Outcome of Treatment of Rectal Cancer

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Abstract

To demonstrate the trend and treatment outcome of rectal cancer after the advent of adjuvant therapy, all case notes of rectal cancer patients admitted to Chulalongkorn Hospital from 1985-1994 were reviewed and cases were followed until 1996. Mean follow-up period was 685.3 days (8-3,193 days). Most rectal tumors were Dukes' C (43.8%), well-differentiated (54.1%) and at the distal third (53.4%). AP resection remained the most common procedure before and after the advent of adjuvant therapeutic options (62.3%). Of 146 patients treated by curative operations, 60 had adjuvant therapies of which radical radiotherapy with or without chemotherapy was the most common. However, chemotherapy was increasingly employed as the neoadjuvant and as combined chemoradiotherapy.

There was a preferential selection of less well-differentiated, more distal, more Dukes' C disease and younger patients for the adjuvant therapy ($p<0.05$). Recurrence rate in the adjuvant group was not different from the surgery group despite significant poorer prognostic indicators (17.4% & 21.7%, $p=0.53$). Mortality was higher in Dukes' B+C patients in adjuvant group (17.3% & 3.4%, $p=0.02$). The outcomes were not different among Dukes' A patients. The complications; i.e. wound problems, gut obstruction; did not increase with the adjuvant treatment. No adverse effect was observed on the healing of colorectal or coloanal anastomoses in the adjuvant group.

Rectal cancer is one of the commonest cancers not only in Western countries but also in Thailand[1-6]. An ongoing problem is its frequent relapse even with all advances in surgical techniques. This is apparently due to its anatomical limitation and nature of the tumor itself. To eliminate the problem of relapse, radiotherapy and chemotherapy are generally employed as adjuncts to surgery in many countries[7]. However, there have been surprisingly few studies in Thailand in relation to this current trend[8,9]. We present here our preliminary information on rectal cancer treatment in our institution covering the period when adjuvant therapy was gaining acceptance.

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SUBJECTS AND METHOD

This is a retro-prospective study of patients who were admitted to Chulalongkorn Hospital from January 1984 to December 1994. The hospital records of all patients who received surgical resection for rectal cancer were reviewed with attention to patients' characteristics, associated diseases, stages of the tumor, pretreatment ASA physical condition, pretreatment CEA level, operative data, non-surgical treatment, pathological data, and outcome of disease. Phone calls and letters were used if the patients were lost from the hospital follow-up clinic.

Two groups of patients were classified according to whether they received any adjuvant therapy. However, we excluded patients (1) without complete operative or pathological reports, (2) with metastatic disease before treatment, (3) with previous treatment from another hospital, and (4) with non-adenocarcinomatous tumor.

About the disease itself, the location (lowest margin) of the tumor was identified by rectal and sigmoidoscopic examination, by radiological findings and finally by operative findings. Stages of disease were determined pathologically using Dukes' classification, and perirectal involvement of the tumor was manually assessed to establish pathological stages in the TNM system of AJCC (American Joint Committee of Cancer)[10].

All surgical procedures were performed by various surgeons in the Department of Surgery. We also identified the duration of operation and patients' preoperative physical condition according to the anesthesiologist ASA system (I, II, III, IV). In the follow-up if a patient developed a recurrent tumor in the pelvis after a curative surgery proven either by digital examination or radiological studies with or without pathologic confirmation, it was regarded as local recurrence. Clinical metastatic disease outside the pelvic cavity was regarded as distant metastasis. On the other hand, if there was no recurrent tumor both inside and outside the pelvis with the normal CEA level until the last date of follow-up, the patient was regarded as disease-free.

The data were collected, summarized, and analyzed by computerizing with SPSS for Windows. Mean, percentage, and ratio were calculated for descriptive results. The *t*-test and Mann-Whitney U tests were used for comparative analysis at p-value of 0.05.

RESULTS

There were 295 cases of rectal cancer admitted to Chulalongkorn Hospital during the 10 years. (Fig. 1) Of the 146 patients who fulfilled the inclusion criteria, 86 cases (58.9%) received surgical treatment alone (Sx), 60 cases (41.1%) had some types of adjuvant therapy (Adj). Of the 149 patients excluded, 99 cases (66.5%) had advanced or metastatic disease before treatment and another 49 cases (32.9%) had incomplete data. One had a non-adenocarcinomatous tumor (leiomyosarcoma). (Table 1)

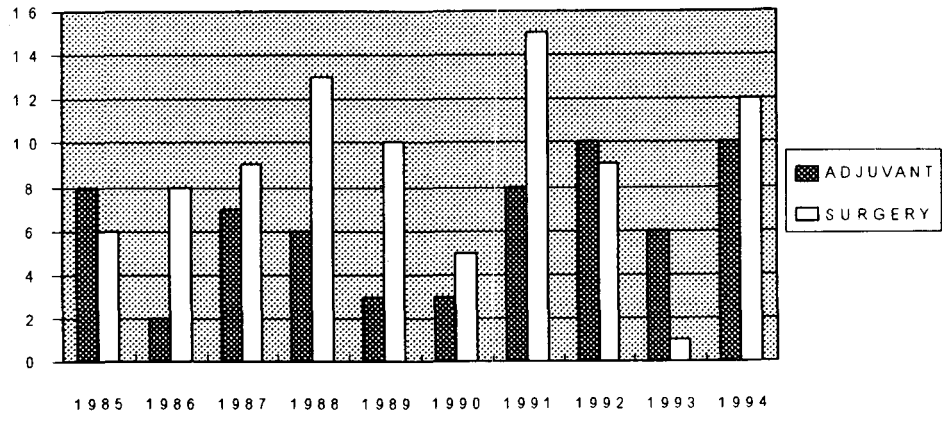

Fig. 1. No. of patients from 1985-1994.

Table 1. Patients with rectal cancer undergoing treatment during 10-yr period.

Groups	Number
Surgery alone (Sx)	86
Sx+Adjuvant (Adj)	60
Metastatic disease	62
Previously treated elsewhere	37
Incomplete data	49
Leiomyosarcoma	1
Total	295

There were 62 cases with distant metastasis discovered either before definitive treatment or at operation. The lung was the most commonly involved organ (38 cases). Other sites included left ovaries (5 cases), supraclavicular nodes (3 cases), omentum (2 cases), mesentery (1 case), and bone (1 case).

Among 146 patients who were included, most were elderly with the mean age of 58.6 ± 15.5 (21-88 yr) and showed slight male preponderance (M:F = 1.38:1). Most tumors (53.4%) located at the distal third of the rectum (Table 2) and 54.1 per cent were found to be well-differentiated (Table 3). Nearly half were Dukes' C, while only one-fourth were Dukes' A. (Tables 4, 5)

Table 2. Location of the tumors.

Location	No. of Pt.	Percentage
Proximal third	37	25.3
Middle third	27	18.5
Distal third	78	53.4
Unknown	4	2.8
Total	146	100

Table 3. Histology of the tumors.

Histology	No. of Pt.	Percentage
Well-diff.	79	54.1
Mod-diff.	42	28.8
Poor-diff.	20	13.7
Unknown	5	3.4
Total	146	100

Table 4. Staging by Dukes' classification.

Stage	No. of Pt.	Percentage
A	35	24.0
B	47	32.2
C	64	43.8

Table 5. Staging by TNM classification.

Stage	No. of Pt.	Percentage
I	35	24.0
II	46	31.4
III	64	43.8
Unknown	1	0.7

Mean level of pretreatment CEA from 68 patients was 12.0 ± 18.8 ng/ml, with the highest level of 92.00 ng/ml in a patient who had T4N1M0 (C2) tumor.

The most common surgical procedure employed was the abdominoperineal resection. (Fig. 2)

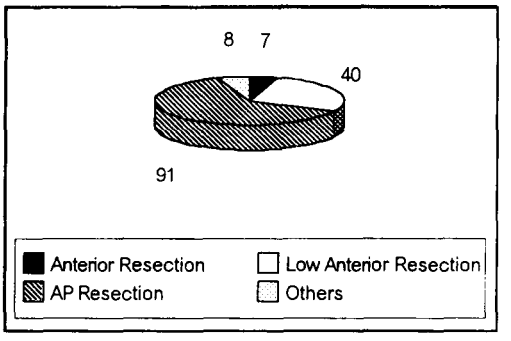

Fig. 2. Types of performed operations.

Among those who had surgery with adjuvant therapy (60 patients), radiotherapy, chemotherapy, and chemoradiotherapy were given to 35 (58.3%), 3 (5.0%), and 22 (36.7%) cases respectively, (Tables 6-8). The use of combined chemoradiation showed a progressive rise and has become the preferred adjuvant therapy since 1993.

Table 6. Radiation alone.

Radiation alone	No. of Pt.	Total dose (cGy) <2,500	2,500-4,000	>4,000	unknown
Preop. XRT	13	0	8	4	1
Postop. XRT	18	1	3	6	8
Sandwich XRT	3	0	0	3*	0
Unknown	1	-	-	-	1
Total	35	1	11	13	10

*All cases received Preop. XRT dose = 4,000 cGy + Postop. XRT dose ≤ 2,500 cGy

Table 7. Chemotherapy alone.

Chemo Alone	Type	No. of Pt.
5FU	postop.	1
5FU+leucovorin	postop.	1
5FU+interferon-2α	postop.	1
Total		3

Table 8. Chemoradiotherapy.

Combined Chemoradiotherapy	No. of Pt.
Preop. Chemoradiation	6
Preop. XRT + Sandwich Chemotherapy	1
Postop. Chemoradiation	12
Sandwich XRT + Preop. Chemotherapy	1
Sandwich XRT + Postop. Chemotherapy	1
Postop. XRT + ? Chemotherapy	1
Total	22

Table 9. Perioperative complications.

Complication	No.	
Wound complication	19	
Infection		13
Disruption		5
Hematoma		1
Urinary complication	15	
Neurogenic bladder		13
Ureteric injury		1
Bladder injury		1
Anastomosis leakage	7	
Intraop. Hemorrhage	4	
Pneumonia	2	
Resp. Failure	2	
Internal hernia	2	
Myocardial ischemia	1	
Congestive heart failure	1	
Gut obstruction	1	
Total	54	

There were only 4 cases who received the radiotherapy by linear accelerator machine. The remaining 53 received radiotherapy through a conventional Cobalt machine.

There were overall 54 peri-operative complications (37.0%) which included 19 wound problems, 15 urinary complications, and 7 anastomosis leakage. (Table 9)

After the mean follow-up of 685.25 days (8-3,193 days) and with a 28.1 per cent loss to follow-up, the overall recurrence rate, metastatic rate, and death rate were 19.2 per cent, 14.4 per cent, and 7.5 per cent, respectively. Mean duration from operation to recurrence, metastasis, and death were 460.3 (120-1513), 641.5 (141-1866), 449.1 (26-1504) days, respectively.

Analysis by Staging

To consider the outcomes of different treatments, a comparison between Sx group and Adj group was done, and some important different characteristics emerged.

The patients in Sx group were significantly older (62.5 & 52.9, $p<0.01$), but had more Dukes' A tumors, 31.4 per cent *vs* 13.3 per cent ($p=0.03$). More advanced diseases were found in the Adj group as 51.7 per cent of Adj group and 38.4 per cent of Sx were in Dukes' C ($p=0.03$). The Adj group had more poorly differentiated tumors and also more tumors at the lower third of the rectum, requiring higher rate of AP resection than in Sx group ($p<0.01$). (Table 10)

Table 10. Types of operations.

	Sx (n=86)	Adj (n=60)
Anterior resection	6	1
Low anterior resection	30	10
AP resection	48	43
Transanal excision	1	0
Hartman's operation	1	1
Coloanal anastomosis	0	4
Pelvic exenteration	0	1
Total	86	60

Both groups showed similar follow-up compliance (p=0.09) and duration (Sx & Adj = 725 & 642 days, p=0.54). The recurrence and metastasis rates were equal, but the Adj group had a statistically higher death rate than the Sx group. Incidence of proctitis was also higher in the Adj group, but not intestinal obstruction and cystitis. (Table 11)

Dukes' A (Stage I) patients

Due to the dissimilarity of disease severity between both groups and the general recommendation to give adjuvant therapy only to high-risk patients (Stage II, III or Dukes' B+C), analyses were conducted separately between Dukes' A (or Stage I) and Dukes' B+C (or Stage II+III) patients.

Among 35 Dukes' A (Stage I) patients, 8 had adjuvant therapy. Their different characteristics including types of operation and associated diseases are shown in Table 12 and 13.

Table 11. Comparison of patients' outcome.

	Sx (n=86)	Adj (n=60)	p-value
Recurrence rate	15 (17.4%)	13 (21.7%)	0.525
Time to recur. (d)	485.7 (120-1,513)	425.4 (172-1,000)	0.729
Metastasis rate	11 (12.8%)	10 (16.7%)	0.513
Time to metas. (d)	744.8 (141-1866)	476.4 (172-1084)	0.379
Overall death	2 (2.3%)	9 (15.0%)	0.004
Time to death (d)	562.0 (376-748)	424.0 (26-1,504)	0.682
Intestinal obstruction	4 (4.7%)	7 (11.7%)	0.115
Proctitis	0	3 (5%)	0.037
Cystitis	0	0	-
Anastomosis leakage	7	0	0.02
Wound complications	7 (8.1%)	10 (16.7%)	0.13

Table 12. Dukes' A patients with adjuvant therapy.

Adjuvant Px	No. of Pt.
Preop. XRT	4
Sandwich XRT	1
Preop. Chemoradiotherapy	1
Postop. Chemoradiotherapy	1
Sandwich XRT + Postop. Chemotherapy	1

Table 13. Different characteristics of Dukes' A patients.

	Sx (n=27)	Adj (n=8)	p-value
Asso. Diseases	15 (55.6%)	1 (12.5%)	0.34
Operations			0.12
APR	15 (55.6%)	6 (75%)	
LAR	9 (33.3%)	0	
AR	2 (7.4%)	0	
Other	1 (3.7%)	2 (25%)	
Total	27	8	

Though Adj. Group was treated with more APR than Sx group, outcomes seemed to be the same in terms of recurrence, metastasis, death, and treatment-related complications. (Table 14)

Dukes' B+C (Stage II+III) patients

In these high risk patients, Sx group had more favorable characteristics than Adj. group. The Adj. group also had poorer ASA physical status (p=0.015), more distal lesion (p=0.030), and poorer tumor histopathology (p=0.013) and therefore needed more frequent AP resections. Those in the Sx. group, however, were older and had more associated diseases (p<0.05).

Nevertheless, they appeared to have similar treatment outcomes except for the death rate which was significantly higher in the Adj. group. (Table 15)

Post-operative adjuvant therapies

It was a possibility that postoperative adjuvant therapies were given because of the failure of a complete tumor resection. All 31 patients with postoperative radiotherapy or chemotherapy were separately analyzed. They were similar to others in the Adj. group in term of age, sex, body

Table 14. Comparison of patients' outcome (Dukes' A).

	Sx (n=27)	Adj (n=8)	p-value
Recurrence rate	3 (11.1%)	1 (12.5%)	0.915
Time to recur. (d)	1208 (903-1,513)	301	-
Metastasis rate	5 (18.5%)	0	0.195
Time to metas. (d)	1116.8 (685-1,866)	-	-
Overall death	0	0	-
Intestinal obstruction	0	0	-
Proctitis	0	0	-
Cystitis	0	0	-
Anastomosis leakage	0	0	-
Wound complications	2 (7.4%)	2 (25.0%)	0.150

Table 15. Comparison of patients' outcome (Dukes' B+C).

	Sx (n=59)	Adj (n=52)	p-value
Recurrence rate	12 (20.3%)	12 (23.1%)	0.728
Time to recur. (d)	325.2 (120-647)	443.1 (172-1,000)	0.355
Metastasis rate	6 (10.2%)	10 (19.2%)	0.177
Time to metas. (d)	372.8 (141-838)	476.4 (172-1,084)	0.675
Overall death	2 (3.4%)	9 (17.3%)	0.015
Time to death (d)	562 (376-748)	424 (26-1,504)	0.682
Intestinal obstruction	4 (6.8%)	7 (13.5%)	0.242
Proctitis	0	3 (5.8%)	0.063
Cystitis	0	0	-
Anastomosis leakage	7	0	-
Wound complications	8 (13.6%)	2 (19.2%)	0.320

weight, associated diseases, ASA status, CEA level, albumin and hemoglobin level, location of tumor, presence of preoperative perforation, type of operation, duration of operation, surgeon, tumor differentiation, and follow-up duration. They, however, presented with fewer preoperative obstructive complications (2.6% *vs* 8.3%) and more Dukes' C disease (59.0% *vs* 48.3%).

DISCUSSION

The patients included in this study were those operated on with curative intent excluding, thereby, a large number with evidence of advanced local disease or of distant metastasis at the time at presentation. This is reflected in the high proportion of early cases, especially Dukes' A (Table 4) , unlike the distribution previously reported from this institution[9]. A number of patients in this study also had preoperative radiation which might have cleared the lymph nodes of metastasis thus increasing the number of early cases. This may be of relevance to 8 patients with Dukes' A tumors in the adjuvant group. (Tables 12, 13) All except one of these patients received pre-operative radiation therapy with or without chemotherapy. The resulting Dukes' A tumors could indicate the "down-staging" effect after the nodes in the mesorectum had become negative. High incidence of metastasis (18.5%, Table 14) probably indicated the understaging of the original disease in this group as CT scan of the liver and lungs or radioactive bone scan were not part of routine preoperative workup. Underinvestigation would probably explain the highest incidence of metastasis to the lung compared to other organs.

This study revealed that during the study period there was no uniform view on how best to employ adjuvant therapies to rectal cancer in this institution. However, it is apparent that there existed a trend for rectal cancer patients in this institution with poorer prognostic features, i.e. poorly differentiated tumor, tumor fixation, tumor of mid or low rectum, and younger age, to undergo adjuvant therapy in addition to surgery. Some of the patients were selected on these findings alone for preoperative radiation with or without chemotherapy. Some other patients received postoperative radiation with or without chemotherapy when the operative finding revealed perirectal infiltration or when there was uncertainty whether the tumour was completely removed. Still others were selected for sandwich therapy. Though there was a lack of uniformity in its administration it can be said that local radical radiation formed the backbone of adjuvant therapy and its effect, if any, must be judged upon the development of local recurrence in these patients.

Interpretation of outcome of treatment in this retrospective study is difficult. Parameters which have important bearing on the development of local recurrence were not adequately described in the case notes such as the extent of perirectal invasion or the completeness of mesorectum excision. The patients in the study were under the care of surgeons of varying skills and expertise. There

was no clear indication in the case notes whether surgery was confidently perceived at the end to be really curative by the operating surgeons, i.e. without gross residual tumor being left behind. Besides, the adjuvant group contained significantly more patients with poorer prognostic indicators. The gravity or seriousness of the original disease in this group is accurately reflected in the high metastatic and death rates (Tables 11, 14, 15) both of which are known to be unaffected by the adjuvant radiation therapy[13-15]. Those who received additional chemotherapy were too few to contribute significantly to the analysis. In spite of the unfavorable circumstances the local recurrence rate of the adjuvant group is the same as in the surgery group (Tables 11, 14, 15). However, a local recurrence rate of 11.1-12.5 per cent in patients with Dukes' A tumors is only slightly higher than expected[12].

Adjuvant therapy did not increase the incidence of wound problems or post-operative intestinal obstruction (Tables 9, 11, 14, 15). However, small bowel obstruction following post-operative radiation to the pelvis was often serious involving multiple matted loops firmly stuck down in pelvis and required tedious operative correction.

Clinical anastomotic leakage occurred in 7 out of 36 patients (19.4%) who had resection and anastomosis (Tables 10, 11) in the surgery group. The leakage rate in this group is well within the range reported by recent studies[16]. That clinical leakage did not occur in the adjuvant group is not related to the adjuvant therapy per se but to the difference in the surgical practice. Resection with low anastomosis in the adjuvant group was always accompanied by temporary proximal colostomy or ileostomy as the operating surgeons were concerned with the state of colonic blood supply and healing following radical local radiation. However, the anastomoses subsequently healed well and all patients had their stoma closed. It is also noteworthy that there were 4 patients with colo-anal anastomoses in the adjuvant group (Table 10) all of whom remained well at last follow-up. It is probable that without adjuvant therapy these patients would have had AP resection instead. Adjuvant therapy apparently provided additional local control to make sphincter saving possible in these patients.

SUMMARY

There is a rising trend in this institution for selection of rectal cancer patients with unfavorable prognostic factors for adjuvant therapy additional to surgery. This does not result in greater morbidity when compared to surgery alone. Though beneficial effect of such adjuvant therapy is not conclusively proven in this study due to lack of proper control for comparison, the local recurrence rate in the relatively unfavorable group receiving adjuvant radiation with or without chemotherapy is no worse than that of the more favorable group receiving surgery alone.

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REFERENCES

1. Indhusorn P, Thirakhupt P, Pitagpravej T. Carcinoma of colon and rectum in Vajira Hospital. Vajira Med J 1972;16:114-20.
2. Pirompak Y. Colorectal cancer: a 5-year retrospective study. Med J Ubon Hosp 1987;8:1-5.
3. Kalayanakoul S, Tasaniyanonda C, Panijayanond P, Chotiprasidhi P. Carcinoma of the colon and rectum: a 5 year experience at Pramongkutklao Hospital, R Thai Army Med J 1988;41:23-30.
4. Intaralak L. Colorectal cancer in Buddachinraj Hospital. Buddhachinaraj Med J 1992;9:51-7.
5. Chindasub S, Indhusorn P, Jesadapatarakul S. Management of carcinoma of the rectum. Vajira Med J 1994;28:33-44.
6. Jenchitr C. Colorectal carcinoma in Lampang Hospital. Bull Lampang Hosp 1994;15:138-45.
7. Rojvachiranonda N, Vajrabukka T, Lertsanguansinchai P, Voravud N. Adjuvant therapy for rectal cancer. Chula Med J 1995;39:138-58.
8. Promratanapongse P. Pattern of recurrence in rectal and rectosigmoid cancer treated with surgery alone : Implication of irradiation as an adjuvant therapy. Royal Thai Army Med J 1986;39: 313-8.
9. Sangsubhan C, Tanphiphat C. Colorectal carcinoma in the Chulalongkorn hospital. Chula Med J 1984;28:1251-63.
10. American Joint Committee on Cancer Manual for

the Staging of Cancer. 4th edition. Philadelphia: J.B. Lippincott Co.,1992.
11. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990; 264:1444-50.
12. McDermott, Hughes ES, Pihl E, Johnson WR, Price AB. Local recurrence after potentially curative resection for rectal cancer in a series of 1,008 patients. Br J Surg 1985;72:34-7.
13. Aleman BM, Bartelink H, Gunderson LL. The current role of radiotherapy in colorectal cancer. European J Cancer 1995;31A:1333-9.
14. Beart RW, Steele GD Jr, Menck HR, Chmiel JS, Ocwieja KE, Winchester DP. Management and survival of patients with adenocarcinoma of the colon and rectum: a national survey of the Commission on Cancer. J Am Coll Surg 1995;181: 225-36.
15. Sinicrope FA, Sugarman SM. Role of adjuvant therapy in surgically resected colorectal carcinoma. Gastroenterology 1995;109:984-93.
16. Pakkastie TE, Ovaska JT, Pekkala ES, et al. A randomized study of colostomies in low colorectal anastomoses. Eur J Surg 1997;163:929-33.

มะเร็งของเรคตัมกับการรักษาเสริม : ผลการรักษาผู้ป่วย 146 รายในโรงพยาบาลจุฬาลงกรณ์

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แม้ว่าจะมีการนำรังสีรักษาและเคมีบำบัดมาใช้รักษาเสริม (adjuvant therapy) สำหรับโรคมะเร็งของเรคตัมนานกว่า 10 ปี แต่ก็ยังไม่เคยมีการศึกษาวิจัยถึงผลการรักษาในประเทศไทย คณะผู้วิจัยได้คัดเลือกผู้ป่วยมะเร็งของเรคตัมทุกรายที่ได้รับการรักษาโดยหวังให้หายขาด ด้วยการผ่าตัดร่วมกับการรักษาเสริม 146 ราย ระยะเวลาติดตามเฉลี่ย 685.3 วัน (8–3,193 วัน) พบว่าผู้ป่วยส่วนใหญ่มีเนื้องอกชนิด well-differentiated (54.1%) อยู่ที่เรคตัมส่วนปลาย (53.4%) และอยู่ในระยะ Dukes' C (43.8%) ผู้ป่วยร้อยละ 62.3 ได้รับการผ่าตัด AP resection การรักษาเสริมที่ใช้บ่อยที่สุดได้แก่ รังสีรักษา (60 ราย) และมีแนวโน้มการใช้เคมีบำบัดเพิ่มมากขึ้น

ผลการศึกษาครั้งนี้ยังพบว่า มีความนิยมในการเลือกใช้การรักษาเสริมกับผู้ป่วยที่โรคมีโอกาสแพร่กระจายหรือกลับเป็นซ้ำได้ง่าย ได้แก่ กลุ่ม Dukes' C กลุ่มที่เป็นมะเร็งที่ปลายเรคตัม และเนื้อมะเร็งที่ไม่ใช่ well-differentiated ($p<0.05$) แต่อัตราการกลับเป็นซ้ำของมะเร็งก็ไม่แตกต่างไปจากกลุ่มผู้ป่วยที่ไม่ได้รับการรักษาเสริม ($p>0.05$) อัตราตายในผู้ป่วย Dukes' B และ C ที่ได้รับการรักษาเสริมมีมากกว่า ($p=0.02$) อย่างไรก็ตาม การรักษาเสริมก็ไม่ได้เพิ่มภาวะแทรกซ้อนในการรักษา เช่น ปัญหาบาดแผลผ่าตัดหรือรอยต่อลำไส้รั่ว ($p>0.05$)

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