 0.005). Within 6 years after CRT, 3 patients died of causes other than esophageal cancer in the IFI group, while 21 patients died in the ENI group (Fig 2). The 3- and 5-year cause-specific survival rates were 97.1 and 91.6% in the IFI group and 90.5% and 88.3% in the ENI group, respectively. No statistically significant differences in cause-specific survival were found between the two groups (HR 1.74 [0.73-4.1–], p = 0.21).

Subsequent therapy after CRT

In the IFI group, 16 patients developed recurrence after achieving CR (3 patients at the primary site, 9 patients had lymph node metastasis outside the radiation field and 4 patients had distant metastases). In the ENI group, 33 had recurrence (11 patients at the primary site, 3 patients at a lymph node inside the radiation field, 5 patients at a lymph node outside the radiation field, and 14

patients with distant metastases). Nineteen patients experienced relapse without distant metastasis. However, due to poor condition or the patient's refusal, only 11 patients (58%) were eligible for curative therapy. In summary, of recurrent patients (n=16 in the IF and n=33 in the ENI groups) after achieving complete remission, 12 (75%) in the IFI group received definitive salvage therapy, 11 (33%) patients did in the ENI group (Fig 3).

Cardiopulmonary toxicities

The 3-year and 5-year cumulative incidences of grade ≥ 3 late cardiopulmonary toxicities were 3.8% and 3.8% in the IFI group, and 9.3% and 14.0% in the ENI group; the incidences of late cardiopulmonary toxicities were significantly higher in the ENI group than in the IFI CRT group (hazard ratio = 2.96, p = 0.04) (Figure 4).

Causes of death

Although there was no significant difference in cause-specific death between the IFI and the ENI groups as mentioned above, cumulative incidences of death were remarkably different (13% in the IFI group and 43% in the ENI

group). More patients (25%) in the ENI group died from disease other than esophageal cancer compared to those (3.8%) in the IFI group. Besides death due to esophageal cancer, causes of death included cardiopulmonary disease in 2 patients (2.6%) in the IFI group and 11 patients (9.4%) in the ENI group, other malignancy in one (1.3%) and in 7 (6.0%), respectively; sudden death accounted for the mortality of 11 patients (9.4%) in the ENI group but none in the IFI group.

Univariate and multivariate analysis for prognostic factors

According to univariate analysis, radiation field, age and ECOG PS were correlated with OS. In multivariate analysis, ENI (hazard ratio [HR] 3.63; 95% CI: 1.78–7.38; $p < 0.001$), age ≥ 70 (HR: 2.65; 95% CI: 1.53–4.58; $p < 0.001$, and ECOG PS = 1 (HR: 2.36; 95% CI: 1.33–4.18; $p = 0.003$) were significant negative prognostic factors for OS (Table 2).

Discussion

From the results of JCOG0502, 57 (27.0%) of 211 clinical N0 cases had pathologic LNMs after surgery. In addition, the frequency of skip LNMs was 36.7%. In ENI covering subclinical lymph node metastasis may be recognized

as a standard treatment for clinical T1N0 cases based on the result of a previous report [6]. However, our study shows that the cause of death in many cases was not due to esophageal cancer but instead due to diseases such as cardiopulmonary disease and other malignancies. Incidences of late toxicities were higher in the ENI group than in the IFI group, and ENI was a poor prognostic factor.

In the RTOG94-05 trial, higher irradiation dose (64.8 Gy) resulted in worse outcome compared to the standard dose (50.4 Gy) [9]. Furthermore, Kato et al. reported all late toxicities of grade >3 were observed within 10% after concurrent CRT at a dose of 50.4 Gy with ENI for Stage II/III esophageal cancer [10]. In that study, the target volume of ENI in which bilateral supraclavicular fossae and superior mediastinal lymph nodes were included only for the upper thoracic primary tumor; this strategy was deployed in order to protect the heart from excessive irradiation. A radiation dose of 50.4 Gy with modified ENI is considered as a standard treatment for advanced ESCC in Japan, since it might reduce the incidence of late toxicities. As for the radiation dose, 60 Gy is still mainstay for locally advanced cases in Japan. However, there have been no discussions regarding of the radiation field. As far as we know, this is the first

study to directly compare the radiation field included in the treatments for patients with clinical T1bN0M0 ESCC.

The CR rates were high in both the IFI and ENI groups (98.7% and 92.3%, respectively). However, between 2007 and 2012, new radiation techniques such as three-dimensional (3D) treatment planning and the 3- or 4-portals techniques were used mainly for the IFI group. For this reason, we cannot exclude the possibility that the progression of irradiation techniques might influence the complete response rate. In the ENI group, the three patients had prolonged esophagitis and 1 patient was performed surgery due to stricture after esophagitis. Findings of active esophagitis under endoscopic observation were regarded as non-CR. In addition, CR for ENI might be inferior to IFI due to non-negligible differences in patient background. There was a certain trend toward significance on the length (p value = 0.14) (Table 1). Therefore, the length of the esophageal cancer might influence complete response rates.

As for the control of lymph node metastasis, ENI can theoretically cover the subclinical lymph nodes that pose a risk of metastasis. Onozawa et al. reported that ENI could effectively prevent regional nodal failure [11], in which only one (1.0%) of 102 patients experienced elective nodal failure without

recurrence at any other site.

Furthermore, Kawaguchi et al. reported the patterns of failure after CRT using IFI in patients with clinical stage I ESCC. Twenty-two (32%) patients experienced recurrence [12]: lymph node recurrence in 11 (50%) patients, local recurrence in 9 (41%) and distant metastasis in 2 (9%). On the contrary, Ishikawa et al. evaluated patterns of failure after CRT using IFI in 68 patients with clinical stage I esophageal cancer, where their IFI had a 3–4 cm margin at the oral and anal sides; only 1 patient (2%) out of 50 with grade T1b cancer developed regional LN failure outside the radiation field [13].

In our study, regional LN failure outside the radiation field was observed in nine patients (12%) in the IFI group. However, all of these patients were eligible to receive curative salvage therapy. Given these results, we suggest that regional LN recurrence can be cured, and might not lead to esophageal cancer death. In the ENI group, 8 patients (6.8%) developed regional LN failure. Three of the patients had failure outside the radiation field, whereas failure occurred inside the radiation field in the other 5 patients. Although ENI may reduce regional nodal failure, few recurrent cases were salvaged by subsequent therapies due to poor condition or the patient’s refusal. This might be caused by radiation toxicities.

Within 6 years after CRT in CR patients, 3 patients died of causes other than esophageal cancer in the IFI group, while 21 patients died in the ENI group (Figure 2).These patients died from various causes like cardiopulmonary disease, and other malignancy. It is probably due to late toxicities associated with chemoradiotherapy

Fukada et al. reported that a radiation field width of the mediastinum was a significant risk factor for both pericardial and pleural effusion [14]. Furthermore, Ishikura et al. pointed out long-term toxicities in patients treated with CRT using a radiation field including the primary tumor, metastatic lymph nodes, and the regional nodes [15]. 8 patients (10%) out of 78 with CR had complications of pericarditis of grade 3 or higher, and 7 patients died of cardiopulmonary diseases. In our study, the 5-year cumulative incidence of grade 3 or higher late cardiopulmonary toxicities was low (3.8%) in the IFI group but high (14.0%) in the ENI group. In the latter group, the radiation field included mediastinal and upper perigastric lymph nodes for all cases. Therefore, all patients in the ENI group received high volumes of radiation to the heart. This might explain the late complications or the deaths from causes other than esophageal cancer.

3D treatment planning was mainly (88%) performed and a 3- or 4-portals

radiation technique was used in the IFI group. In contrast, 2D treatment planning and anterior-posterior opposed portal was mostly used in the ENI group. 3D treatment planning and a multiple portal technique may reduce toxicities related to radiation. Mackley et al. reported reduced acute esophagitis in patients with locally advanced esophageal cancer, due to the 3D treatment planning [16]. We infer that 3D treatment planning with 3- or 4-portals used in the IFI group might contribute to lower incidences of late toxicities. Therefore, a confounding factor in this study may be radiation treatment planning (2D planning or 3D planning).

The limitations of our study include those inherent to all retrospective series, in that they contain some bias: 1) chronological differences that can greatly influence clinical outcomes such as salvage therapy, 2) imbalances in patient and tumor factors–although in this study they are relatively small because the selection of radiation field depended on the period, 3) imbalances in radiation technique, 4) inadequate information about causality of death. Considering the above, these biases may affect the outcomes. The best way to establish the adequate radiation field for ESCC with cT1bN0M0 is to conduct a randomized prospective trial comparing two radiation fields between IFI and modified ENI.

In conclusion, IF irradiation would be better than ENI for the patients with

stage I ESCC who received definitive chemoradiotherapy because of the differences of frequency of late toxicities.

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Figure 1. Overall survival

Figure 2. Progression free survival

Triangles show deaths from causes other than esophageal cancer.

Figure 3. Response to CRT, first site of failure and post therapy

Figure 4. Cumulative incidences of grade 3 or higher late cardiopulmonary toxicities

Table 1. Baseline characteristics

Table 2. Univariate and multivariate analysis

Compliance with ethical standards

Conflict of interest Ken Kato received honoraria from Eli Lilly and Beigene; and research funding from ONO, MSD, Merck Serono and Shionogi Co and Ltd. Narikazu Boku received honoraria from Taiho, Chugai, Eli Lilly, Ono and BMS; and research funding from Taiho and Ono. YN, HS, SI, YN, AT, TU, YI and JI report no potential conflicts of interest.

Uncategorized References

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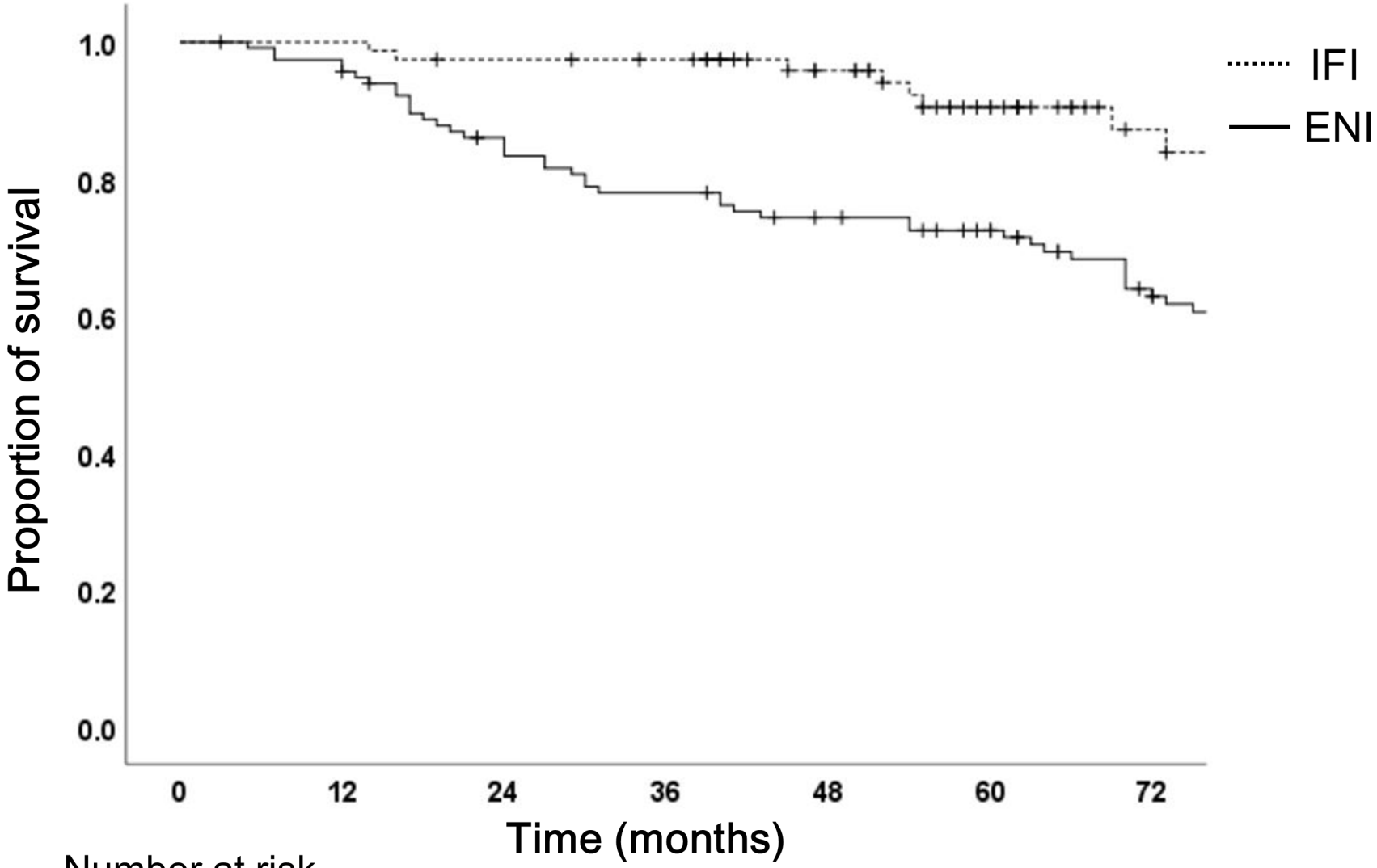
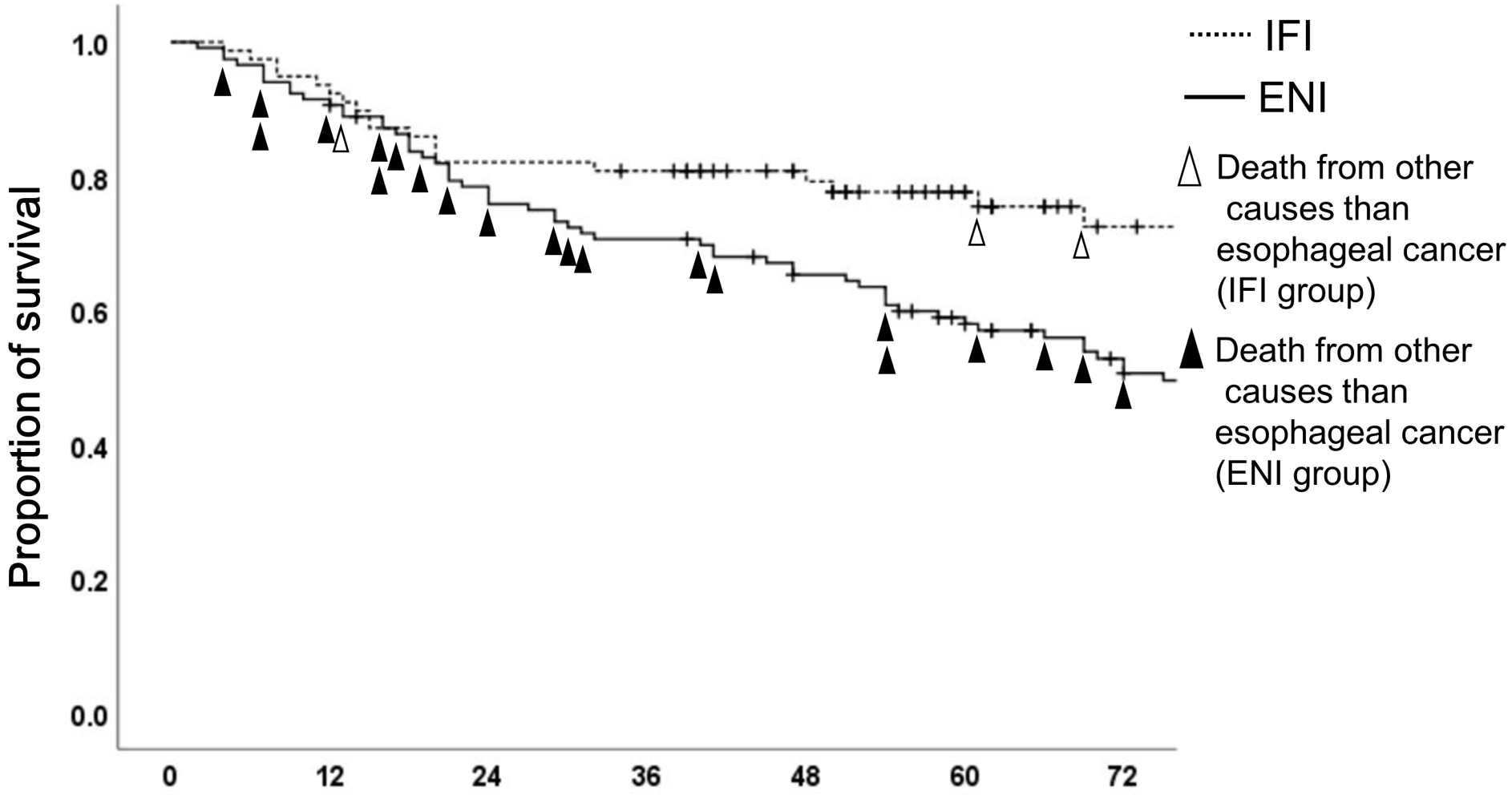
Fig 1. Overall survival



Number at risk

IFI	78	78	75	73	58	41	26
ENI	117	110	95	87	80	72	55

Fig. 2 Progression free survival



Number at risk

IFI	78	72	64	62	50	36	23
ENI	117	105	87	81	72	59	46

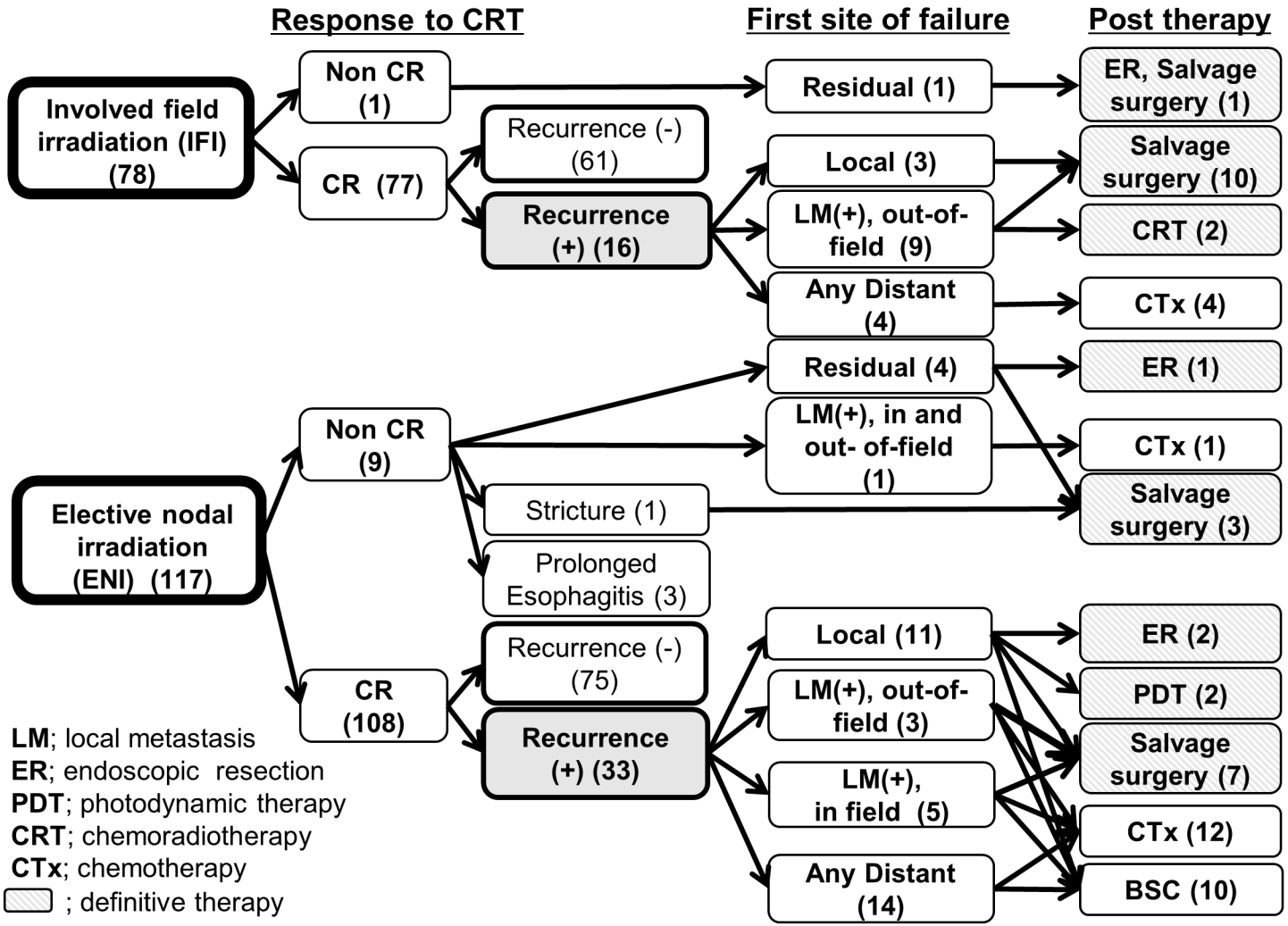
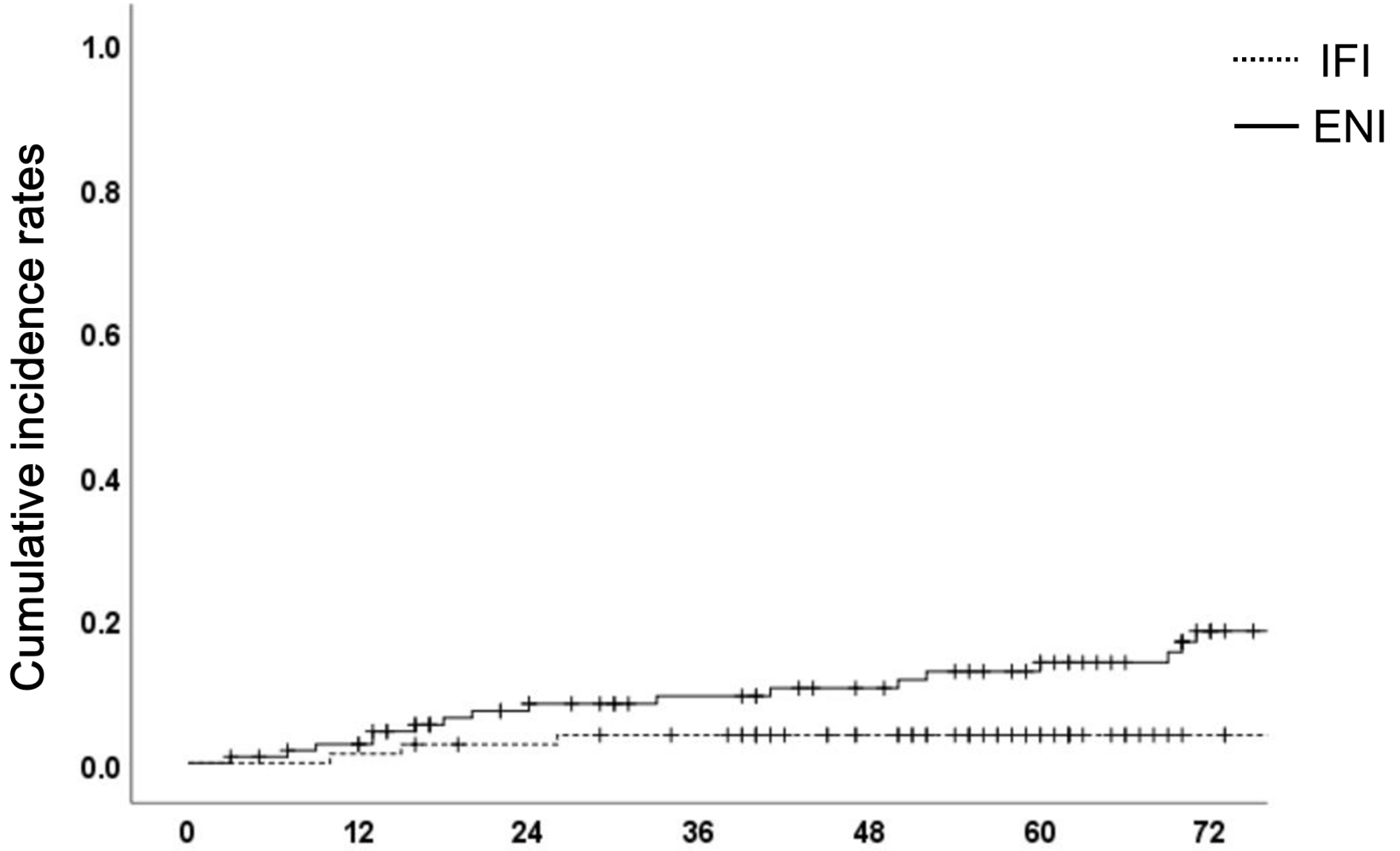


Fig. 3 Response to CRT, first site of failure and post therapy

Fig. 4 Cumulative incidence rates of ≥ grade 3 late cardiopulmonary toxicities

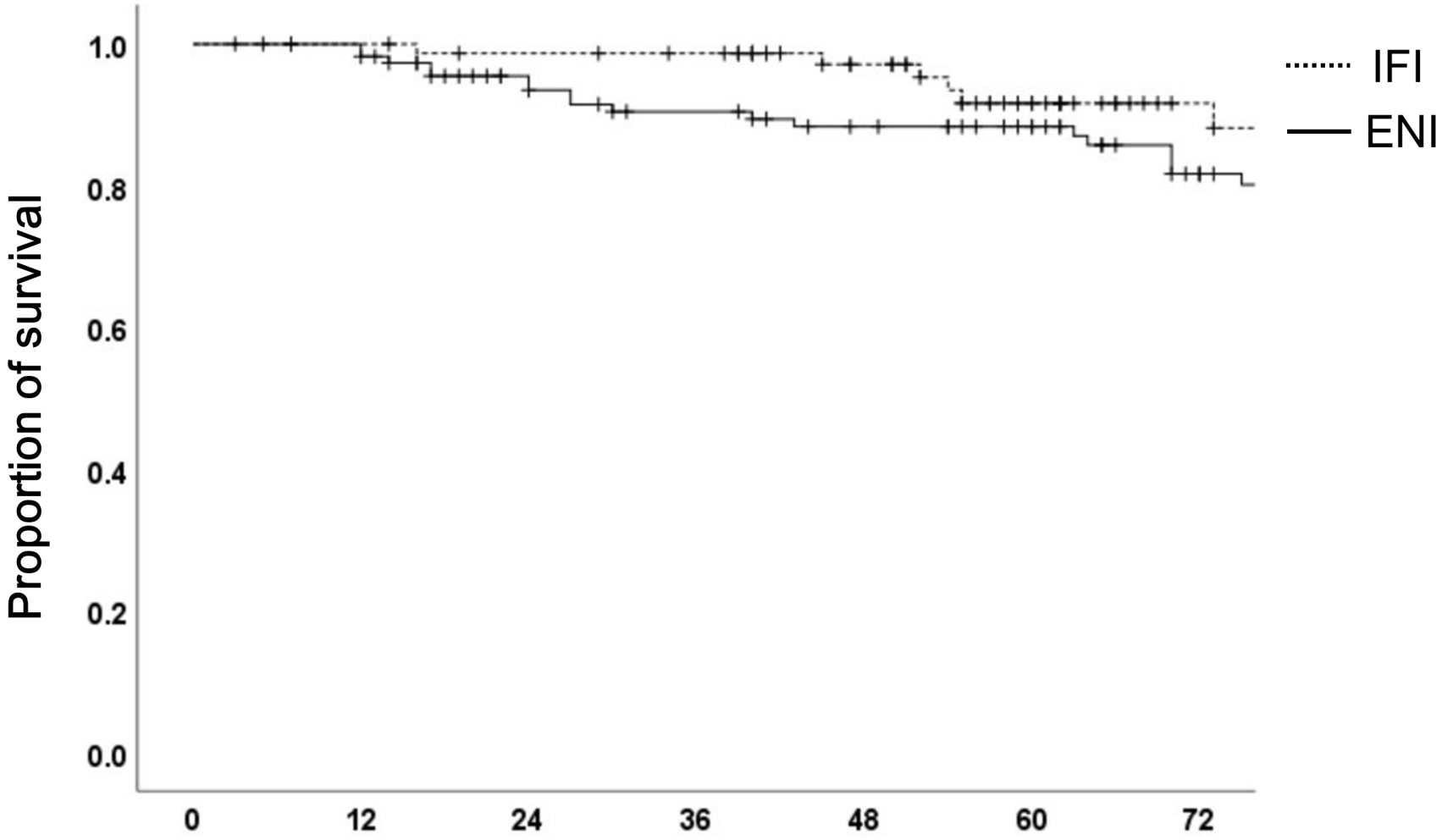


Number at risk							
IFI	78	77	74	71	57	39	25
ENI	117	109	91	85	78	67	50

Table 1. Baseline Characteristics

	Involved field irradiation (IFI), n=78	Elective nodal irradiation (ENI), n=117	P value
Follow up time - months			
Median (range)	62.0 (19-188)	111.5 (3-185)	＜0.01
Gender			
Male	66 (85%)	103 (88%)	0.49
Female	12 (15%)	14 (12%)	
Age (years)			
Median	66.5	68	0.27
Range	44-82	49-84	
ECOG PS			
0	62 (80%)	91 (78%)	0.77
1	16 (20%)	27 (22%)	
Tumor Location			
Upper-Middle	61 (78%)	79 (68%)	0.10
Lower	17 (22%)	38 (32%)	
Endoscopic tumor length (mm)			
Median (range)	30 (8-80)	30 (10-180)	0.14

Supplemental Fig. 1 Cause specific survival



Number at risk

IFI	78	77	75	73	58	39	25
ENI	117	109	91	85	78	67	50

Supplemental table 1. Complete response (CR) rate

	Involved field irradiation (IFI), N=78	Elective nodal irradiation (ENI), N=117	p-value
Response –no.(%)			
CR	77 (98.7%)	108 (92.3%)	0.12
non-CR	1 (1.3%)	9 (7.7%)	

Supplemental table 2. Causes of death

Causes of death	IFI, n=78 (%)	ENI, n=117 (%)	p value
All	**10 (13)**	**50 (43)**	**<0.001**
Esophageal cancer	7 (9.0)	20 (17)	0.11
Other than esophageal cancer	**3 (3.8)**	**29 (25)**	**<0.001**
Cardiopulmonary disease	2 (2.6)	11 (9.4)	0.06
Constrictive pericarditis	0	1	
Pneumonia	1	7	
Acute heart failure	0	3	
Pulmonary embolism	1	0	
Other malignancy	1 (1.3)	7 (6.0)	0.11
Other solid cancer	1	5	
Hematological malignancy	0	2	
Others	0 (0)	11 (9.4)	**0.005**
Sepsis	0	3	
Sudden death	0	1	
Suicide	0	1	
Unknown	0	5	
Esophageal perforation*	0	1	

*There was no evidence of cancer progression