

Comparative Survival Effectiveness between Pre-operative and Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: A Retrospective Study in Phramongkutklao Hospital

Pyada Park MD*,
Pramook Phromratanapongse MD*, Supakajee Saengruang-Orn PhD*

* Department of Radiology, Phramongkutklao Hospital, Bangkok, Thailand

Background: In earlier years, postoperative chemoradiotherapy was a recommended standard treatment for locally advanced rectal cancer. Based on several clinical trials, the pre-operative approach was then considered a favorable optimal time to deliver the treatment due to significant improvement in local tumor control. Given that, both pre-operative and postoperative approaches were performed in Phramongkutklao Hospital.

Objective: This study compared 2-year disease-free survival (DFS) between pre-operative and postoperative chemoradiotherapy in locally advanced rectal cancer.

Material and Method: A retrospective study was conducted in 78 patients with clinical stage T3, T4 or node-positive disease who had received either pre-operative or postoperative concurrent chemoradiation that was carried out between 2004 and 2008. The combined multimodality approach consisted of Fluorouracil (5-FU) based chemotherapy and a long course of radiation therapy. After the last session of chemoradiotherapy in the pre-operative group, surgery was performed 4-6 weeks later followed by remaining cycles of chemotherapy whereas the postoperative group began chemoradiotherapy 4-6 weeks after surgery. The primary end point was 2-year disease-free survival (DFS).

Results: Of the eligible 78 patients, 19 patients (9 pre-operative, 10 postoperative) had recurrence during the first two years after completion of radiotherapy by which the first event of recurrence was classified as either local recurrence only, distant metastasis only, or both local and distant recurrence. The 2-year DFS between these two groups was not statistically different (78.6% pre-operative vs. 72.2% postoperative, $p = 0.521$), however, the pre-operative, concurrent chemoradiotherapy provided a possible DFS benefit. No statistical difference in overall toxic events between the two treatment groups; however, there is a tendency to develop more toxicity in the postoperative group.

Conclusion: No significant statistical difference in 2-year DFS between the pre-operative and postoperative but possible DFS benefit was suggested in pre-operative group.

Keywords: Locally advanced rectal cancer, Pre-operative chemoradiotherapy, Postoperative chemoradiotherapy

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Rectal cancer is known worldwide as the third most common cancer in both men and women with the expected estimation of 39,670 new cases in the United States (22,620 cases in men; 17,050 cases in women) in 2010⁽¹⁾. Early detection and improved treatment modalities of the rectal cancer contributed to decrease in mortality rate and increase in overall survival. According to Cancer in Thailand 2001-2003, newly registered cases during 2001 to 2003 were reported 5,694

cases nationwide; 3,135 men and 2,559 women⁽²⁾. The Phramongkutklao Cancer Registry Report 2009 included number of newly registered patients with rectal cancer in colorectal cancer group revealing a total of 164 patients; 99 men and 65 women⁽³⁾. In general, colorectal cancer can occur in both male and female at any age of adulthood; however, the risk of colorectal cancer increases at age 50 and older with higher incidence and mortality rate in men than in women⁽⁴⁾.

A multimodality approach has been widely accepted as a standard practice in patients with locally advanced rectal cancer (stage 2 and 3) during the past decades. The additional administration of radiotherapy and chemotherapy to the standard surgical resection

Correspondence to:

Park P, 14/67 Soi Chomrom 13, Chaengwattana Road 14 Kasetnived Village, Laksi, Bangkok 10210, Thailand.
Phone: 08-6305-4269
E-mail: pyadapark@yahoo.com

were established in the attempt to improve the treatment outcome. Initially, administration of concurrent chemoradiotherapy after surgery had been widely performed in potentially curative, locally advanced cases to improve both local control and overall survival as compared to surgery alone or surgery plus radiation. Several randomized trials investigated the optimal time to administer concurrent chemoradiotherapy in which the outcome favorably suggested pre-operative approach due to significantly improved local tumor control with associated reduction of toxicity events⁽⁵⁻¹³⁾. In the randomized study of Swedish Rectal Cancer Trial, a short course of pre-operative radiotherapy (25Gy in 1 week before curative surgery) for rectal cancer proved to reduce local recurrence rate and improve survival⁽¹⁴⁾. The German Rectal Cancer Group assigned the multimodality therapy in patients with clinical T3, T4 or node-positive disease to receive randomly either pre-operative or postoperative treatment. This prospective randomized trial concluded that the 5-year locoregional recurrence rate was significantly decreased in pre-operative arm (6% in pre-operative treatment vs. 13% in postoperative treatment, $p = 0.006$); whereas, no difference in improving overall survival between the two groups⁽¹⁵⁾.

Pre-operative concurrent chemoradiotherapy has potential advantage over postoperative chemoradiotherapy in several ways such as tumor down staging and better ionizing radiation response by which consequently improved resection rate and local control. The main disadvantage of the pre-operative treatment is the possible overtreatment of the early stage tumors due to unavailable histopathological information for accurate staging⁽¹⁾. Multimodality approach has been a standard practice in the treatment of locally advanced rectal cancer at Phramongkutklao Hospital. The Division of Radiation Oncology has provided supplemented radiation treatment to both neoadjuvant and adjuvant therapeutic approaches in respect to achieve effective local control. In the setting of Fluorouracil (5-FU) based chemoradiation, the present study was designed to compare the results of two treatment groups based on time of multimodality approach in addition to curative surgery.

Objective

To compare the effectiveness of pre-operative chemoradiotherapy versus postoperative chemoradiotherapy in locally advanced rectal cancer patients in Phramongkutklao Hospital; the primary end point was

disease-free survival (DFS) and the secondary end points were local and distant recurrence rates including toxic events of combined multimodality treatment.

Material and Method

The medical records of patients with clinical stage T3, T4 or node-positive disease who visited the Division of Radiation Oncology, Phramongkutklao Hospital from 2004 to 2008 were reviewed and stratified into two groups based on the approach time of chemoradiotherapy in addition to curative surgery: pre-operative, concurrent chemoradiation group and postoperative, concurrent chemoradiation group. Eligible patients from both groups included histopathological confirmation of adenocarcinoma, TNM stage 2/3 without evidence of known metastasis, no other associated malignancy, and no prior history of pelvic radiation or surgery for other treatment. Primary source for TNM staging was based on American Joint Committee on Cancer (AJCC) at the time of diagnosis⁽¹⁾. Both groups must be given with combined modality treatment of both 5-FU based chemotherapy and radiotherapy to the whole pelvis. The patients from pre-operative group initially received concurrent chemoradiotherapy followed by surgery 4-6 weeks after completion then adjuvant chemotherapy was administered to complete the regimen. In patients who were assigned to postoperative treatment, chemoradiotherapy was delivered 4-6 weeks after surgery then followed by adjuvant chemotherapy to complete the regimen. The eligibility criteria were listed in Table 1.

The usual radiation dose given in the pre-operative approach was 45 Gy (1.8-2.0 Gy/F) with or without additional tumor bed boost of 5.4 Gy in 3F after surgery in some cases whereas postoperative radiation dose was given a total of 50 Gy with or without tumor bed boost. The radiation was administered to isocenter of the pelvis using three or four-field box technique with or without cone-down boost. The simulation portal films and dosimetry data were reviewed and the radiation was delivered with either cobalt-60 or linear accelerator (Linac). The curative surgical methods of either lower anterior resection (LAR) or abdominoperineal resection (APR) were decided by surgeons in respect to the individual's appropriate approach.

Regular follow-up of at least first 2 years after completed radiotherapy with sufficient medical records of investigation and laboratory results was considered adequate for evaluation in the present study. Three-

Table 1. Lists of criteria for patient eligibility or ineligibility

Eligibility criteria	
1. Diagnosed of locally advanced rectal cancer (stage 2 or 3) without distant metastasis.	
2. Any age group and gender.	
3. No evidence of other previous or concomitant primary malignancy at the time of initial diagnosis.	
4. Histopathologic evidence of adenocarcinoma.	
5. No previous history of pelvic irradiation or major surgery.	
6. Patients who received concurrent chemoradiotherapy either for preoperative or postoperative treatment with 5-FU based regimen of chemotherapy.	
7. Patients who followed-up periodically at least first two years after completed treatment with documented investigation.	
Ineligibility criteria	
1. Diagnosed of stage 1 or 4 of rectal cancer.	
2. Patients who had received pelvic irradiation or any major surgical treatment in the pelvic cavity before diagnosis of rectal cancer.	
3. Patients with previous or concomitant primary malignancy at the time of initial diagnosis.	
4. Patients who received chemotherapy or immunotherapy prior treatment of rectal cancer.	
5. Patients who terminated treatment or uncompleted the protocol therapy for any reason before completion.	
6. Patients who lost follow-up during the first two years after completed treatment.	
7. Patients with proven malignant rectal tumor other than adenocarcinoma.	

Table 2. Characteristics of the eligible patients with locally advanced CA rectum at Phramongkutklao Hospital

Characteristics	Preoperative chemoradiotherapy (n = 42)	Postoperative chemoradiotherapy (n = 36)	p-value
Age			0.960
>50 years	36 (85.7%)	31 (86.1%)	
<50 years	6 (14.3%)	5 (13.9%)	
Range	32-87	29-74	
Median age	62	61	
Sex			0.630
Male	27 (64.3%)	25 (69.5%)	
Female	15 (35.7%)	11 (30.5%)	
Staging			0.181
Stage 2	25 (59.5%)	17 (47.2%)	
Stage 3	15 (35.7%)	19 (52.7%)	
Unknown	2 (4.7%)	0 (0%)	
Tumor histopathology			0.938
Well differentiated	9 (21.4%)	6 (16.6%)	
Moderately differentiated	27 (64.2%)	25 (69.4%)	
Poorly differentiated	1 (2.4%)	0 (0%)	
Unknown	5 (12.0%)	5 (13.9%)	

month intervals for the initial first two years then six-month intervals for the next three years has been recommended for routine follow-up. In general, the initial first two years of post-treatment surveillance included history and physical examination every 3-6 months, serial carcinoembryonic antigen (CEA) level every 3-6 months, colonoscopy in 1 year (except those who did not receive pre-operative colonoscopy due to lesion obstruction, colonoscopy is advised in 3-6 months), annual chest/abdominal/pelvic CT, and consideration

of proctoscopy every 6 months for patients status post LAR. Alternative surveillance may consider PET-CT in the setting of isolated CEA elevation with negative findings in other investigations. The toxicities resulted from protocol therapy were experienced in some patients from both treatment groups. Toxic events related to the treatment were collected based on adverse effect criteria called Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

The diagnosis of local recurrence within 2

Table 3. Results of two years of disease-related events after completed radiotherapy

	Preoperative Chemoradiotherapy (n = 42)	Postoperative Chemoradiotherapy (n = 36)	<i>p</i> -value
Recurrence or metastasis			0.528
Locoregional recurrence	2 (4.7%)	3 (8.3%)	
Distant metastases	7 (16.6%)	5 (13.8%)	
Locoregional recurrence with distant metastasis	0 (0%)	2 (5.5%)	
Expired	0 (0%)	0 (0%)	
Isolated CEA rising	2 (4.7%)	4 (11.1%)	0.652

Table 4. Toxic effects of concurrent chemoradiotherapy according to the time of therapeutic approach*

Type of toxic effect	Preoperative approach (n = 42)	Postoperative approach (n = 36)	<i>p</i> -value
Gastrointestinal effects	9 (21.4%)	12 (33.3%)	0.237
Bladder problems	5 (12.0%)	5 (13.8%)	1.000
Dermatologic effect	1 (2.4%)	4 (11.1%)	0.175
Hematologic effect	4 (9.5%)	3 (8.3%)	1.000
Anastomotic leakage	1 (2.4%)	2 (5.5%)	0.593
Stricture of anastomotic site	2 (4.7%)	1 (2.7%)	1.000
Fistula	0 (0%)	2 (5.5%)	0.210

* Some patients had more than one toxic effect

years after completed treatment relied on documented investigations such as clinically palpable mass, positive imaging, histopathological biopsy, and CEA elevation. The effectiveness of treatment outcome by comparing the optimal delivery time of the chemoradiotherapy was assessed by number and time to local recurrence and/or distant recurrence during the first two years of follow-up in each arm. The local recurrence (LR) was defined as time of recurrence after completion of combined therapy including surgery until local tumor recurrence was evident (such as anastomotic site, pelvic sidewall, surgical wound, or periregional areas). Those with recurrence outside the pelvic region or far in distance from the original tumor site were considered distant recurrence/metastasis of rectal cancer.

Statistical analysis

Analyses are based on accumulated numbers of eligible patients from both pre operative and postoperative groups who presented with recurrences during the initial first 2-year follow-up. Characteristics of the patients are presented as number and percentage in which Chi-square test or Fisher's exact test were used to compare proportions. To establish statistics of 2-year DFS curves between two groups, the Kaplan-

Meier method was used. A *p*-value less than 0.05 was considered statistically significant.

Results

Between 2004 and 2008, new cases of 182 patients with rectal cancer were reported to visit the division of Radiation Oncology at Phramongkutklo hospital for proper radiation treatment. As thoroughly reviewed from the past medical records, only 78 patients with clinical stage T3, T4 or node-positive disease with regular follow-up of at least first two years after complete radiotherapy were eligible for assessment. The patients received concurrent chemoradiotherapy for locally advanced rectal cancer of which 42 received preoperative treatment and 36 received postoperative treatment. A hundred and four patients were not included in the present study because they did not meet the inclusion criteria: 49 patients never completed a minimum 2 years follow-up or were lost to documented follow-up, 17 patients were referred from other hospitals for irradiation purposes only in Phramongkutklo hospital, 13 patients were stage 1 or 4 of disease, 9 patients terminated during the process of treatment, 5 patients had previous major pelvic surgery, and 4 did not have adenocarcinoma.

In the pre-operative therapy arm, 27 patients (64.3%) were male and 15 patients (35.7%) were female with median age of 62 years (range 32-87 years). The postoperative therapy arm included 25 male patients (69.5%) and 11 female patients (30.5%) with median age of 61 (range 27-74 years). All patients had proven pathological reports of adenocarcinoma by which the differentiation of tumor histopathology was graded as well differentiated, moderately differentiated, and poorly differentiated. The tumor histopathology in the pre-operative group showed 9 well-differentiated (21.4%), 27 moderately differentiated (62.2%), and 1 poorly differentiated (2.4%) tumors. Five patient medical records (12.0%) of the pre-operative group did not specify tumor differentiation. On the other hand, the postoperative group demonstrated 6 well-differentiated (16.6%) and 25 moderately differentiated (69.4%) tumors with no report of poorly differentiated tumor whereas no tumor differentiation was documented in 5 cases (13.9%).

The primary tumor extension, positive nodes or distant metastasis was classified based on TNM staging system. Only locally advanced rectal cancer stage 2 and 3 were assessed in both two-treatment groups. Twenty-five patients (59.5%) with stage 2, 15 patients with stage 3 (35.7%) and two remaining patients (4.7%) without specific TNM staging were observed in the pre-operative group. The latter two patients were referred as locally advanced rectal cancer without definable details of TNM staging. The postoperative group revealed 17 patients (47.2%) with stage 2 and 25 patients (69.4%) with stage 3. The characteristics of the eligible patients from both groups did not reveal significant statistical differences.

A regular follow-up during the first two years after completion of radiotherapy was required to assess the first event of locoregional recurrence. Two patients (4.7%) developed local recurrence only and 7 patients (19%) developed distant metastases without local recurrence in the pre-operative group. Recurrence of free durations from the date of initial treatment of the two patients with local recurrence was approximately 13 and 17 months, respectively. Seven of the patients with distant metastases had a range of 8 to 23 months of recurrence free durations with the median time of 19 months. Post-treatment surveillance in preoperative group showed 2 patients (4.7%) with isolated CEA elevation in the setting of negative image study and colonoscopy. One of the patients had a persistent CEA rising during the follow-ups but negative in the repeated colonoscopy and CT chest/abdomen scan. Gradual

decline in CEA level was proven after the following year. The other patient with isolated CEA elevation (not exceeding 10 ng/ml) had underlying chronic kidney disease, one in postoperative group, 3 patients (8.3%) had local recurrence only, 5 patients (13.3%) had distant metastasis without local recurrence and 2 patients (5.5%) were found to develop both distant metastasis and local recurrence. Four patients with isolated CEA elevation were observed; two of which known chronic kidney disease had been stated as a possible cause and the other two patients had persistent CEA rising without underlying illness or clinical symptoms. One of the latter patients had no documentation of additional alternative investigation but close monitoring of the CEA level while the other one was noted to send for PET scan but the patient refused to work up further and chose to monitor CEA periodically every 3 months instead.

Of these eligible 78 patients, 19 patients (9 pre-operative, 10 postoperative) had locoregional recurrence as mentioned above. No deaths were encountered in either treatment group. The 2-year DFS for pre-operative patients was 78.6% vs. 72.2% for postoperative patients. The HR was 0.74 (95% CI, 0.38-1.83; $p = 0.521$), suggesting a possible benefit for pre-operative therapy (Fig. 1).

The toxicities during or after protocol therapy were experienced in some patients from both treatment arms. The categories of adverse events were broadly listed but the details from collected information were not sufficient to grade severity according to the descriptions from adverse events criteria (CTCAE)⁽¹³⁾. The adverse effects between pre-operative and postoperative groups consisted of gastrointestinal

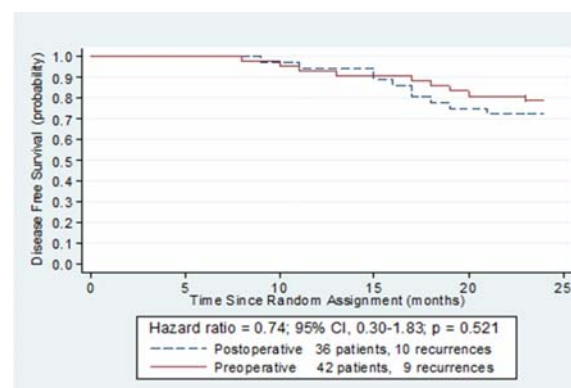


Fig. 1 Disease-free survival of 78 patients from preoperative or postoperative chemoradiotherapy. Recurrence referred to local, distant, or both.

effects (21.4% vs. 33.3%), bladder problems (12% vs. 13.8%), dermatological effects (2.4% vs. 11.1%), hematological effects (9.5% vs. 8.3%), anastomotic stricture (4.7% vs. 2.7%), and anastomotic leakage (2.3% vs. 5.5%). Fistula (5.5%) was found in the postoperative group but none from the pre-operative group. The gastrointestinal effects, dermatological effects, anastomotic strictures, and fistulas were more developed in the postoperative group. However, toxicities between two groups were not significantly different in statistics.

Discussion

Regarding to NSABP R-03 trial, significant 5-year DFS was achieved with pre-operative patients 64.7% as compared with postoperative patients 53.4% ($p = 0.011$)⁽¹⁰⁾. The German rectal cancer group, however, did not demonstrate 5-year DFS benefit but confirmed significant differences in locoregional recurrence rates between pre-operative and postoperative groups (6% pre-operative vs. 13% postoperative, $p = 0.006$) with associated toxicity reduction in both acute and long-term toxic effects⁽¹⁵⁾. The similar multimodality approaches were given in Phramongkutklo hospital, however, the effectiveness between pre-operative and postoperative concurrent chemoradiotherapy in locally advanced rectal cancer did not show significant statistical differences in 2-year local recurrence and distant metastasis. Since the present study was designed to assess 2-year DFS instead of 5-year DFS, such timing difference cannot yet be proven to contradict or disagree with the results from other trials. Even though neither group showed statistical difference in 2-year DFS, a possible DFS benefit was suggested in pre-operative concurrent chemoradiotherapy. By using the collected data from routine medical records in this retrospective study, some required information had been missed or insufficient to meet the eligible criteria a side from stage 1 and 4 patients. Therefore, out of 182 new cases from 2004 to 2008, less than half or 78 eligible patients were available to conduct the study. Limited information and details on toxicity effects created difficulty in grading the toxic effects and dividing into acute and long-term side effects.

Conclusion

Although no statistical difference in 2-year DFS was achieved in comparing pre-operative and postoperative chemoradiotherapy, the pre-operative approach is encouraged as a possible 2-year DFS benefit had been demonstrated.

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Potential conflicts of interest

None.

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การเปรียบเทียบประสิทธิผลการรักษาของผู้ป่วยมะเร็งส่วนปลายสุดของลำไส้ใหญ่ระยะลุกลามเฉพาะที่ระหว่างการให้ยาเคมีบำบัดร่วมกับการฉายรังสีก่อนผ่าตัดกับการให้ยาเคมีบำบัดร่วมกับการฉายรังสีหลังผ่าตัดในโรงพยาบาลพระมงกุฎเกล้า

พียดา ปาร์ค, ประมุข พรหมรัตน์พงส์, สุภชาติ แสงเรืองอ่อน

ภูมิหลัง: การรักษาผู้ป่วยมะเร็งส่วนปลายสุดของลำไส้ใหญ่ระยะลุกลามเฉพาะที่ (locally advanced rectal cancer) ในช่วงหลายทศวรรษก่อนหน้านี้นี้ ได้ให้การรักษาแบบมาตรฐานดั้งเดิมคือการให้การรักษาเสริมหลังผ่าตัดไปแล้ว โดยการให้ยาเคมีบำบัดร่วมกับการฉายรังสีจากผลการศึกษาในทางคลินิก มีหลายงานวิจัยยืนยันว่าการให้การรักษาด้วยยาเคมีบำบัดร่วมกับการฉายแสงรังสีก่อนนำไปผ่าตัดสามารถเพิ่มอัตราการควบคุมโรคเฉพาะที่ (local control) ได้ดีกว่าการรักษาเสริมก่อนผ่าตัดจึงกลายเป็นมาตรฐานในการรักษา locally advanced rectal cancer ในเวลาต่อมาจนถึงปัจจุบัน ที่ผ่านมามีการรักษาเสริมก่อนผ่าตัด (preoperative concurrent chemoradiotherapy) และหลังผ่าตัด (postoperative concurrent chemoradiotherapy) ทั้งสองวิธีนี้ได้มีการปฏิบัติรักษาผู้ป่วย locally advanced rectal cancer ในโรงพยาบาลพระมงกุฎเกล้าจนถึงปัจจุบันแต่ผู้ป่วยที่ได้รับการรักษาเสริมก่อนผ่าตัดมีจำนวนมากกว่า

วัตถุประสงค์และวิธีการ: การศึกษาในครั้งนี้จึงเปรียบเทียบผลลัพธ์ของการรักษาระหว่างสองวิธี

ผลการศึกษา: เป็นการศึกษาวิจัยเชิงพรรณนาโดยศึกษาย้อนหลังพบจำนวนผู้ป่วย 78 ราย ที่วินิจฉัยเป็น locally advanced rectal cancer ระยะ II หรือ III และได้รับการรักษาเสริมก่อนผ่าตัดหรือหลังผ่าตัดในช่วงปี พ.ศ. 2547 ถึง พ.ศ. 2551 การรักษาดังกล่าวประกอบด้วย Fluorouracil (5-FU) based และการฉายรังสีแบบมาตรฐานบริเวณเชิงกราน ผู้ป่วยที่ได้รับการรักษาเสริมก่อนผ่าตัดจะได้รับการผ่าตัด 4-6 สัปดาห์หลังสิ้นสุดของการรักษาเสริมและรับยาเคมีบำบัดต่อจนครบสูตร ส่วนผู้ป่วยที่ได้รับการผ่าตัดมาก่อนจะได้รับการรักษาเสริมประมาณ 4-6 สัปดาห์หลังการผ่าตัด การศึกษาในครั้งนี้มุ่งเน้นที่ระยะเวลาของการปลอดโรคช่วง 2 ปี หลังเริ่มการรักษา (2-year disease free survival หรือ 2-year DFS)

ผลการศึกษา: ในจำนวนผู้ป่วยทั้งหมดที่ได้ทำการศึกษาพบว่า 19 ราย (9 ราย รักษาเสริมก่อนผ่าตัด, 10 ราย รักษาเสริมหลังผ่าตัด) พบการเกิดโรคซ้ำ ซึ่งการเกิดโรคซ้ำจะรวมถึงการเกิดโรคซ้ำเฉพาะที่ การเกิดโรคซ้ำ ระยะห่างไกลออกไปจากตำแหน่งโรคเดิมหรือการเกิดทั้งสองอย่างร่วมกันในด้าน 2-year DFS ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่าง 2 กลุ่ม (78.6% preoperative vs. 72.2% postoperative, $p = 0.521$) แต่ในกลุ่มผู้ป่วยที่ได้รับการรักษาเสริมก่อนผ่าตัดพบว่ามีความโน้มที่จะได้รับประโยชน์ในด้าน DFS มากกว่าในด้านผลข้างเคียงการรักษาไม่มีความแตกต่างในด้านสถิติแต่มีความโน้มที่จะเกิดขึ้นมากกว่าในกลุ่มที่ได้รับการรักษาเสริมหลังผ่าตัด

สรุป: ไม่พบความแตกต่างด้านสถิติของ 2-year DFS ระหว่าง 2 กลุ่มการรักษา แต่พบว่ากลุ่มที่ได้รับการรักษาเสริมก่อนผ่าตัดมีความโน้มที่จะได้รับประโยชน์ในด้าน DFS
