Neoadjuvant Chemoradiotherapy with Volumetric-modulated Arc Therapy for Medium-distal Oesophageal and Gastro-oesophageal Junction Carcinoma

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Abstract. *Aim: to appraise the role of volumetric-modulated arc therapy (VMAT) in the neoadjuvant chemoradiotherapy management of advanced medium and distal oesophageal cancer in terms of toxicity and response to treatment. Patients and Methods: Thirty patients were treated according to the neoadjuvant chemoradiation followed by surgery versus surgery-alone trial scheme with VMAT radiation therapy. Patients presented mainly T3-T4 stage (80%) and N1-2 (96.6%) disease. The chemotherapy scheme consisted of 3-5 cycles, while a radiotherapy course of 41.4 Gy in 23 fractions was administered to all patients. Results: The median age of patients was 65 years, and there was a predominance of males (80%), smokers or ex-smokers (90%) and modest alcohol habit (80% negative). Primary tumor localisation was in the medium and distal third of the oesophagus in 57% of the cases, the rest being in the gastro-oesophageal junction. Modest toxicity profiles were observed, with limited incidence of grade 2-3 events. Partial or complete response was observed in more than 90% of the cases (radiological/metabolic) and was confirmed after surgical intervention (67% partial or complete and 27% stable response). Tumor down-staging was recorded in 67% of patients and nodal down-staging in 50%. Conclusion: VMAT was applied in the context of neoadjuvant chemoradiotherapy for the treatment of medium and distal oesophageal carcinoma with satisfactory results in terms of tolerance and toxicity*

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Key Words: Oesophageal cancer, neoajuvant radiochemotherapy, RapidArc.

Oesophageal cancer is one of the 10 most common malignancies worldwide (1). The majority of oesophageal tumors have a poor prognosis as they are locally advanced or with distant spread of disease at diagnosis.

Nowadays, preoperative chemoradiotherapy (CRT) is considered the standard curative treatment for locally advanced oesophageal or gastro-oesophageal tumors. Radiotherapy plays an important role in the management of localized or locally advanced oesophageal cancer with regional or distant lymph node involvement, as it can sterilize micrometastatic nodes and cancer cells of the peri-oesophageal fat that are not removed by surgery.

CRT has been investigated by several authors with evidence of improved outcome compared to surgery-alone (2-5). An Irish study with induction radiotherapy delivered with 40 Gy in 15 fractions and two cycles of 5-fluorouracil and cisplatin-based chemotherapy provided a significant survival advantage over surgery-alone (6). A pathological complete response (pCR) was achieved in 25-31% of patients with preoperative regimen.

In the Chemo-Radiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), induction CRT followed by surgery not only improved local control but also overall survival (7). The study was of preoperative radiotherapy to a total dose of 41.4 Gy in 23 fractions concomitant with chemotherapy with weekly carboplatin and paclitaxel followed by surgery in patients with potentially operable oesophageal or gastro-oesophageal junction cancer. pCR was observed in 29% of patients.

Based on this evidence, in November 2012, our Institution implemented a similar induction CRT regimen. Differently from the conformal radiotherapy technique applied in the CROSS study, the radiation treatments were based on the volumetric-modulated arc therapy in its RapidArc form (VMAT RA). The purpose of the present study was to evaluate the clinical results in terms of

tolerability and toxicity, surgical morbidity and pathological response to treatment

Patients and Methods

This was an observational retrospective study of patients with a diagnosis of oesophageal or gastro-oesophageal junction adenocarcinoma or squamous cell cancer. All patients were treated in agreement with ethical conditions from the Helsinki declaration. All patients underwent staging with chest-abdome computed tomography (CT) and full-body ^{18}Fluoro-Desossi-Glucose-Positron Emission tomography (^{18}FDG-PET/CT); endoscopic ultrasound of the oesophagus with fine-needle aspiration biopsy of the suspected nodes was performed when necessary.

Each case was discussed in a multi-disciplinary meeting with experienced radiologists, medical oncologists, radiation oncologists, nuclear medicine physicians, pathologists and surgical oncologists involved in the treatment. All patients had indication by the multi-disciplinary team for treatment with neoadjuvant CRT. Treatment consisted of preoperative chemotherapy and radiotherapy followed by surgery. Patient's characteristics are given in Table I.

Chemotherapy. On days 1, 8, 15, 22, and 29, carboplatin targeted at an area under the curve of 2 mg/ml per minute and paclitaxel at a dose of 50 mg/m^2 of body-surface area were administered intravenously. All patients received premedication with dexamethasone, clorfenamine, and ranitidine, as well as standard antiemetic agents. The patients were closely monitored for toxic effects of chemotherapy with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.10 (8).

Radiotherapy. Conformal radiotherapy to a total dose of 41.4 Gy in 23 fractions was delivered. Radiotherapy consisted of VMAT RA delivered with a TrueBeam linear accelerator (Varian Medical systems, Palo Alto, CA, USA) with 10 MV photon flattening-filter-free beams. Simulation CT with intravenous contrast was acquired for all patients, positioned supine with their arms above their head immobilized with a thermoplastic mask. All patients were also subject to ^{18}FDG-PET/CT. The clinical target volume (CTV) was delineated to include the gross tumor and nodal disease, as identified from the endoscopic and the imaging studies. Regional nodes and the celiac axis were also added to the CTV. The planning target volume (PTV) was created by the expansion of CTV with 20 mm in the craniocaudal and 15 mm in the radial directions. Organs at risk (OAR) for treatment planning included the lungs, heart, spinal cord and involved stomach, liver and kidneys. VMAT RA plans were optimised with the Eclipse Treatment Planning System version 11 (Varian Medical Systems). The dose was prescribed as the mean dose to PTV with the constraints that at least 95% of the target received 99% of the prescription dose. A near-to-maximum dose constraint was set to 107%. One or two arcs were used as needed to meet the above target constraints. Normal tissue dose constraints were consistent with current standard practice with priority on maximum spinal cord dose and volumetric heart and lung dose (explicit constraints are reported together with the results in Table II). Position verification was performed with daily cone beam-computed tomographic.

Table I. *Descriptive statistics for the patient cohort*.

	Number of patients (%)
Median age and range (years)	65 (42-79)
Gender	Male: 24 (80.0%)
	Female: 6 (20.0%)
Performance status (WHO)	0: 8 (26.7%)
	1: 22 (73.3%)
Smoking risk factor	Yes: 12 (40.0%)
	No: 3 (10.0%)
	Ex smoker: 15 (50.0%)
Alcohol risk factor	Yes: 2 (7%)
	No: 28 (93%)
Earlier gastro esophageal pathologies	Yes: 6 (20.0%)
	No: 24 (80.0%)
Primary tumor localization	Medium-distal: 7 (23.3%)
	Distal: 10 (33.3%)
	Gastro-esophageal junction: 13 (43.3%)
Primary tumor histology	Adenocarcinoma: 22 (73.3%)
	Squamous cell carcinoma: 7 (23.3%)
	Undifferentiated carcinoma: 1 (3.3%)
Histological grading	G1: 1 (3.3%)
	G2: 3 (10.0%)
	G3: 11 (36.7%)
	Unknown: 15 (50%)
T Stage	T1: 0 (0.0%)
	T2: 6 (20.0%)
	T3: 21 (70.0%)
	T4: 3 (10.0%)
N Stage	N0: 1 (3.3%)
	N1:22 (73.3%)
	N2: 7 (23.3%)
Chemotherapy scheme	CBDCA+TAX: 30 (100%)
Chemotherapy cycles	3: 3 (3.3%)
	4: 13 (43.3%)
	5: 14 (46.7%)
Radiotherapy dose prescription	41.4 Gy in 23 fractions (1.8Gy/fr): 30 (100%)
Surgery	Yes: 30 (100%)

Approximately 6 weeks after CRT, patients were re-evaluated with chest-abdomen CT, endoscopy and PET-CT. Curative resection was performed in cases with no evidence of metastatic disease.

Surgery. Surgery was generally planned 8 weeks after the end of radiotherapy. Resective surgery consisted of either thoracic or cervical transthoracic esophagectomy (squamous cell carcinoma and Siewert type I or proximal type II cancer) or abdominal enlarged total gastrectomy (Siewert distal type 2 or type 3 cancer) according to the proximal site of the tumor. In transthoracic esophagectomy, extended or total mediastinal lymphadenectomy was performed; abdominal lymphadenectomy included nodes at the celiac trunk and those along the common hepatic and splenic artery at the upper border of the pancreas. Post-surgical complications were scored according to the Clavien-Dindo classification. Grade III complications would require surgical, endoscopic or radiological

Table II. *Summary of the dose volume histogram analysis for the target volumes and organs at-risk for the entire cohort of patients. Data are reported as averages±standard deviation and range.*

Organ	Volume (cm^3)	Parameter	Objective	Mean±SD	Range
CTV	298±153	Mean (Gy)	41.4 Gy	41.6±0.2	41.1-41.9
		$D_{1\%}$ (Gy)	Minimise	42.5±0.3	41.9-43.3
		$D_{98\%}$ (Gy)	>40.5 (98%)	40.8±0.4	40.2-41.4
		$V_{95\%}$ (%)	>95%	99.9±0.1	99.6-100.0
PTV	650±269	Mean (Gy)	41.4 Gy	41.4±0.0	41.4-41.4
		$D_{1\%}$ (Gy)	Minimise	42.8±0.3	42.3-43.6
		$D_{98\%}$ (Gy)	>39.3 (95%)	39.9±0.4	38.8-40.6
		$V_{95\%}$ (%)	>95%	97.5±1.6	92.5-99.9
Left kidney	169±38	Mean (Gy)	Minimise	7.4±4.3	0.9-17.3
		D_{1cm3} (Gy)	Minimise	24.4±10.6	2.1-41.9
		V_{15Gy} (%)	<35%	17.8±17.0	0.0-52.7
Right kidney	173±41	Mean (Gy)	Minimise	4.9±2.9	0.9- 11.6
		D_{1cm3} (Gy)	Minimise	16.7±7.2	5.2-30.1
		V_{15Gy} (%)	<35%	6.4±11.4	0.0-41.2
Spine	49.3±17.2	$D_{0.1cm3}$ (Gy)	<20 Gy	18.9±5.2	10.7-33.3
Stomach*	195±118	Mean (Gy)	Minimise	26.1±9.4	4.3-38.9
		D_{1cm3} (Gy)	Minimise	40.3±5.2	21.5-43.5
Duodenum*	64.3±54.9	Mean (Gy)	Minimise	12.0±7.4	1.5-21.3
		D_{1cm3} (Gy)	Minimise	23.6±12.4	2.9-40.8
Small bowel	1250.±800	Mean (Gy)	Minimise	10.7±4.8	2.8-19.7
		D_{3cm3} (Gy)	<36 Gy	35.5±6.0	20.2-41.8
Heart	696±156	Mean (Gy)	Minimise	15.9±5.2	0.9-29.1
		D_{1cm3} (Gy)	Minimise	41.7±3.2	21.6-42.9
Left lung	1693±433	Mean (Gy)	<15 Gy	10.1±3.5	3.1-16.4
		V_{20Gy} (%)	<20%	7.9±5.4	0.8-20.8
Right lung	2018±428	Mean (Gy)	<15 Gy	10.6±4.2	2.6-18.9
		V_{20Gy} (%)	<20%	10.1±7.7	0.7-32.8
Trachea*	18.6±7.2	$D_{0.1cm3}$ (Gy)	Minimise	23.9±19.5	0.3-42.9

CTV: Clinical Target Volume; PTV: planning target volume; Dx%: dose received by at least x% of the volume; Vx%: volume receiving at least x% of the dose; *partially included in the PTV for some patients.

intervention; grade IV would be lifr-threatening complication requiring intensive care management; grade V would imply death of a patient. The Mandard and Becker regression scale for histological assessment of the response to neoadjuvant treatment was used. With the Mandard scale, five histological regressions based on the vital tumor tissue at the ratio of fibrosis were defined. These ranged from complete regression up to tumor without changes of regression. With the Becker scale, the grading of tumor regression was based on the estimation of the percentage of vital tumor tissue in relation to the macroscopic tumor bed. This is divided in three grades from complete regression without residual tumor up to no regression.

Results

Between November 2012 and October 2014, 41 consecutive patients with potentially resectable locally advanced carcinoma of the subcarinal oesophagus or gastro-oesophageal junction were treated with concurrent CRT. Table I summarizes patients' characteristics at baseline. The male/female ratio was 24/6, with a median age of 65 years (range=42-79 years). All patients presented with a good Eastern Cooperative Oncology Group performance status at study entry of 0-1.

Twenty-two patients (73.3%) had an adenocarcinoma, seven patients (23.3%) had squamous cell carcinoma, and one patient had undifferentiated carcinoma (3.3%).

Most tumors were located in the distal oesophagus (33.3%) or at the oesophago-gastric junction (43.3%), only seven patients (23.3%) had medium-distal tumor location.

One patient did not complete the neoadjuvant regimen due to impairment of their general condition. Of the remaining 40 patients, 30 underwent surgery. Two patients are still under re-staging after induction treatment. One patient refused surgery, three patients died during treatment (acute myocardial infarction and aortic dissection), one patient had an impairment of their general condition, and progression of disease (metastatic disease) was observed in three cases.

Delivery and toxic effects of chemoradiotherapy. A total of 14 patients (46.7%) received the full treatment regimen of

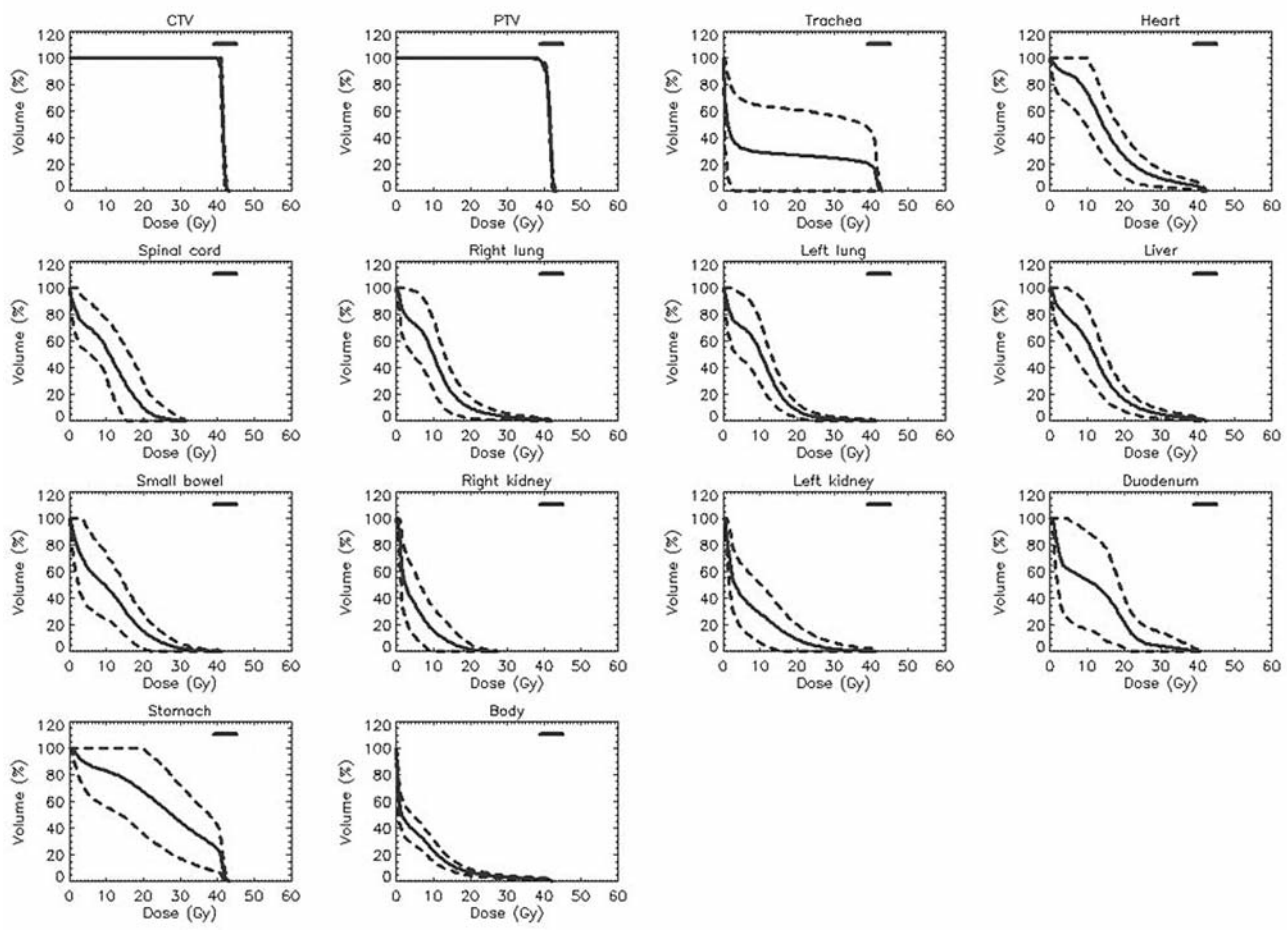

Figure 1. *Average dose–volume histograms for the patient cohort (solid lines). Dashed lines represent the inter-patient variability at 1 standard deviation. CTV: Clinical target volume; PTV: planning target volume; BODY: entire CT scan minus the target volumes.*

five cycles of chemotherapy, while 16 patients (53.3%) received incomplete chemotherapy (3-4 cycles). The reason for not completing all chemotherapy cycles was haematological toxicity in five out of 11 patients. In eight out of 28 patients (28%), grade 3 haematological toxicities were observed; no grade 4 toxic effects were reported. Non-haematological toxic effects of grade 3 occurred in less than 7% of patients, and were mainly represented by dysphagia.

Table II summarises the planning dosimetric characteristics of the radiotherapy treatments. Figure 1 shows the average dose volume histograms for the patients. A summary of the toxicity profile that was registered during and after neoadjuvant treatment is presented in Table III.

Surgery. Thirty patients underwent surgery out of 41 cases (73.17%), generally after a mean of 8 weeks after the end of radiotherapy; all surgeries resulted in R0 resection. In-hospital and 30-day mortality after resection were 6.1% (two patients: one due to anastomotic dehiscence and one to respiratory failure) and 9.1% (one due to massive haematemesis), respectively. The postoperative morbidity rate was 51.5%; major morbidity (Clavien Dindo ≥3) was 23.4%.

Pathological and radiological response. Pathological and radiological response to neoadjuvant treatment are summarised in Table IV. Two experienced radiologists and nuclear medicine physicians specialized in gastro-oesophageal cancer reviewed both pre- and post-neoadjuvant treatment CT images and PET/CT images, respectively. The sensitivity of CT and PET/CT were 94% and 95% respectively *versus* final histology.

Based on the results of the post-surgical histological assessment, disease control was observed in 93.3% of the cases. pCR was achieved in eight (26.7%) patients; of these tumors in four were squamous cell carcinoma and four were adenocarcinoma. Out of the 22 patients with residual disease,

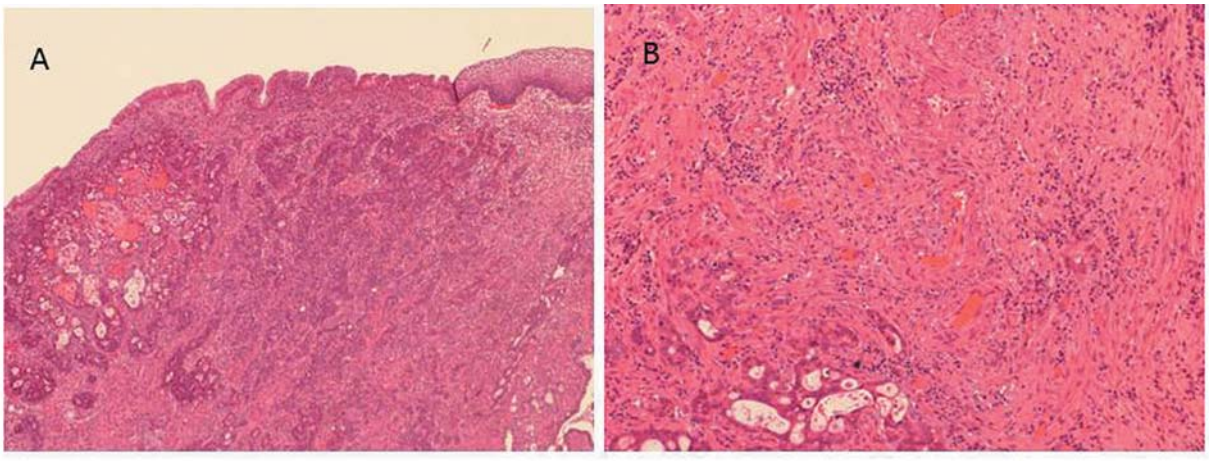

Figure 2. *Two examples of post-surgical specimen analysis. A: The left panel shows the haematoxylin-eosin staining with ×10 magnification of a case of gastro-oesophageal adenocarcinoma after neoadjuvant therapy. A residual tumor immediately under the epithelium was observed with surrounding defined reaction, characterized by acute and chronic inflammation with proliferation of small dilated and congested vessels, in a fibrotic stroma. B: The right panel shows a focus of residual adenocarcinoma, surrounded by congested vessels and chronic lympho-plasmacellular inflammation, after radiochemotherapy (haematoxylin-eosin staining, ×40 magnification.*

two had T upstaging, eight had unchanged T staging and 12 had T down-staging.

Fifty-three percent (16/30) of patients were lymph node-negative on final histology. Following neoadjuvant treatment, there was a 53.3% reduction in lymph node disease compared to the initial N staging. Considering that on initial staging more than 90% of cases had lymph node-positive disease, we had 14 cases with residual nodal disease.

pCR to neoadjuvant CT-RT did not differ significantly according to tumor histology (p=0.10); we noted a weak advantage of squamous cell carcinoma over adenocarcinoma, as known from literature.

The present data showed that after neoadjuvant treatment, there is no correlation with the degree of tumor regression and the histological type of cancer for adenocarcinoma *versus* squamous cell carcinoma.

Figure 2 shows two examples of post-surgical specimen analysis with partial response. In the first panel, a residual tumor immediately under the epithelium was observed, with surrounding defined reaction, characterized by acute and chronic inflammation with proliferation of small dilated and congested vessels, in a fibrotic stroma. The Figure also shows in the second panel a focus of residual adenocarcinoma, surrounded by congested vessels and chronic lympho-plasmacellular inflammation, after CRT.

Table III. *Toxicity profiles after neo-adjuvant chemo-radiotherapy with volumetric-modulated arc therapy.*

	Grade			
Toxicity	G0	G1	G2	G3
Asthenia	11 (36.7%)	16 (53.3%)	2 (6.7%)	1 (3.3%)
Leucopenia	10 (33.3%)	8 (26.7%)	6 (20.0%)	6 (20.0%)
Neutropenia	20 (66.7%)	3 (10.0%)	5 (16.7%)	2 (6.7%)
Thrombocytopenia	20 (66.7%)	9 (30.0%)	0 (0.0%)	1 (3.3%)
Nausea	18 (60.0%)	8 (26.7%)	4 (13.3%)	0 (0.0%)
Vomit	28 (93.3%)	1 (3.3 %)	1 (3.3%)	0 (0.0%)
Mucositis	23 (76.7%)	7 (23.3%)	0 (0.0%)	0 (0.0%)
Dysphagia	4 (13.3%)	20 (66.7%)	6 (20.0%)	0 (0.0%)
Nephrotoxicity	29 (96.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
Stomatitis	24 (80.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)
Diarrhea	27 (90.0%)	2 (6.7%)	1 (3.3%)	0 (0.0%)
Sypsis	19 (63.3%)	7 (23.3%)	4 (13.3%)	0 (0.0%)

Discussion

Multimodal therapy consisting of neoadjuvant CRT followed by surgery is currently standard practice in many oncology Centres (9-13). Walsh *et al*. had a pCR of 25% after multimodal therapy and a survival advantage favouring the CRT group at three years (2).

Bosset *et al*., with the Fondation Française de Cancérologie Digestive and EORTC Gastrointestinal Tract Cancer cooperative Group conducted a study on 282 patients (5). Compared to the group treated with surgery-alone, the group treated preoperatively with chemoradiotherapy had longer disease-free survival, a longer interval-free of local disease, and a higher frequency of curative resection. However, there were more postoperative deaths in the group treated preoperatively with CRT.

Table IV. *Response to chemotherapy, radiotherapy and surgery.*

Radiological response	Stable: 3 (10.0%) Partial: 20 (66.7%) Complete: 7 (23.3%)
Metabolic response	Stable: 2 (6.7%) Partial: 17 (56.7%) Complete: 11 (36.7%)
Surgical response	Progressive: 2 (6.7%) Stable: 8 (26.7%) Partial: 12 (40.0%) Complete: 8 (26.7%)
Intervention duration mean and range (min)	291±47 (172:392)
Hematic losses (cm^3)	193±108 (50:400)
Post-surgical complications	No: 16 (53.3%) Yes: 14 (46.7%)
Clavien Dindo classification of post-surgical complications	0: 16 (53.3%) I: 0 (0.0%) II: 7 (23.3%) III: 3 (10.0%) IV: 2 (6.7%) V: 2 (6.7%)
T Pathological stage post-surgery	T0: 8 (26.8%) T1: 7 (23.3%) T2: 4 (13.4%) T3: 11 (36.7%)
N Pathological stage post-surgery	N0: 16 (53.3%) N1: 6 (20.0%) N2: 5 (16.7%) N3: 3 (10.0%)
T Staging change between surgery and diagnosis	+1: 2 (6.7%) 0: 8 (26.7%) –1: 9 (30.0%) –2: 2 (6.7%) –3: 8 (26.7%) –4: 1 (3.4%)
N Staging change between surgery and diagnosis	+2: 2 (6.7%) +1: 5 (16.7%) 0: 8 (26.7%) –1: 11 (36.7%) –2: 4 (13.4%)

Burmeister *et al*. found that the multimodal-therapy group had more complete resections than did the group treated with surgery-alone, and had fewer positive lymph nodes (14).

The multi-center phase III randomized trial CROSS study showed that neoadjuvant CRT improved OS compared to surgery-alone in patients with resectable (T2-3N0-1M0) oesophageal or gastro-esophageal junction cancer (7). The CRT consisted of weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg/ml per minute) and paclitaxel (50 mg/m^2) for 5 weeks and concurrent radiotherapy (41.4 Gy/23 fr per 4.6 weeks), followed by surgery. R0 margin resection was achieved in 92% of patients in the CRT–surgery group *versus* 69% in the surgery group ($p<0.001$). A pCR was achieved in 29% of patients who underwent resection after CRT. Postoperative complications were similar in the two treatment groups.

The meta-analysis of Kranzfelder *et al*. analyzed the benefits of neoadjuvant treatment: R0 resection was significantly higher after neoadjuvant treatment. A significant survival benefit for neoadjuvant CRT was evident, with no increase in morbidity rate (15).

The regimen adopted in the present study was neoadjuvant concurrent CRT according to the CROSS scheme. The radiation treatment dose was the standard 41.4 Gy but delivered using an intensity-modulated radiotherapy with VMAT RA technique. The rationale for this choice is that intensity-modulated radiation therapy was demonstrated to be superior to three-dimensional conformal radiotherapy or other forms of intensity modulation in a variety of studies (16-23).

In our study, all patients underwent PET/computed tomographic prior to neoadjuvant CRT, in the majority of cases in the simulation phase, to provide staging information and also to improve radiotherapy target definition. Six weeks after neoadjuvant treatment, all patients were studied with CT and PET/CT for a morphological and metabolic data, respectively. Different and conflicting data exist on the role of PET/CT in predicting response of oesophageal cancer to neoadjuvant therapy (24-26). In our study, we found no correlation of metabolic response and pathological definitive results. The assessment of early response to CRT using PET/CT detected three cases of distant metastases, so these were excluded from surgery.

The present study demonstrates that patients with potentially resectable locally advanced distal oesophageal or gastro esophageal junction cancer can be safely treated with the combination of intravenous paclitaxel (50 mg/m^2) and carboplatin, administered five times during a 4-week radiotherapy (VMAT) period with a total dose of 41.4 Gy given in 23 fractions of 1.8 Gy, with a significant CR.

According to these data, we believe that dose escalation might increase response after neoadjuvant treatment.

Conclusion

VMAT RA was applied in the context of neoadjuvant CRT for the treatment of medium and distal oesophageal carcinoma. Treatment compliance and tolerance were adequate and toxicity and surgical morbidity within mild-modest levels. Partial or complete response was observed in the majority of the patients prior to surgery and confirmed with pathological examination after intervention. The approach is therefore considered safe and effective.

Conflicts of Interest

L. Cozzi acts as Scientific Advisor to Varian Medical Systems and is Clinical Research Scientist at Humanitas Cancer Center. All other co-Authors have no conflicts of interest in regard to this study.

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Received March 31, 2015
Revised April 22, 2015
Accepted April 24, 2015