Retrospective evaluation of the impact of dose escalation using pre-operative simultaneous integrated boost volumetric modulated arc therapy on the outcome of locally advanced rectal cáncer patients

Ahmed Elashwah (ashwah_a80@yahoo.com)
Kasr Aleini center of clinical oncology,(NEMROCK), cairo univeristy
Abdullah Alsuhaibani
King Saud University
Alaa Abduljabbar
King Faisal Specialist Hospital & Research Centre
Nasser Alsanea
King Faisal Specialist Hospital & Research Centre
Samar Alhomoud
King Faisal Specialist Hospital & Research Centre
Luai Ashari
King Faisal Specialist Hospital & Research Centre
Shouki Bazarbashi
King Faisal Specialist Hospital & Research Centre
Ali Aljubran
King Faisal Specialist Hospital & Research Centre
Ahmed Alzahrani
King Faisal Specialist Hospital & Research Centre
Ahmed Awad
Radiation Oncology Department, National Cancer Institute (NCI), Cairo University
Hadeel Almanea
King Faisal Specialist Hospital & Research Centre
hussah Alhussini
King Faisal Specialist Hospital & Research Centre
Mohammed Alshabanah
King Faisal Specialist Hospital & Research Centre

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Abstract

Background

Radiation therapy has a well-established role in the management of locally advanced rectal cancer (LARC) patients. Several strategies have been investigated to improve the pathological complete remission (PCR) rate including radiation dose escalation utilizing simultaneous integrated boost volumetric modulated arc therapy (SIB-VMAT) technique.

Methods

evaluating the outcome of preoperative SIB-VMAT concomitant with Capecitabine to patients diagnosed with LARC who were treated at King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia during the period January 2013 - December 2019.

Results

The study enrolled 134 patients. The median age at diagnosis was 59 (25-102) years. All patients received pre-operative concurrent chemo-radiation therapy (CCRT) using SIB-VMAT with oral capecitabine. Neoadjuvant chemotherapy was administered prior to CCRT in 32 patients (23.9%). The dose of radiation was 55 Gy in 94 patients (70.1%), while 40 patients (29.9%) received 50 Gy. All patients completed the CCRT treatment without breaks. No records of acute and late grade III and IV toxicities. Acute toxicity grades I and II occurred in 40 patients (29.9%). Curative surgery was performed in all patients with a median interval of 11 (6-52) weeks between the end of CCRT and the date of surgery. No reported 30-days postoperative mortality and no grade III and IV Clavien-Dindo complications. PCR was reported in 26 patients (19.4%), while pathologically negative nodes (pN0) were achieved in 103 patients (76.9%). Adjuvant chemotherapy was utilized in 57 patients (42.5%). The 5-year local recurrence-free survival (LRFS), disease-free survival (DFS), and overall survival (OS) were 93.2%, 67.1%, and 87.3%, respectively. Only Tumor regression grade (TRG) was significantly correlated with LRFS,(p-value 0.043). On multivariate analysis, only (TRG) and achievement of pN0 were significantly correlated with DFS,(p value<0.001).

Conclusion

Dose escalation utilizing (SIB-VMAT) in the preoperative treatment of LARC is well tolerated and provides effective local control.

Background

In the year 2020, colorectal cancer (CRC) was the 3rd commonly diagnosed malignancy worldwide in men after lung and prostate cancer and the 3rd leading cause of cancer mortality after lung and liver cancer. In women, CRC is the 2nd malignancy in incidence after breast cancer and the 3rd leading cause of mortality after breast and lung cancer **(1).**

In Saudi Arabia, CRC is the most commonly diagnosed cancer in men and the third in women with 1659 new reported cases in 2016, representing about 13% of all diagnosed cancers **(2).**

Radiation therapy has a well-established role in management of locally advanced rectal cancer (LARC) patients with reduction in the incidence of local recurrence rate with near complete shift from adjuvant to the neo adjuvant era due to the improved local control rate and less toxicity for neo adjuvant over adjuvant radiation therapy **(3).**

New radiation techniques such as intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) have been frequently used over the last 20 years for the treatment of rectal cancer. It is associated with better dose conformity, better sparing of organs at risk (OARs) and lower toxicity in comparison to the more traditional techniques (2D and 3D conformal radiation therapy [3DCRT]) **(4,5).**

The addition of concomitant chemotherapy to preoperative radiotherapy (CCRT) resulted in a significant increase in local control rate with a slight increase in acute toxicity, but there was no increase in postoperative morbidity. However, no significant improvement in overall survival was observed in any study **(6).**

Using the standard CCRT approach (radiation therapy dose of 45-50.4 Gy/25–28 fractions in 2 phases concomitant with 5 -FU based chemotherapy), only about 11–18% of patients will achieve a pathological complete remission (pCR) **(7–12)**. As this group of patients shows a better overall prognosis compared to patients with less or no response **(13)**, several strategies have been investigated to improve the pCR rate including radiation dose escalation that could be achieved through the addition of more fractions in conventional fractionation, utilize altered fractionation regimes or add a brachytherapy boost. The reported pCR rates with dose escalation ranged from 0 to 50% with an average of 22% **(14).**

The simultaneous integrated boost (SIB)-IMRT/VMAT techniques allows the simultaneous delivery of different dose levels to different target volumes within a single treatment fraction which allows for radiation therapy dose intensification. Many studies evaluated the role of radiation dose intensification utilizing SIB-IMRT technique along with concurrent 5-FU based chemotherapy in the treatment of LARC. It found a strong correlation between increased radiation dose and higher pCR rates, along with an acceptable toxicity profile **(15)**

In our study we retrospectively evaluated the outcome of patients diagnosed with LARC who were treated with pre-operative (SIB-VMAT) technique concomitant with Capecitabine.

Methods

The medical records of patients diagnosed with LARC who were treated with preoperative SIB-VMAT at the Oncology Center at King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia (KFSH&RC) were retrospectively evaluated. Data retrieved included: demographic data, clinical (c) TN stage, tumor size (cranio-caudal dimension), tumor distance from the anal verge (AV distance),

circumferential radial margin (CRM) status on magnetic resonance imaging (MRI) (considered positive if tumor is less than 1 mm away from the mesorectal fascia), pre-operative chemotherapy data, radiation therapy data, surgical data, post-operative morbidity and mortality, pathological TN stage (pTN), Tumor regression grade (TRG), actual number of retrieved lymph nodes, adjuvant chemotherapy data, late toxicity data, site and date of recurrence and status (alive without disease, alive with disease or dead).

All patients diagnosed with rectal cancer underwent: full laboratory work up including tumor markers, full colonoscopy assessment, rigid proctosigmoidoscopy, endorectal ultrasound (ERUS), endoscopic guided biopsy, Computed Topography (CT) chest, abdomen and pelvis and Magnetic resonance imaging (MRI) of the pelvis.

All the patients were evaluated and managed by a multidisciplinary team that included: colorectal surgeons, medical and radiation oncologists, abdominal radiologists, gastrointestinal pathologists, enterostomal therapists and hereditary colorectal tumor registrars.

All the patients included in this study were diagnosed with LARC and satisfied the following inclusion criteria: age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, pathologically proven adenocarcinoma for rectal lesion up to 15 cm from the anal verge, adequate hematological, renal and hepatic functions, **(c)** T3, T4 and/or lymph node positive (cN+) by MRI pelvis and/or ERUS, and no evidence of distant metastatic disease.

All patients were planned to receive preoperative CCRT (SIB-VMAT 55 Gy/25 fractions/ 5 weeks' concomitant with oral daily Capecitabine 825 mg/m2/12h 5 days per week/ 5 weeks. The dose of radiation therapy was reduced to 50 Gy in some patients when our acceptance criteria for (OARs) were not met mostly due to the small bowel. For more details about radiation therapy plans, volumes and acceptance criteria, please review our previous published study **(16).**

Neoadjuvant chemotherapy for an average of 4 months was used in our center in patients with cT4B and/or upfront unresectable disease to improve tumor surgical resectability. Adjuvant chemotherapy was used for those patients who did not receive neoadjuvant chemotherapy and did not achieve PCR post CCRT with pathologically (pT3, T4) and/or had pathologically node positive disease (pN+). Different regimens were utilized as neoadjuvant or adjuvant chemotherapy (including FOLFOX, CAPEOX and Capecitabine). The type and number of chemotherapy regimens were decided by medical oncologist based on several factors including: age, performance status (PS), co-morbidities, T N stage, in addition to the choice of the patient.

All the patients were followed once weekly during CCRT to assess for acute toxicity. Acute toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 **(17)**. In order to assess response to CCRT and exclude metastasis, a repeated MRI and CT were performed for all patients prior to surgical treatment.

Surgery was performed after an elapsed period of (6–12) weeks post CCRT. The 30 days Postoperative complications rates were evaluated according to the Clavien-Dindo grading system (**18).**

Tumor regression grade (TRG) was assessed according to the American Joint committee on Cancer (AJCC) staging manual, 8th edition and the College of American Pathologists (CAP) guidelines as modified by Rayan, et al **(19)**. The patients in our study were divided into two groups for comparison (good responders including grade 0,1) and poor responders (grade 2,3).

All patients were kept under regular follow with medical oncology and/or colorectal surgery teams.

Follow up intervals were as follow: every 3–4 months during the first 2 years, every 6 months during the 3rd-5th year and then annualy. Follow up included: history, physical examination, complete laboratory work up with tumor markers, CT chest, abdomen and pelvis. Colonoscopy is usually performed at one and 3 years after the initial colonoscopy and then subsequently every 5 years as long as there are no clear indications to be conducted earlier.

Primary end point for our study was 5-year local recurrence free survival (LRFS). Secondary end points included: 5-year disease free survival (DFS), 5-year overall survival (OS) and late toxicity.

Statistical Analysis

Statistical analysis was conducted utilizing IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Quantitative variables were described as median and range. Qualitative variables were described as numbers and percentages. Pearson's Chi-square test or Fisher's exact test was used to test the relationship between qualitative variables.

DFS was calculated from the surgery date till the date of documented recurrence, death or last follow up. OS was calculated from the date of diagnosis till the date of death or date of last follow up. Survival analysis was performed utilizing the Kaplan-Meier method, and a comparison between two survival curves was conducted using the log-rank test.

Multivariate analysis was performed using the Cox-proportional hazard regression model with the forward likelihood ratio method for the factors affecting survival on univariate analysis. Hazard ratio (HR) with its 95% confidence interval (CI) was used for risk estimation. All tests were two-tailed. A p-value < 0.05 was considered significant.

Results

A total of 134 patients were included in this study; the median age at diagnosis was 59 (25–102) years, detailed patients and tumor characteristics are listed in Table 1. The details of radiation and chemotherapy treatments are listed in Table 2. All patients completed the CCRT treatment course with no breaks. There were no incidents of grade III and IV acute or late toxicities. The details of acute and late toxicities are listed in Table 3.

Table 1
patients and tumor characteristics.

Characteristics	Number of patients (%)
Median age (range) in years	59 (25–102)
Gender	82 (61.2%)
Male	52 (38.8%)
female	
Eastern Cooperative Oncology Group (ECOG) performance status	55(41.0%)
0	60(44.7%)
1	19(14.3%)
2	
Clinical (c) T Stage	7 (5.2%)
T2	95 (70.9%)
T3	32 (23.9%)
T4	
Clinical (c) N Stage	14 (10.4%)
N0	47 (35.1%)
N1	73 (54.4%)
N2	
Clinical (c) Tumor size (cranio caudal dimension)	5 (2–11)
Median (range) in CM	15 (11.5%)
< 4	119 (88.8%)
≥ 4	
Clinical (c) Circumferential radial margin CRM)	59 (44.0%)
Negative	75 (56.0%)
Positive	
Distance from anal verge in CM	50(37.3%)
≤ 5	84(62.7%)
> 5	6 (0–15)
Median (range)	

Table 2
treatment characteristics

Treatment characteristics		Number of patients
Pre-operative chemotherapy **(n = 32)**	1.Regimens	10 (31.2%)
	-FOLFOX	22 (68.8%)
	-CAPEOX	6 (3–15)
	2.Median (range) number of cycles	
Pre-operative radiation therapy **(n = 134)**	Dose	94 (70.1%)
	55 Gy	40 (29.9%)
	50 Gy	
Surgery **(n = 134)**	1.Type	94 (70.1%)
	-AR	40 (29.9)
	-APR	11 (6–52)
	2.Median (range) time in weeks from end of CCRT till surgery.	11 (1–25)
	3.Median (range) number of dissected LN.	7(5–21)
	4. Median (range) post-operative hospital stay in days	
Adjuvant chemotherapy **(n = 57)**	1.Regimens	5 (8.8%)
	-FOLFOX	32 (56.1)
	-CAPEOX	20 (35.1)
	=Capecitabine	6 (3–8)
	2.Median (range) number of cycles	

Table 3
Reported acute and late toxicities.

Toxicity		Number of patients
Acute (n = 40) *	Dysuria	30(75%)
	Anal pain	28(70%)
	Diarrhea	21(52.5%)
	Nausea	20(50%)
	Fatigue	15(37.5%)
Late (n = 10) **	GIT(n = 7)	1(14.3%)
	Anastomosis leak	1(14.3%)
	Anastomosis stricture	5(71.4%)
	Small bowel obstruction	
	Genitourinary(n = 4)	2(50%)
	Rectovaginal fistula	2(50%)
	Ureteric obstruction	
* Many patients developed more than one acute toxicity.		
**one patient developed both GIT and genitourinary late toxicity.		

Curative surgery was performed in all patients with a median interval of 11 (6–52) weeks between the end of CCRT and the date of surgical intervention. There was no 30-days post-operative mortality. There were also no Clavien-Dindo grade III and IV postoperative complications. Details about the type of surgery are listed in Table 2. Pathological response to treatment is listed in Table 4, PCR was reported in 26 patients (19.4%), while (pN0) was achieved in 103 patients (76.9%).

Table 4
response and treatment outcome

Parameters		Number of patients
Tumor regression grade (TRG)	0	26(19.4%)
	1	37(27.6%)
	2	58(43.3%)
	3	13(9.7%)
	Good responders (G0,1)	63(47%)
	Poor responders (G2,3)	71(53%)
Pathological T stage (YpT)	0	26(19.4%)
	1	10(7.4%)
	2	36(26.9%)
	3	56(41.8%)
	4	6(4.5%)
Pathological nodal status (pN)	pN0	103 (76.9%)
	pN+	31 (23.1%)
Follow up	Median (range) in months	59.1 (7.9-104.8)
Relapse	No	95 (70.9%)
	yes	39 (29.1%)
Site of relapse(n = 39)	Lung	14(35.9%)
	Local	7(17.9%)
	Liver	5(12.8%)
	Lymph nodes	5(12.85)
	Peritoneum	2(5.1%)
	More than 1 site	6(15.4%)

After a median follow up time of 59.1 (7.9-104.8) months, the 3 and 5-year DFS are 69.3% and 67.1% respectively, Fig. 1. Local relapse occurred in 8 patients (5.9%): 7 Patients developed isolated local recurrence while 1 patient developed local recurrence and distant metastasis. The cumulative 5-year LRFS was 93.2%. One patient (14.7%) with isolated local recurrence was salvaged with re-surgery, but all the others received palliative chemotherapy.

Systemic relapse occurred in 32 (23.9%) patients. The most common site of relapse in 19 patients (59.3%) was the lungs. Lung metastatectomy was performed in 11 (78.5%) out of 14 patients with an isolated lung recurrence. The 3 and 5-year OS was 95.3% and 87.3%, respectively, Fig. 2.

In relation to LRFS, only TRG was significantly correlated with LRFS in univariate analysis, p value 0.043, Table 5.

Table 5
Significant correlations between multiple parameters with LC, DFS and OS in univariate and multivariate analysis.

Parameters	DFS		OS	LRFS
	Univariate p value	Multivariate HR (CI)	Univariate p value	Univariate p value
TRG (good vs poor responders)	< 0.001	3.9 (2.1–7.5)	0.056	0.043
Pathological nodal status (pN0 vs pN+)	< 0.001	4.3 (2.3–7.9)	0.019	-
Clinical (c) T stage (T2,T3 vs T4)	0.008	-	-	-
Clinical (c) tumor size (< 4 vs ≥ 4 cm)	0.035	-	-	-
Clinical (c) CRM (negative vs positive)	0.015	-	-	-

In relation to DFS, univariate analysis included: pathological response to treatment (TRG), pathological node status, clinical stage, tumor size and CRM. All achieved a significance level of P-value < .05. When these variables were included in a multivariate analysis, only TRG (good responders) and pN0 achieved significance at P-value < 0.05, Table 5 and Fig. 3.

In relation to OS, univariate analysis included: pathological response to treatment (TRG) and pathological node status. Only pN0 achieved significance at P-value < o.05 at multivariate analysis, Table 5 and Fig. 4.

Discussion

In this study, the PCR rate achieved was 19.4%.This is higher than the reported before in many studies using neoadjuvant CCRT in conventional fractionations: Roh et al **(20)**, Park et al **(21)**, and Sauer et al **(22)**, where the PCR rate were 15%,17%, and 8% respectively. Our current study PCR also is 2.5 times higher than our earlier PCR rate of 7.6% as reported in a previous study from our institution **(23).** The main difference between the current study and the previous one from our institution is the dose and the technique of pelvic radiation: SIB-VMAT technique was used in the current study with a total dose of 50–55 Gy in 25 fractions compared to 3DCRT technique in the previous study where dose of 50.4 Gy given over 28 fractions in 2 phases (26% of patients received radiation therapy only). This difference was not

so evident between SIB-IMRT and 3DCRT techniques in another study conducted by Bong et al, where the incidence of PCR was 9% vs 7%, respectively **(24).** The PCR rate in our study was slightly lower than that achieved by Zhu et al **(25)**,19.4% vs 23.7% respectively. That difference might be attributed to the use of oxaliplatin (weekly) in addition to capecitabine concomitant with radiation therapy followed by one cycle of CAPEOX in all patients pre operatively in Zhu et al **(25)** study.

Local recurrence (LR) occurred in our study only in 8 (5.9%) patients with a 5-year LRFS of 93.2%. This is much lower than the study conducted by Zhu et al **(25)** where the 3-year local recurrence rate was 14.6% despite the higher PCR rate achieved by zhu et al at 23.7% vs 19.4% in our study. This might be attributed to the fact that the surgery in our study was conducted by board certified colorectal surgeons and not general surgeons. In comparison to Sibel et al **(26)**, where the 5-year local control (LC) rate was 75.5% vs. 93.2% in our study, one might postulate that the higher radiation dose 55 Gy that used in 70% of cases in our study vs dose of 50.4 GY that used in Sibel et al study **(26)** .

Only TRG was significantly correlated with LRFS in univariate analysis; this supports the prognostic significance of PCR that was shown before in many studies **(10,11).**

The 3-year DFS and OS: 69.3% and 95.3%, respectively in this study is higher than the 3-year DFS and OS of 63.8% and 77.4%, respectively in Zhu et al study **(25)**. That might be attributed to the better local control rate in our study. The same applies to the better 5-year DFS and OS in our study; 67.1% and 87.3%, respectively; in comparison to the study conducted by Sibel et al **(26)**, where the 5 years DFS and OS were 66.7% and 73.1%, respectively.

By comparing our 5-year LR rate, DFS and OS with those studies utilizing neoadjuvant CCRT in conventional fractionation; we found better 5-year LR rate of 5.9% vs 10.7% and 6% in Roh et al **(20)** and Sauer et al **(22)** respectively, with comparable 5-year DFS of 67.1% vs 64.7% and 68% in Roh et al **(20)** and Sauer et al **(22)** respectively, with better 5-year OS of 87.3% in current study vs 74.5% and 76% in Roh et al **(20)** and Sauer et al **(22)** respectively. Moreover, in current study we have better 3-year DFS of 69.3% and 5-year OS of 87.3% in comparison to 67% and 81%, respectively noted in Alzahrani et al study **(23).** That improvement in LRFS, DFS and OS in our study in comparison of above mentioned studies is probably attributed to the better PCR rate achieved in our study.

The lungs were the most common site of relapse in 19/32 (59.3%) patients. This is compatible a review conducted by Guraya **(27)**, where he found pulmonary recurrence is commonly associated with rectal tumors, while liver metastasis is commonly associated with colon cancer.

Only TRG and achievement of pN0 were independent prognostic variables with regard to DFS on multivariate analysis. This was similarly noted by Zhu et al in their study **(25)** where TRG was independent prognostic factor for DFS.

In addition to the improved outcome in our study in comparison to the above-mentioned studies using conventional fractionations, we found also significant improvement in toxicity profile as no patients in

the current study developed grade III or IV acute toxicity and only 40 (29.8%) patients developed grade I and II toxicities, in comparison to incidence of acute toxicities ≥ grade III of 52%,15%, and 27% in Roh et al **(20)**, Park et al **(21)**, Sauer et al **(22)**, respectively. The incidence of acute toxicities in our study was found also to be lower than reported in other studies using SIB-IMRT; in Zhu et al study **(25)** the incidences of acute grade III hematologic toxicity, diarrhea and radiation dermatitis were 3.8%, 10.3%, and 17.9%, respectively. In another study conducted by Sibel et al **(26)**, the incidences of grade III diarrhea and cystitis were 10% and 7.5% respectively. The incidence of late toxicity also was very low in our study. Late toxicity developed in only 10 (7.4%) patients with no reported grade III or IV toxicity.That reduction in the incidence of acute and late toxicities in our study with no incidents of grade III or IV toxicities might be attributed to the strict dose constrains for (OARs) especially to the small bowel. The irradiated volumes were limited to 0 and < 20 cc in doses higher than 50 and 45 Gy, respectively **(28).** in 40 patients (29.8%), we were not able to achieve these bowel limitations, so we decreased the used radiation dose to 50 Gy instead of 55 Gy.

The main two limitations of our study is the relatively small number of patients and the retrospective design.

Conclusion

Dose escalation using (SIB-VMAT) in the preoperative treatment of LARC is well tolerated and offers effective long term local control.

Declarations

Ethical Approval and consent to participate

This research has been approved by the Research Advisory Council (RAC)and Research ethics committee at the King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia (RAC Project # 2161 247)."

Conflicting Interests

The authors declare no competing interests regarding the production of this paper. The authors have no personal financial or institutional interests in any of the drugs, materials, or devices described in this paper.

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Data Availability statement

All data are available with the corresponding author and can be provided upon request.

Author contribution

Material preparation, data collection, and analysis were performed by Ahmed Elashwah, Abdullah Alsuhaibani and Ahmed Awad [A.E, A.S, and A.A respectively). Surgical management and post-operative follow up done by Alaa Abduljabbar, Nasser Alsanea, Samar Alhomoud and Luai Ashari (A.J, N.A, S.A, L.A respectively). The radiation therapy indications, treatment planning, and follow-up during radiation therapy are done by Abdullah Alsuhaibani , Ahmed Elashwah and Mohammed Alshabanah (A.S, A.E, and M.A respectively). All chemotherapy indications and treatment were decided by Shouki Bazarbashi , Ali Aljubran , Ahmed Alzahrani (S.B, A.JUB, Ah. Z respectively). All the histopathological tests and examinations were performed by Hadeel Almanea, hussah Alhussini (H.A, hu. A respectively). The first draft of the manuscript was written by Ahmed Elashwah [A.E] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent for publication

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Statements

All methods were carried out in accordance with relevant guidelines and regulations.

All experimental protocols were approved by a Research Advisory Council (RAC) at the King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia (RAC Project # 2161 247).

Informed consent was obtained from all subjects and/or their legal guardian(s).

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Figures

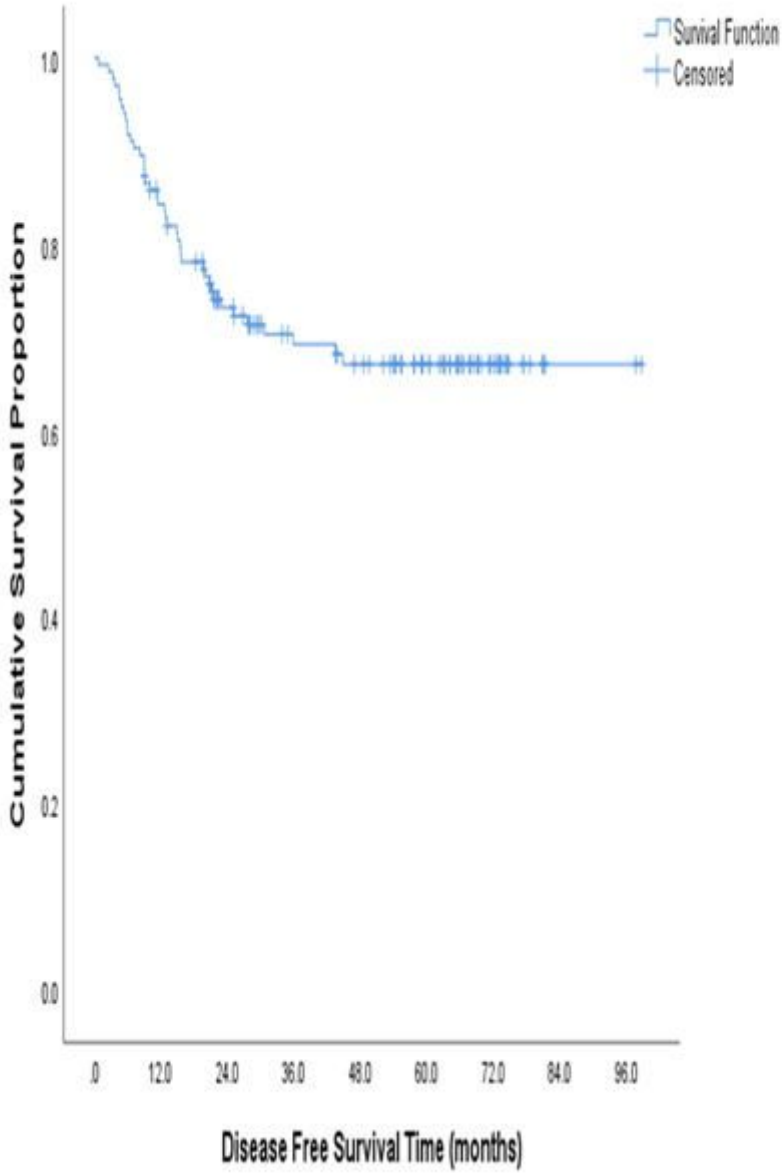


Figure 1

DFS for whole patients' population.

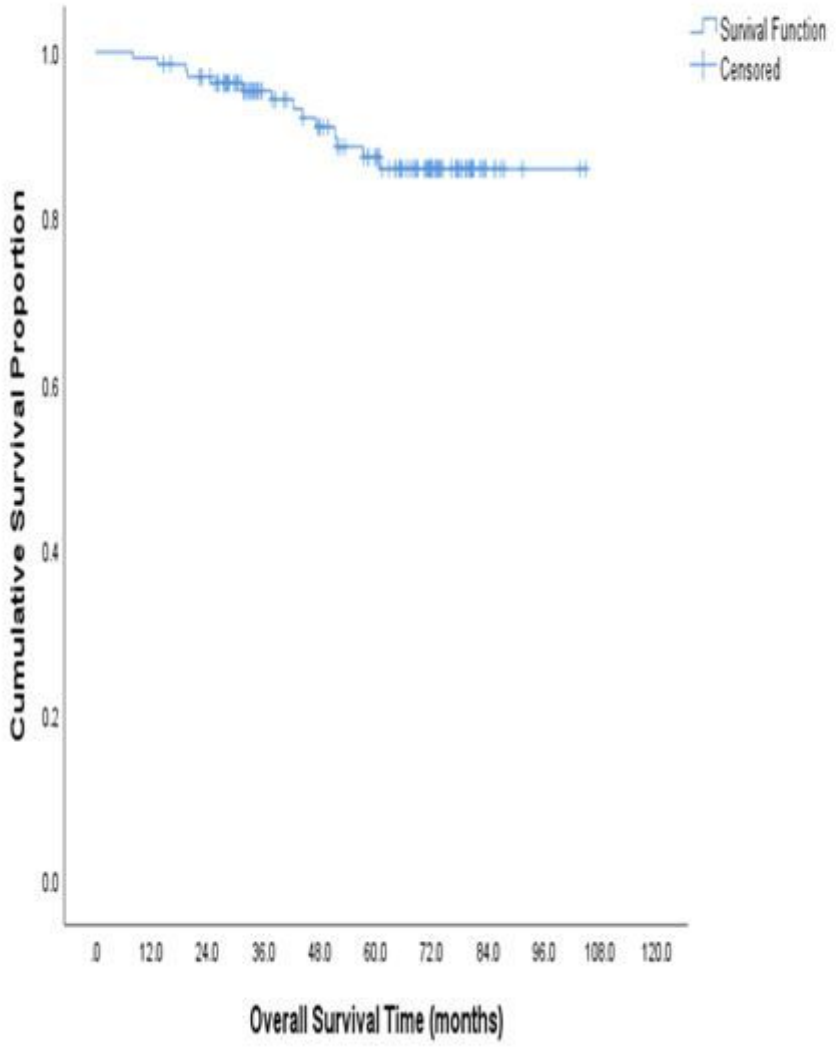
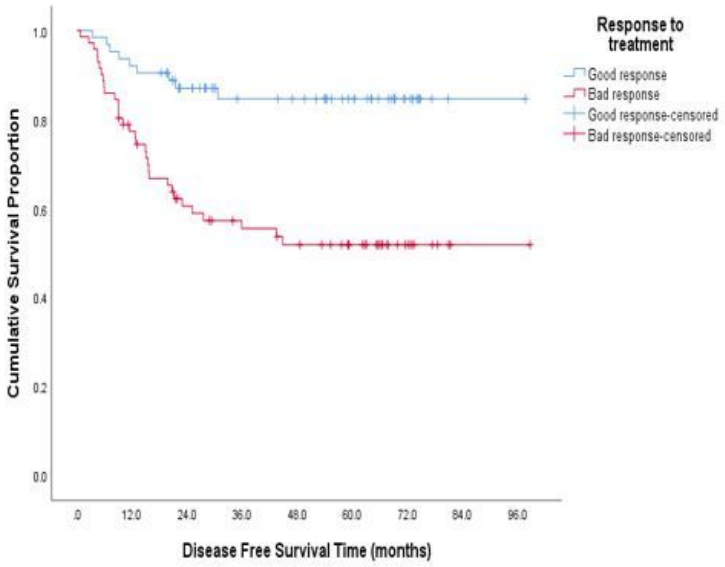
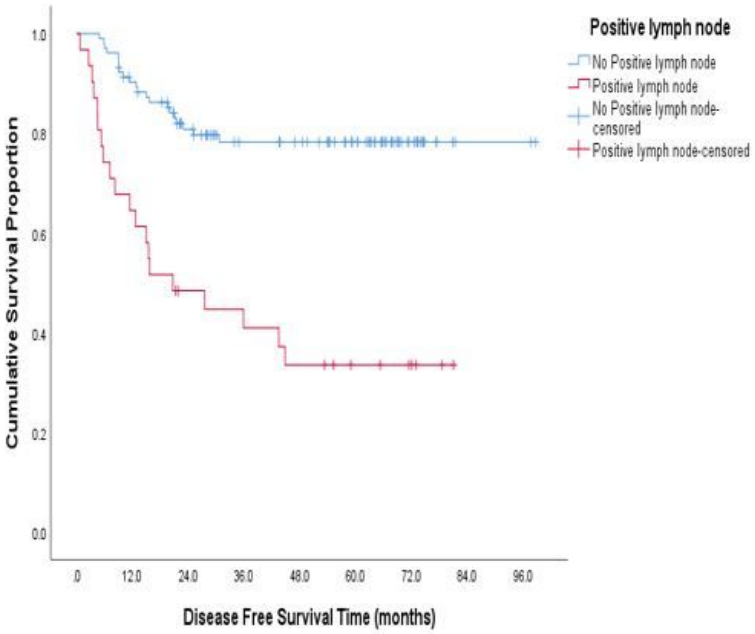


Figure 2

OS for whole patients' population.



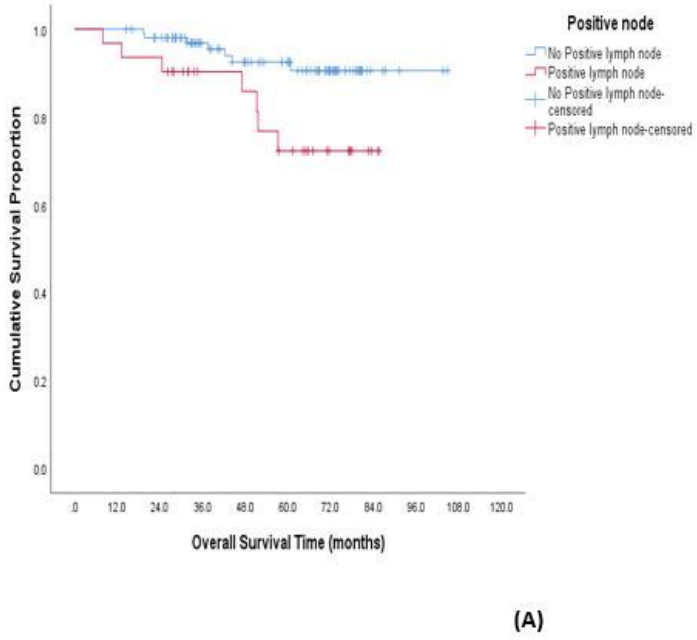
(A)



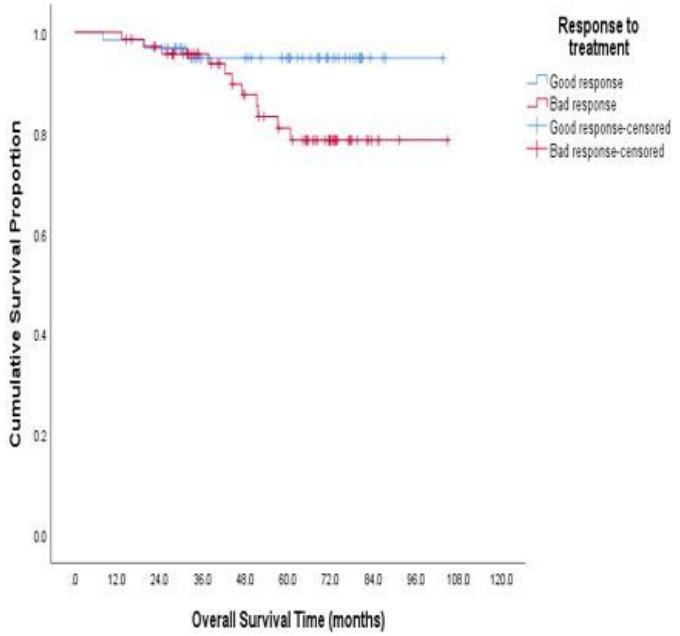
(B)

Figure 3

Factors significantly correlate with DFS on multivariate analysis, **(A)** TRG (good responders grade 0,1 vs poor responders grade 2,3), **(B)** pathological node status (pN0 vs pN+).



(A)



(B

Figure 4

Factors significantly correlate with OS on univariate analysis, **(A)** pathological node status (pN0 vs pN+). **(B)** TRG (good responders grade 0,1 vs poor responders grade 2,3)