Reevaluation of Oral Adjuvant Chemotherapy for T3 Lower Rectal Cancer: A Multicenter Collaborative Retrospective Cohort Study

Hidejiro Kawahara (kawahide@outlook.jp)
Kokuritsu Byoin Kiko Nishisaitama Chuo Byoin https://orcid.org/0000-0002-8618-1556
Masaichi Ogawa
Tokyo Jikeikai Ika Daigaku Katsushika Iryo Center
Katsuhito Suwa
Tokyo Jikeikai Ika Daigaku Fuzoku Daisan Byoin
Ken Eto
Tokyo Jikeikai Ika Daigaku Fuzoku Byoin Honin

Research

Keywords: oral adjuvant chemotherapy, lower rectal cancer, intensive chemotherapy disease free survival

Posted Date: August 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-61717/v1

Abstract

Aim: This study aimed to evaluate the usefulness of oral adjuvant chemotherapy (OAC) for T3 lower rectal cancers without lateral lymph node metastasis.

Methods: Between 2010 and 2014, 110 patients with T3 lower rectal cancer without lateral lymph node metastasis, 80 years of age or younger, who underwent curative resection at four Jikei University Hospitals were enrolled in this retrospective study. Of these, 94 patients underwent neither preoperative chemoradiotherapy (CRT) nor intensive chemotherapy after surgery: 47 patients who did not receive OAC for a pathological diagnosis of stage II cancer and 47 patients who did receive OAC for a pathological diagnosis of stage III cancer. The remaining 16 patients received intensive oxaliplatin-based combination chemotherapy after surgery without preoperative CRT.

Results: The 5-year disease-free survival (DFS) of the 47 patients in stage II was 82.6%, whereas that of the 63 patients in stage III was 63.1% (p=0.033). The 5-year DFS of the 16 patients who received intensive chemotherapy after surgery was 81.3%, which was similar to the DFS of stage II patients, whereas that of the 47 patients with OAC alone was 58.2% (p=0.048).

Conclusion: Intensive oxaliplatin-based combination chemotherapy after surgery was better for 5-year DFS than OAC among stage III patients. OAC is not suitable as adjuvant chemotherapy for patients with stage III lower rectal cancer even if no lateral lymph node metastasis is detected.

Introduction

Postoperative adjuvant chemotherapy is systemic chemotherapy that is performed after surgery to prevent recurrence and improve the prognosis of patients who have undergone R0 resection [1]. In the Japanese Society for Cancer of the Colon and Rectum Guidelines 2010 [2], the indications for systemic adjuvant chemotherapy are as follows: (1) stage III colorectal cancer (colon and rectal cancer) for which R0 resection has been performed; (2) maintenance of the function of major organs, bone marrow, liver function, and renal function; and (3) patients who have stage II colorectal cancer with a high risk of recurrence. Recommended therapies covered by Japanese National Health Insurance are as follows: (1) 5-fluorouracil (5-FU) + levofolinate calcium (l-LV), (2) tegafur uracil (UFT) + calcium folinate (LV), (3) capecitabine, and (4) infusional 5-fluorouracil and folinic acid plus oxaliplatin (FOLFOX4 or mFOLFOX6). In principle, the recommended administration period is 6 months. In our institutions, patients with T3 rectal cancer undergo adjuvant chemotherapy according to the guidelines. However, the usefulness of oral adjuvant chemotherapy (OAC) for T3 lower rectal cancers without lateral lymph node metastasis has not been elucidated.

Methods

The Ethics Committee for Biomedical Research of the Jikei Institutional Review Board approved the protocol of this study [30-249(9270)]. Between 2010 and 2014, 110 patients with T3 lower rectal cancer

without lateral lymph node metastasis, 80 years of age or younger, who underwent curative resection at four Jikei University Hospitals were enrolled in this retrospective study. Of these patients, 94 underwent neither preoperative CRT nor intensive chemotherapy after surgery: 47 patients who did not receive OAC for a pathological diagnosis of stage II cancer and 47 patients who did receive OAC for a pathological diagnosis of stage III cancer. The remaining 16 patients received intensive chemotherapy after surgery without preoperative CRT (Table I). All patients (n=110) underwent total mesorectal excision (TME) with bilateral autonomic nerve preservation without lateral pelvic lymph node dissection. Disease-free survival (DFS) and the received treatments were retrospectively compared between groups. The medical records of all patients were reviewed and classified according to the Japanese Classification of Colorectal Carcinoma [3]. According to this classification, T3 corresponds to invasion of the subserosa.

Oral adjuvant chemotherapy after surgery

For 6 months after surgery, patients with stage III disease (n=47) received oral S-1 (Taiho Pharmaceuticals Co., Ltd., Tokyo, Japan) or capecitabine (Xeloda; Hoffmann-La Roche, Basel, Switzerland), whereas patients with stage II disease (n=47) received no adjuvant chemotherapy.

Intensive chemotherapy after surgery

The intensive chemotherapy group (n=16) received oxaliplatin-based combination regimens (infusional 5-fluorouracil and folinic acid plus oxaliplatin [FOLFOX], S-1 (Taiho Pharmaceuticals Co., Ltd., Tokyo, Japan) plus oxaliplatin [SOX], capecitabine plus oxaliplatin [CapeOX]) for 6 months after surgery.

Treatment schedule

All patients were followed for 5 years; during this period, physical examinations, routine blood analyses, and serum CEA measurements were conducted every two months after surgery. CT was performed every 6 months or when a patient's serum CEA value was higher than the normal level of 5.0 ng/ml. Colonoscopy was performed every year or when a stool sample was positive for blood. Positron emission tomography (PET) or PET/CT was occasionally employed to detect occult metastasis for patients who had equivocal conventional imaging studies.

Statistical analysis

Continuous variables are expressed as the mean and range. The Wilcoxon rank-sum test was used for the comparison of continuous variables, and a chi-squared test was used for the comparison of categorical data. DFS after surgery was examined by the Kaplan-Meier method and by log-rank analysis. Variables affecting postoperative recurrence were analyzed using the Cox proportional hazards regression. A *p*-value of less than 0.05 indicated significance. All data were analyzed with IBM SPSS Statistics, version 24.0 (IBM Japan, Ltd, Tokyo, Japan).

Results

Comparison of DFS between stage II rectal cancer and stage III rectal cancer

Significant differences were identified in only lymphatic invasion (Table 2). The 5-year DFS of the 47 patients in stage II was 82.6%, whereas that of the 63 patients in stage III was 63.1% (p=0.033) (Figure 1).

Comparison of DFS between the intensive and oral adjuvant chemotherapy groups

Significant differences were identified in only the recurrence sites (Table 3). Local recurrence and lymph node metastasis after surgery were not identified in the intensive chemotherapy group, whereas 6 patients with local recurrence (13%) and 2 patients with lymph node metastasis (4%) were found in the OAC group postoperatively. The 5-year DFS of the 16 patients who received intensive chemotherapy after surgery was 81.3%, which was similar to the DFS of stage II rectal cancer, whereas that of the 47 patients who received oral adjuvant chemotherapy after surgery was 58.2%, (p=0.048) (Figure 2).

Cox proportional hazards regression for postoperative recurrence

To determine the variables affecting postoperative recurrence, 5 variables (age, gender, type of adjuvant chemotherapy, number of lymph node metastases, and surgical approach) were analyzed using Cox proportional hazards regression. Only type of adjuvant chemotherapy was identified independent contributing factors to postoperative recurrence (p=0.049). The intensive chemotherapy reduced the postoperative recurrence risk to approximately 40% of the hazard ratio in the OAC group (Table 4).

Discussion

Between 1990 and 2004, postoperative chemotherapy with leucovorin (LV)-modulated 5-fluorouracil (5-FU + l-LV) was the standard of care for stage III colon cancer, based on a 26% relative reduction in mortality with respect to that of surgery alone [4]. The oral fluoropyrimidine capecitabine and S-1 can be effective alternatives to 5-FU + l-LV as adjuvant chemotherapy. In a randomized phase III study of capecitabine vs bolus 5-FU + l-LV (Mayo Clinic regimen), capecitabine showed an equivalent DFS to 5-FU + l-LV and was associated with significantly fewer adverse events [5]. UFT + LV and capecitabine showed non-inferiority to 5-FU + 1-LV [6]. S-1 showed non-inferiority to UFT + LV [7]. Thus, OAC has been considered the gold standard of care as adjuvant chemotherapy for stage III colorectal cancer in Japan since then.

In 2004, the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial demonstrated that the addition of oxaliplatin to 5-FU + l-LV improved both DFS and OS in patients with stage III colon cancer [8]. Oxaliplatin-based combination regimens such as FOLFOX, SOX, and CapeOX have been considered the gold standard care as adjuvant chemotherapy for stage III colorectal cancer in Japan since 2004. However, the usefulness of OAC for T3 lower rectal cancers without lateral lymph node metastasis has not been elucidated.

In this study, the 5-year DFS of the intensive oxaliplatin-based combination chemotherapy group after surgery was 81.3%, which was similar to the DFS of patients with stage II rectal cancer who received no

adjuvant chemotherapy. Meanwhile the 5-year DFS of the OAC group after surgery was 58.2%. Significant differences were found between the two groups (p = 0.048). Furthermore, intensive chemotherapy reduced the postoperative recurrence risk to approximately 40% of the hazard ratio in the OAC group according to Cox proportional hazards regression analysis. Some large-scale randomized controlled trials have reported that oxaliplatin-based combination therapy for patients with stage III colon cancer was associated with a significant reduction in the risk of recurrence and an improved prognosis compared with those of 5-FU + l-LV, which was comparable to OAC [9, 10].

The most adverse event among patients who receive oxaliplatin combination therapy is the greater incidence of sensory peripheral neuropathy than that for OAC. The incidence of sensory peripheral neuropathy was significantly lower in a 3-month administration group than in the 6-month administration group [11]. In the ACHIEVE trial, the postoperative recurrence rate of a 3-month CapeOX-administered group was similar to that of the 6-month administered group, especially in patients with a low risk of recurrence. The 3-year DFS of the 3-month and 6-month administration groups were also similar [12]. The optimal oxaliplatin administration period as adjuvant therapy is still debated.

In conclusion, oxaliplatin combination intensive chemotherapy after surgery was better for 5-year DFS than OAC in stage III colorectal cancer. OAC is not suitable as adjuvant chemotherapy for patients with stage III lower rectal cancer even if no lateral lymph node metastasis is detected.

Abbreviations

OAC: Oral adjuvant chemotherapy; CRT: Preoperative chemoradiotherapy; DFS: Disease-free survival; TME: Total mesorectal excision; FOLFOX: Infusional 5-fluorouracil and folinic acid plus oxaliplatin; SOX: S-1 plus oxaliplatin; CapeOX: Capecitabine plus oxaliplatin; PET: Positron emission tomography; LV: Leucovorin; MOSAIC: Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer

Declarations

Ethics approval and consent to participate

The Ethics Committee for Biomedical Research of the Jikei Institutional Review Board approved the protocol of this study [30-249(9270)]. Individual patient consent is not required.

Consent for publication

There is no use of details, images, or videos relating to an individual person.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no competing interests.

Funding

None.

Authors' contributions

HK: Study design, data collection, statistical analysis, manuscript redaction. MO, KS, and KE: Data collection and manuscript redaction. All authors read and approved the final manuscript.

Acknowledgements

None.

Author details

[1]Department of Surgery, Kashiwa Hospital, the Jikei University School of Medicine, Chiba, Japan.

[2]Department of Surgery, Katsushika Medical Center, the Jikei University School of Medicine, Tokyo, Japan

[3]Department of Surgery, the Third Hospital, the Jikei University School of Medicine, Tokyo, Japan

[4]Department of Surgery, the Jikei University School of Medicine, Tokyo, Japan

References

1. National Institute of Health Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990;264: 1444–1450.
2. Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol. 2012;17(1):1–29. doi:10.1007/s10147-011-0315-2. Epub 2011 Oct 15. PMID: 22002491.
3. Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma, 2nd English edn. Tokyo:Kanehara Co. Ltd; 2009.
4. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol. 2004;22:1797–806.
5. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352:2696–704.
6. Shimada Y, Hamaguchi T, Mizusawa J, et al. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levo– folinate in

patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer. 2014 Sep;50(13):2231–40.

7. Yoshida M, Ishiguro M, Ikejiri K, et al. S–1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS–CC trial). Ann Oncol. 2014 Sep;25(9):1743–9.
8. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350:2343–51.
9. André T, Boni C, Mounedji-Boudiaf L, et al. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004 Jun;3(23):2343–51. 350(.
10. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011 Apr;10(11):1465–71. 29(.
11. Kotaka M, Yamanaka T, Yoshino T, et al. Safety data from the phase III Japanese ACHIEVE trial: part of an international, prospective, planned pooled analysis of six phase III trials comparing 3 versus 6 months of oxaliplatin–based adjuvant chemo– therapy for stage III colon cancer. ESMO Open. 2018 Apr 24;3(3):e000354.
12. Grothey A, Sobrero AF, Shields AF, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. N Engl J Med. 2018 Mar;29(13):1177–88. 378(.

Tables

Table 1 Charactaristics of all patients

Characteristic	n=110
Mean age (range), years	65.2 (36 - 80)
Gender, n (%)	
Male	69 (63)
Female	41 (37)
Mean tumor diameter (rang), mm	56.8 (14-108)
Pathology, n (%)	
Well differentiated adenocarcinoma	28 (26)
Moderately differentiated adenocarcinoma	73 (66)
Others	9 (8)
Lymphaic invasion, n(%)	
Negative	31 (28)
Positive	79 (72)
Venus invasion, n(%)	
Negative	36 (33)
Positive	74 (67)
Stage, n(%)	
	47 (43)
	63 (57)
Surgical procedure, n(%)	
Low anderior resection	65 (59)
Abdominoperineal resection	40 (36)
Intersphincteric resection	2 (2)
Hartmann operation	3 (3)
Surgical technique, n(%)	
Laparoscopic surgery	46 (42)
Open surgery	64 (58)
Recurrence site, n(%)	
Lung	20 (18)

Liver	10 (9)
Brain	2 (2)
Lymph node	2 (2)
Local	6 (5)

Table 2: Comparison of charactaristics between stage and stage

Characteristic	Stage (n=47)	Stage (n=63)	p value
Mean age (range), years	65.2 (36 - 80)	64.7 (36 - 80)	0.595
Gender, n (%)			0.416
Male	27 (57)	42 (67)	
Female	20 (43)	21 (33)	
Mean tumor diameter (rang), mm	55.4 (14-90)	57.8 (15-108)	0.670
Pathology, n (%)			0.426
Well differentiated adenocarcinoma	13 (28)	15 (24)	
Moderately differentiated adenocarcinoma	31 (66)	42 (67)	
Others	3 (6)	6 (9)	
Lymphaic invasion, n(%)			0.005
Negative	20 (43)	11 (17)	
Positive	27 (57)	52 (83)	
Venus invasion, n(%)			0.543
Negative	17 (36)	19 (30)	
Positive	30 (64)	44 (70)	
Surgical procedure, n(%)			0.965
Low anderior resection	27 (58)	38 (60)	
Abdominoperineal resection	18 (38)	22 (35)	
Intersphincteric resection	1 (2)	1 (2)	
Hartmann operation	1 (2)	2 (3)	
Surgical technique, n(%)			0.242
Laparoscopic surgery	23 (49)	23 (37)	
Open surgery	24 (51)	40 (63)	
Recurrence site, n(%)			0.308
Lung	6 (13)	14 (22)	
Liver	2 (4)	8 (13)	
Brain	1 (2)	1 (2)	
Lymph node	0 (0)	2 (3)	

Local	0 (0)	6 (10)

Table 3: Comparison of charactaristics between the intenstive and orl chemotherapy after surgery groups in stage

Characteristic	Intenstive therapy (n=16)	Oral chemotherapy (n=47)	p value
Mean age (range), years	60.5 (36 - 77)	66.2 (40 - 80)	0.055
Gender, n (%)			0.682
Male	10 (63)	32 (68)	
Female	6 (37)	15 (32)	
Mean tumor diameter (rang), mm	66.9 (20-100)	54.8 (15-108)	0.051
Pathology, n (%)			0.592
Well differentiated adenocarcinoma	5 (31)	10 (21)	
Moderately differentiated adenocarcinoma	9 (56)	33 (70)	
Others	2 (13)	4 (9)	
Lymphaic invasion, n(%)			0.590
Negative	4 (25)	7 (15)	
Positive	12 (75)	40 (85)	
Venus invasion, n(%)			0.403
Negative	3 (19)	16 (34)	
Positive	13 (81)	31 (66)	
Surgical procedure, n(%)			0.317
Low anderior resection	8 (50)	30 (64)	
Abdominoperineal resection	8 (50)	14 (30)	
Intersphincteric resection	0 (0)	1 (2)	
Hartmann operation	0 (0)	2 (4)	
Surgical technique, n(%)			1.000
Laparoscopic surgery	6 (38)	17 (36)	
Open surgery	10 (62)	30 (64)	
Recurrence site, n(%)			0.003
Lung	2 (13)	12 (26)	
Liver	2 (13)	6 (13)	
Brain	1 (6)	0 (0)	

Lymph node	0 (0)	2 (4)
Local	0 (0)	6 (13)

Table 4: Multivariate analyses using the Cox proportional hazard model for postoperative recurrence

Variable	Hazard Ratio (95% confidence interval)	P value
Age (years)		
70 ≦	1.188 (0.508 - 2.782)	0.691
﹥70	1	
Gender		
Female	1.179 (0.496 - 2.804)	0.709
Male	1	
Adjuvant chemotherapy		
Intenstive chemotherapy	0.415 (0.117 - 1.467)	0.049
Oral chemotherapy	1	
Number of lymph node metastases		
4 ≦	1.151 (0.475 - 2.788)	0.755
﹥4	1	
Surgical technique		
Laparoscopic surgery	0.599 (0.234 - 1.537)	0.287
Open surgery	1	

Figures

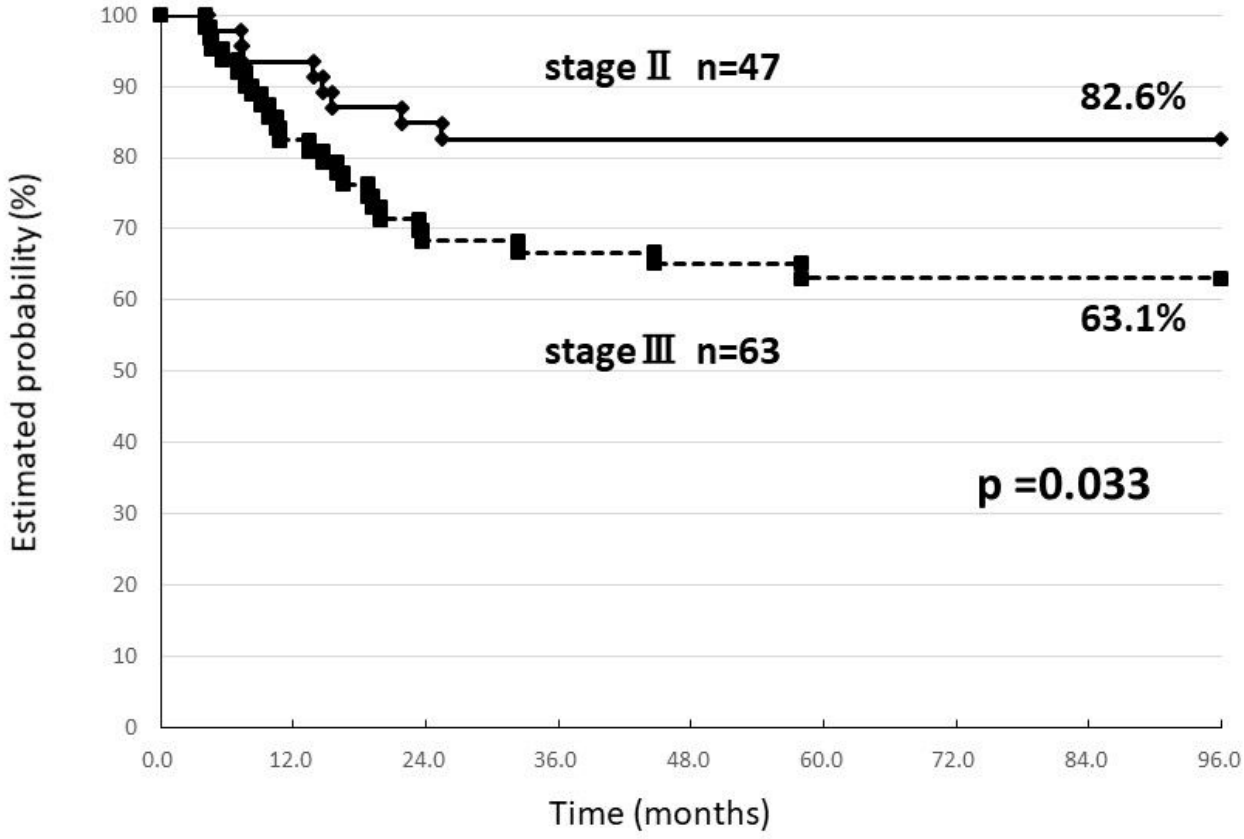

Figure 1

Comparison of DFS between stage II rectal cancer and stage III rectal cancer

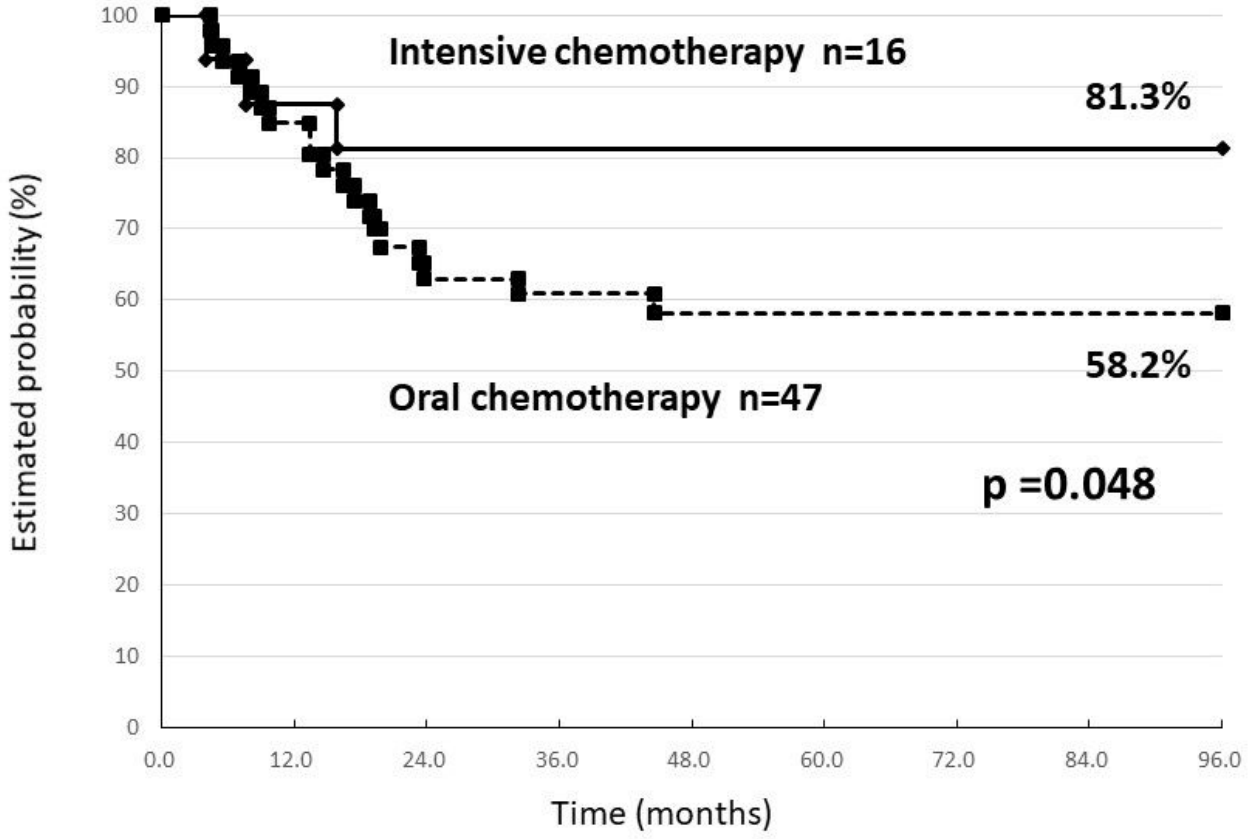

Figure 2

Comparison of DFS between the intensive and oral adjuvant chemotherapy groups