Phase II, Non-Randomized Study of Chemo-Chemoradio-Chemo Sequential Therapy Compared With Concomitant Chemoradiotherapy In Magnetic Resonance Imaging Defined, Locally Mid/Low Advanced Rectal Cancer

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Abstract

Objective

The conventional preoperative CRT provides local tumor control in most LARC patients. However, long-term survival has not obviously improved. Thus, the optimal neoadjuvant treatment is still controversial. Sandwich therapy may be associated with better efficacy.

Methods

The present study is a single-center, open-label, phase II, non-randomized trial (Clinical trials number: NCT02022852). Pathological diagnosis of eligible patients were as rectal adenocarcinoma and they were clinically confirmed by MRI as cT3-4NxM0, with distal border located≤10cm from anal verge. Hundred and seventy-two patients between July 2013 and July 2015 were enrolled for the trial. The enrolled patients were non-randomly assigned into two treatment types (arm A and arm B). Patients in arm A received capecitabine-based concurrent CRT 25 fractions. In contrast, arm B patients received sequential therapy as induction CapeOx for two cycles, followed by 25 fractions CRT, finally adding one consolidation CapeOx cycle. After preoperative treatment, TME with different adjuvant therapy types were performed in patients.

Results

With treatment processing, 48 patients were excluded from the trial due to personal reasons and intolerance to treatment toxicities. Finally, there were 61 patients in arm A and 63 patients in arm B (70.9% vs. 73.2%). The 5-years DFS and OS didn't show significant difference in two arms. However, the postoperative complications of arms A and B were 4.9% and 17.5% (P=0.027).

Conclusions

Sandwich therapy may lead more postoperative complications than conventional CRT, so that the safety should further research. Compared with conventional CRT, sandwich therapy doesn't show significant advantage in survival.

Introduction

As widely reported, concurrent chemotherapy with radiation is recommended as a classical neoadjuvant treatment for locally advanced rectal cancer (LARC) (1–3). Comparatively, the addition of fluoropyrimidine to radiation therapy can achieve significant local control (4) and a higher pathological complete response (pCR) rate(5) than single postoperative and preoperative radiotherapy. Notably, the addition of oxaliplatin to the regimens, such as CapeOx and FOLFOX, results in higher rates of PCR (6, 7). Moreover, the addition of targeted agents, such as cetuximab, panitumumab, and bevacizumab to preoperative fluoropyrimidine-based chemoradiation therapy (CRT), was not be endorsed by the clinicians group due to severe toxicities (8, 9) and similar pCR rates(10). Thus, based on available published data,

the standard treatment of LARC patients with non-metastatic cancers includes preoperative CRT with concurrent fluoropyrimidine, total mesorectal excision (TME), and postoperative adjuvant chemotherapy(4). However, fundamental issues such as poor compliance with adjuvant therapy(11) remain unresolved. Hence, neoadjuvant chemotherapy's extending strategy in rectal cancer remains an ever-evolving subject in clinical research.

Due to rectal cancer's unique anatomical characteristics, radiotherapy and chemotherapy have always been the focal points of therapeutic management. Meanwhile, some clinical trials have reiterated neoadjuvant chemotherapy's utility, such as CapeOx or FOLFOX, with satisfactory therapeutic management and improved treatment tolerance(12, 13). Unfortunately, there are substantial little effects on overall survival (OS) despite various treatment types eradicating micro-metastases.

Clinically, patients receiving neoadjuvant CRT therapy typically have delayed surgery (usually for 6–8 weeks) due to radiation-induced pelvic fibrosis and tissue edema. The delay, which leads to progressive disease (PD), potentially increases the operation's technical difficulty and the risk of surgical complications. Hence, the extensive study by experts on chemotherapy's addition (preoperative chemoradiation and definitive surgery)(14).

Therefore, based on the above background knowledge, our center proposed a “Sandwich” neoadjuvant approach where each enrolled patient would receive induction chemotherapy (CRT sequential consolidation chemotherapy) before TME surgery. The trial aims to: (i) investigate the effect of delivering two cycles of CapeOx induction chemotherapy, followed by (ii) capecitabine-based concurrent CRT, and (iii) one cycle of CapeOx additional chemotherapy between chemoradiation and surgery. The primary endpoint is a 5-years disease-free survival (DFS). This trial was registered with ClinicalTrials.gov, number NCT02022852.

Method

2.1 Patients

The study (No. NCT02022852) is a single-center, open-label, non-randomized trial, phase Ⅱ study with a similar design. Patient were non-randomly assigned (1:1) to receive capecitabine-based concurrent CRT (Arm A) and induction chemotherapy (Sandwich therapy) (Arm B). All the patients received TME after completing preoperative treatment. The same surgical team carried out the surgeries. The hospital central ethics committee approved the study protocol. All participants provided written informed consent. The study was conducted following the principles of the Declaration of Helsinki and Good Clinical Practice.

Eligible patients were between the ages of eighteen and seventy-five with a diagnosis of rectal adenocarcinoma suitable for radical resection. Cancer was clinically confirmed by magnetic resonance imaging (MRI) as cT3-4 Nx M0 and a distal border located<10 cm from the anal verge. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 and an adequate hematologic, liver, and renal function. Critical exclusion criteria were a metastatic disease, prior

radiotherapy or chemotherapy, clinically significant cardiac disease, known peripheral neuropathy, and other cancer types. After surgery, diagnostic thoracic and abdominopelvic computed tomography (CT) should be performed every 6-months for 5-years. The follow-up time was from the trial date to July 2020.

2.2 Preoperative treatment

In the study, enrolled patients were non-randomly assigned in parallel (1:1) to receive two treatment types. Patients in arm A received capecitabine-based concurrent CRT before TME surgery. The preoperative treatment included radiotherapy 2Gy/day (per fraction) five times a week (continued 5-weeks for a total dose of 50 Gy in 25 fractions) while simultaneously taking oral capecitabine 850/m^2 twice a day from the date of initial radiotherapeutic management. In arm B, patients received sequential therapy as induction CapeOx (oxaliplatin + capecitabine) for two cycles (repeat every 3 weeks), followed by 25 fractions CRT, finally adding one consolidation CapeOx cycle.

2.3 Surgery and adjuvant therapy

TME surgery was performed for arm A patients 8-weeks after completing CRT. In contrast, surgery was carried out for 3-weeks for patients in arm B after completing all sequential therapy. The same surgical team performed the TME for both arm groups with a complete radical surgical resection (R0). Adjuvant therapy began 4–6 weeks after surgery. In arm A, patients received six postoperative adjuvant CapeOx treatment cycles, while patients in arm B received only three cycles of postoperative adjuvant CapeOx.

2.4 Study measurement and endpoint

The study's primary endpoint was 5-year DFS, which was defined as the time between the random assignment and local recurrence, metastasis, or death. The second endpoints were 5-years OS, pCR, and postoperative complications. All surgical specimens were carried out following a standardized protocol, which includes TNM classification based on the sixth edition of the American Joint Committee on Cancer (AJCC). Two senior pathologists evaluated all specimens. PCR was considered as no viable tumor cells in both lymph nodes and the primary tumor.

2.5 Statistical analysis

The 5-year OS and DFS was calculated using the Kaplan–Meier method. The $\chi 2$ test was used to compare clinicopathological parameters. All statistical tests were two-sided. Significance was set at $P < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences Program (SPSS Inc. Chicago, IL, USA, Version 25).

Results

3.1 Patients characteristics

At first, 172 patients were enrolled between July 2013 and July 2015. In arm A, eight patients were excluded from the trial due to toxicities (9.4%), while twelve patients entirely quit the trial for subjective

reasons. However, in arm B, eleven patients were excluded from the therapy due to toxicities (12.8%), while seven patients entirely quit the trial for subjective reasons. A total of 61 patients in arm A (70.9%) and 63 patients in arm B (73.2%) completed the treatment regimen (**Table 1 and Fig. 1**). As a result of extended preoperative therapy, patients in arm B had excellent therapeutic compliance and a higher degree of completed postoperative therapy than patients in arm A. Finally, patients' detailed clinicopathological parameters shown in the **Table 2.**

Table 1
Patients exclusion data.

Event*	Treatment Group, No. (%)	
	Arm A	Arm B
No. of patients	86	86
PD	3 (3.5)	3 (3.5)
Palliative surgery	2 (2.3)	2 (2.3)
Toxicity	8 (9.4)	11 (12.8)
Obstruction	1 (1.2)	2 (2.3)
Blood	0	1 (1.2)
Perforation	1 (1.2)	0
Hematological	5 (5.8)	6 (7.0)
Radiation dermatitis	1 (1.2)	2 (2.3)
Subjectivity	12 (13.9)	7 (8.2)
Refused surgery	2 (2.3)	3 (3.5)
Refuse adjuvant CT	2 (2.3)	1 (1.2)
Non-finish adjuvant CT	8 (9.3)	3 (3.5)
Finish	61 (70.9)	63 (73.2)
Abbreviations: PD, progressive disease; CT, chemotherapy.		

Table 2. Patients clinical characteristics

Characteristics	Treatment Group, No. (%)	
	Arm A	Arm B
No. of patients	61	63
Mean Age, years	59.4±11.3	49.5±10.2
Male sex		
Male	44 (72.1)	53 (84.1)
Female	17 (27.9)	10 (15.9)
Clinical T category		
cT3	31 (50.8)	43 (68.3)
cT4	30 (49.2)	20 (31.7)
Clinical N category		
cN0	32 (52.5)	37 (58.8)
cN1	13 (21.3)	13 (20.6)
cN2	16 (26.2)	13 (20.6)
Mean distance from anal verge, cm (SD)	4.1±1.4	4.8±2.0
0-5	34 (55.7)	28 (44.4)
5-10	27 (44.3)	35 (55.6)

Abbreviation: SD, standard deviation.

3.2 Surgery and histopathology

Patients who received TME in both arms had a similar operation (170 ± 60.4 vs. 163.2 ± 53.4, $P = 0.521$) (**Table 3)**. The hospital time did not show a significant difference between the two groups ($P = 0.370$). Due to the varying distance in the anal verge, surgeons apply optimal surgical resections for rectal cancer patients. Notwithstanding, there were no apparent differences in surgical procedures ($P = 0.079$). Although, patients in arm B had a higher postoperative complication than patients in arm A (17.5% vs. 4.9%, $P = 0.027$). **Table 4** showed no significant differences in the pCR rate in both arms; nonetheless, arm A had a similar rate with arm B (21.3% vs. 19.0%, $P = 0.159$). The was also no statistical difference in the postoperative histopathology parameters in both arms.

Table 3
Parameters related with surgery and postoperative metastasis site

Variables	Treatment Group, No. (%)		
	Arm A	Arm B	P
No. of patients	61	63	
Mean operation time, minute (SD)	170 ± 60.4	163.2 ± 53.4	0.521
Hospital stay, day (SD)	13.1 ± 4.0	12.6 ± 4.6	0.370
Operative procedure			0.079
Dixon	23 (37.7)	32 (50.8)	
Mile	32 (52.5)	30 (47.6)	
Hartman	6 (9.8)	1 (1.6)	
Complication	3 (4.9)	11 (17.5)	0.027
Metastasis			
None	39 (64.0)	47 (74.6)	0.470
Lung	10 (16.4)	6 (9.5)	
Liver	10 (16.4)	7 (11.1)	
Relapse	1 (1.6)	2 (3.2)	
Bone	0	1 (1.6)	
Brain	1 (1.6)	0	

Abbreviation: SD, standard deviation.

Table 4
Summary of treatment outcome

Variable	Treatment Group, No. (%)		
	Arm A	Arm B	P
No. of patients	61	63	
ypT			0.159
pCR	13 (21.3)	12 (19.0)	
T1	1 (1.6)	1 (1.6)	
T2	4 (6.6)	14 (22.2)	
T3	40 (65.6)	32 (50.8)	
T4	3 (4.9)	4 (6.4)	
ypN			0.817
N0	44 (72.1)	47 (74.6)	
N1	9 (14.8)	10 (15.9)	
N2	8 (13.1)	6 (9.5)	
PNI	8 (13.1)	8 (12.7)	0.945
LVI	4 (6.6)	4 (6.3)	0.962
TD	12 (19.7)	6 (9.5)	0.109
Abbreviations: PNI, perineural invasion; LVI, lymphovasctdar invasion; TD, Tumor Deposits			

3.3 Survival and outcome

The 5-year OS for arm A and arm B was 67.2% and 76.2%, respectively. On the other hand, the 5-year DFS for arm A and arm B was 63.9% and 74.6%, respectively. Overall, arm B's survival rate was always higher than arm A ($P > 0.05$) **(Fig. 2)**. The metastasis trend of postoperative patients did not show a significant difference between the two arms ($P > 0.05$) **(Table 3)**.

Discussion

As reported by Sauer et al, CRT is becoming as a standard treatment method for rectal cancer patients (4, 15). The result of these articles shows that CRT could improve the local control rate and sphincter preservation rate, although with no survival benefit. As we know, two conditions should be satisfied for popularizing of new technology in the field of tumor treatment, great survival rate and high quality of life. So that, there is a question why CRT can acquire excellent local control, without improving the patients'

OS time. Compared with CRT patients, patients done the novel sandwich therapy which has a significantly great compliance and a better survival time.

A tumor is always considered a systemic disease, and published reports have shown that CRT efficiently controls local status, although it cannot prevent distant metastasis. It is generally known that chemotherapy is an effective method to inhibit metastasis. Thus, we design a clinical trial that includes chemotherapy (before and after CRT). The treatment style aims to eliminate micro-metastasis and deceased distant metastasis rate, which also means a higher pCR rate. Significantly, adding chemotherapy helps extend OS. In this trial, arm A (canonical CRT) was regarded as the control group, while arm B (Sandwich therapy) an observation group to evaluate the therapeutic management of rectal cancer. The final statistics concerning patients who finished the entire treatment regimen were analyzed to assess the advantages and disadvantages of the two treatment styles.

With the advances in technology and the gradual widespread application of CRT, rectal cancer local relapse had been efficiently controlled, although OS and DFS remain unimproved(16). In a phase-II trial, patients received different extra cycles of mFOLFOX6 between CRT and TME, a safe approach to acquiring longer DFS and high pCR rates (17). On the other hand, induction chemotherapy was added before the CRT and compared with the “no-induction chemotherapy group.” The 5-year DFS and OS was similar in the two groups (64% vs. 62%, 78% vs. 75%) (13). This trial shows that sandwich therapy mode may provide an extra benefit for patients’ survival with a longer survival time than the canonical CRT group, with no statistical.

The second endpoint of the trial is the pCR. Unfortunately, in arm B, the sandwich mode did not improve the pCR rate than arm A. Other research reported that one-cycle induction capecitabine, standard CRT, and two-cycle consolidation chemotherapy did not significantly improve the pCR rate than standard CRT (18). Relatively, Garcia et al. conducted a phase-II trial where patients underwent surgery at different weeks after CRT. After adding different cycles of consolidation chemotherapy, the pCR rate increased (14).

Herein the following text, we explain the advantages of sandwich therapy. First, arm B patients had an added advantage of therapeutic extension (particularly adjuvant therapy) compared to patients in arm A. As reported in other research, they had a different conclusion that patients who received induction chemotherapy before CRT might have reduced compliance with consolidation therapy (19). Second, arm B patients received more Dixon surgery than arm A. Thus, this might mean sandwich therapy improved the degree to which the anal sphincter muscle was protected. As validated by Ishihara et al, the laparoscopic TME following CRT was safe and feasible, even if CRT impairs tissue delamination (20). From Table 3, operation time and hospital time did not show a significant difference between the two arms. Hence, the result shows that sandwich therapy might alleviate the technical difficulties of surgery, whereas improving overall postoperative outcome.

Relatively, sandwich therapy enhanced the entire patients' compliance and did not increase TME difficulty, which leaves us wondering: is there an additional treatment risk? In this analysis, sandwich therapy brought more therapeutic toxicities than canonical CRT. On the other hand, patients who received

sandwich therapy might have more postoperative complications than arm A. Quezada et al. (21) reported that different preoperative therapy (CRT, neoadjuvant therapy, and TNT) did not impair patients bowel function after TME. However, sandwich therapy mode remarkably raised patients' compliance, positively affecting contradiction between doctors and patients'.

At present, total neoadjuvant therapy (TNT) model can be divided into two types: neoadjuvant chemotherapy (NAC) followed by CRT or CRT followed by NAC, due to the different sequence of chemotherapy and CRT(22), rarely reports about Sandwich therapy type. In our analysis, this novel sandwich therapy model benefits for not only patients who own risk of sphincter preservation but also the patients vulnerable to occur distant metastasis. Limit to single institution, our trail can't obtain ideal result. The small sample size may lead error to the final result that is unavoidable. In the other side, non-randomized trial of chosen treatment type is effected by clinicians and patients' subjectivity wills that may have a certain deviation. In the future, treatment mode of rectal cancer in the perioperative period will be diversified that optimal treatment type is obviously important for CRC patients. It's maybe a good choice to suggest the "sandwich therapy" to rectal cancer patients. Certainly, the definite therapeutic effect still need to be confirmed by follow-up trails.

Conclusion

This study indicated that sandwich therapy may lead more postoperative complications than conventional CRT. Then, sandwich therapy doesn't show significant advantage in survival compared with conventional CRT. The safety and mode of sandwich therapy still need further research.

Declarations

Authors' contributions

Y-LL and B-BC: study concept and design. T-YX and Y-LL: acquisition of data. P-H, B-MZ, C-XS, X-YG, W-NX and Y-YW: analysis and interpretation of data. T-YX and Y-LL: drafting of the manuscript. B-BC: critical revision of the manuscript for important. T-YX and Y-LL: statistical analysis.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Conflicts of interest

All the authors declare that there is no conflict of interest

Ethical Statement and consent to participate

This study's Clinical trials number is NCT02022852 and first posted on 30/12/2013.The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The design and conduct of the study are in accordance with the Declaration of Helsinki and Chinese regulations. Ethics committee of Harbin medical university cancer hospital has approved the study protocol (ID number KY2016-19). All participants provided written informed consent.

Consent for publication

Not applicable.

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Figures

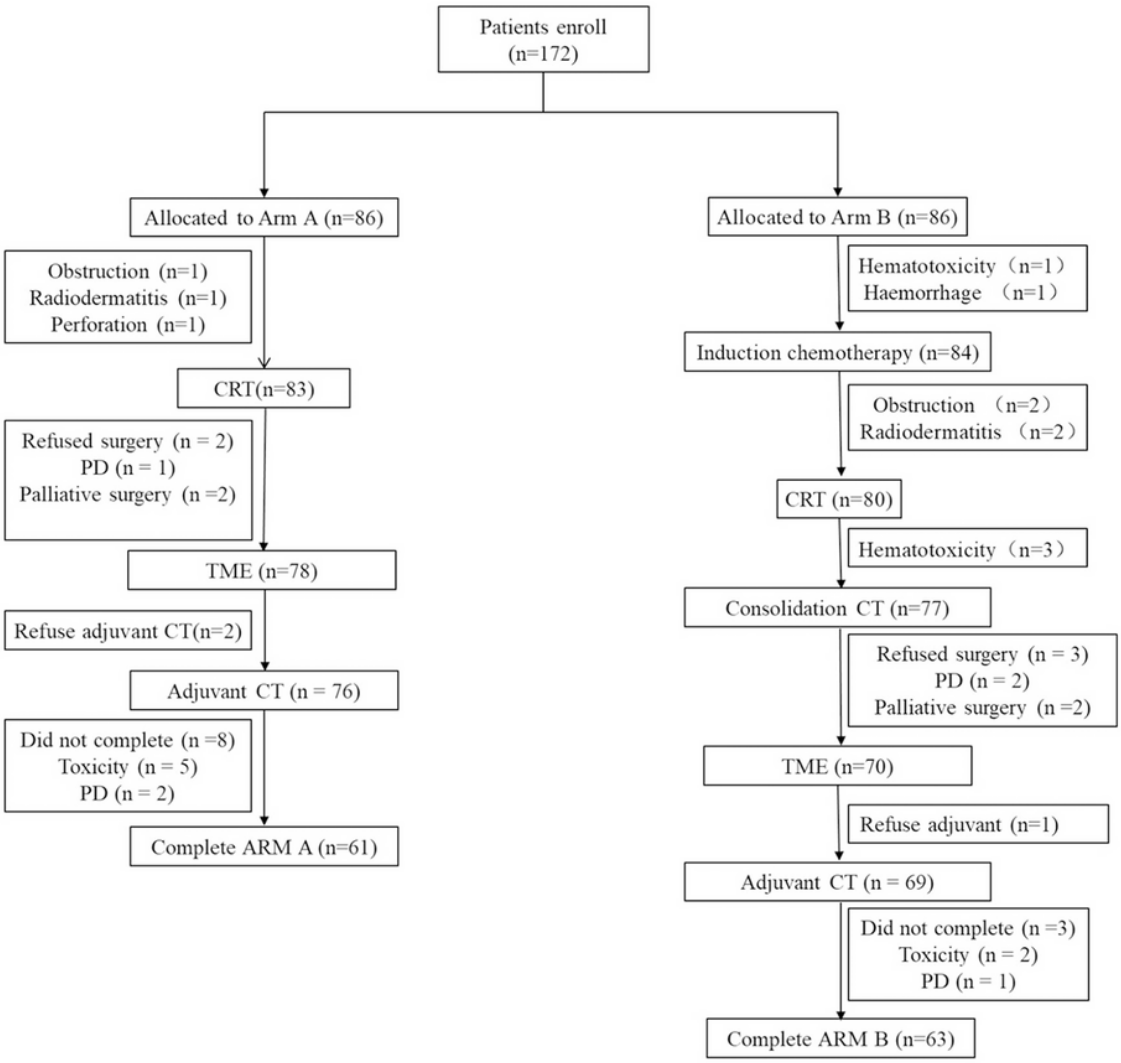

Figure 1

The flow chart of trial

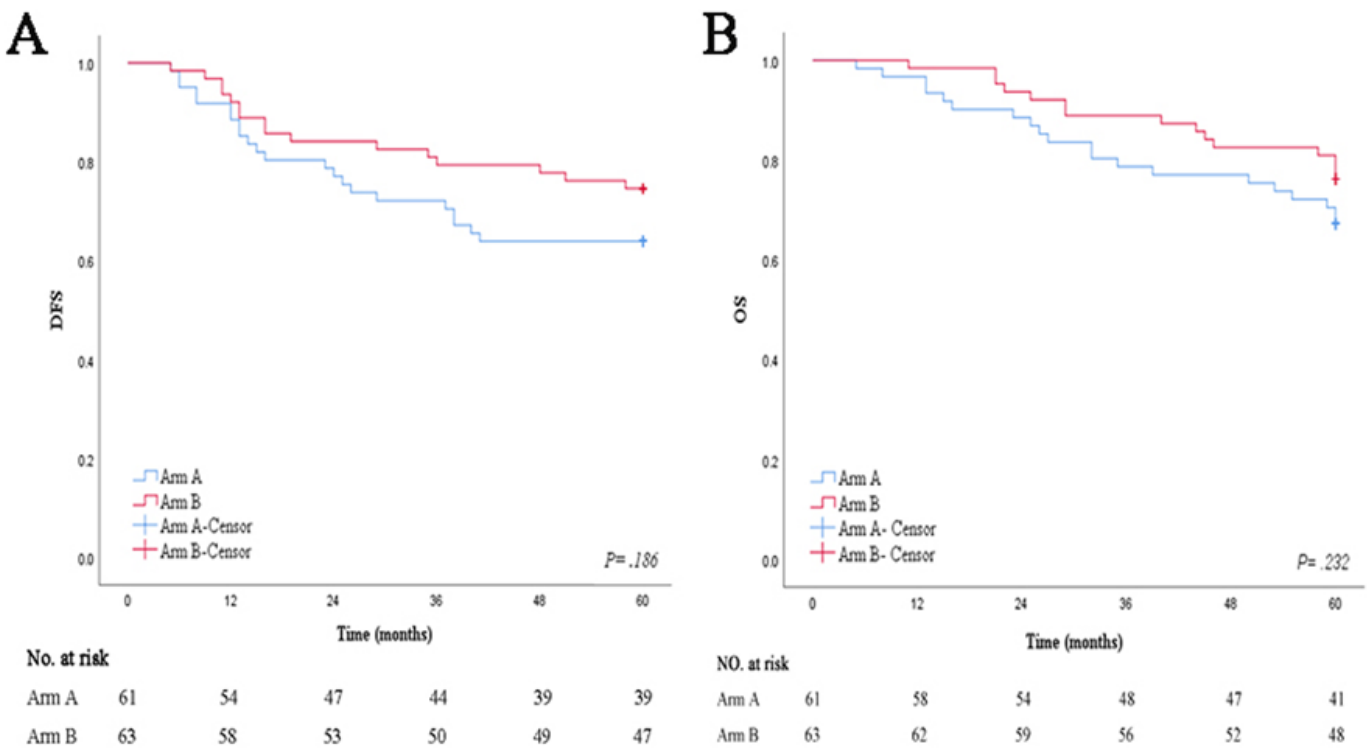

Figure 2

The Kaplan-Meier survival curves (A) 5-years DFS; (B) 5-years OS.