

VÝSLEDKY LÉČBY KARCINOMU REKTA A REKTOSIGMOIDEA V KUVAJTU - RETROSPEKTIVNÍ ANALÝZA

TREATMENT OUTCOME OF RECTAL AND RECTOSIGMOID CANCER IN KUWAIT - A RETROSPECTIVE ANALYSIS

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ABSTRACT

Aim: Incidence of rectal and rectosigmoid cancer has wide geographical variation. Disease pattern in developing countries is different from developed countries. This analysis was undertaken to describe patient profile and to review the outcome of adjuvant therapy for rectal and rectosigmoid cancer at Kuwait Cancer Control Center. **Patients and Methods:** We retrospectively evaluated rectal and rectosigmoid cancer patients diagnosed between 1998 - 2004. One hundred and ninety three patients with rectal and rectosigmoid cancer were included. Only 11% of the patients were diagnosed with stage I disease, 28% with stage II, 53% were stage III, and 7.9% were stage VI. About 76.6% underwent anterior resection while 23.3% underwent abdomino-perineal resection or Hartman procedure. Only 63.2% of the patients received radiotherapy, and of those only 36 patients had preoperative radiotherapy. Only 35.2% of patients received adjuvant chemotherapy. **Results:** The male to female ratio was 1.4 and the median age of the patients was 52.11 years. Cancer of the rectum constituted 64.2% while rectosigmoid cancer constituted 35.8% of the cases. About 17.7% had tumor located within 5 cm from anal verge. Locally advanced or metastatic disease were found in 67.6%. Tumor involving more than 1/3 of the lumen circumference was found in 49.1% of cases. Liver was the most frequent site (14.5%) of metastasis followed by lung (4.1%). Well, moderately and poorly differentiated adenocarcinoma constituted 16.8%, 68.8% and 14.5% of the cases, respectively. The disease free survival was influenced significantly by the lymph nodes status and chemotherapy. Among the whole group, the local recurrence was 18.7%, while the disease free survival and overall survival were 42.7 and 90.04%, respectively. **Conclusions:** Rectal cancer in Kuwait differs from western countries with a high propensity for locally advanced tumors because of delayed referral and misdiagnosis.

Key Words: rectal cancer, Adjuvant treatment, Radio-chemotherapy.

Introduction:

In Kuwait rectal and rectosigmoid cancer (RRC) is the sixth most common cancer in Kuwaiti males and the ninth in Kuwaiti females (3).

In the year 2003, the age standardized incidence rate (ASIR world) for RRC among Kuwaiti males was 2.8 while it was 4.0 among Kuwaiti females. On the other hand, non-Kuwaiti males and females showed ASIR of 2.0 and 3.3 respectively. Mortality rate from RRC was 2.6 /100,000 among Kuwaitis (3). On the other hand, ASIR world of cancer of the rectum in USA was 8.36 in males and 4.87 in females. England showed 11.59 for males and 5.63 for females. Algeria showed a much lower rate 0.52 and 0.51 among males and females respectively, while in Oman the incidence among males were 1.92 and 0.76 among females.

Although surgery is the main stay of treatment of RRC, radiotherapy (XRT) and chemotherapy play a vital role. There have been significant improvements in its management over the past two decades leading to improved local control and overall survival. These include total mesorectal excision, pre-operative XRT and 5-Fluorouracil (5-FU).

Aim of Study:

The aim of this study was to evaluate the results of 'standard' surgery followed by adjuvant XRT or radio-chemotherapy for RRC treated at Kuwait Cancer Control Center (KCCC) from 1998 to 2004.

Patients and Methods

The medical files of 193 patients seen at the KCCC between 1998 and 2004 were retrospectively reviewed. The staging system was modified according to the AJCC system 2002. All of the patients were treated for RRC. Out of 154 patients underwent surgery, anterior resection (AR resection) was performed in 76.6% of cases while only 17.5%, and 5.8% had abdomino-perineal resection (A-P resection) and Hartman procedure respectively. The distribution of patients who underwent AR resection according to stage was 13.8%, 30.3%, 53.2% and 2.8% for AJCC stage I, II, III and VI respectively. On the other hand, 11.1%, 25.9% and 63% of patients with AJCC stage I, II and III respectively, underwent A-P resection.

Radiotherapy was given 6-8 weeks following surgery and consisted of a 6/18 MV photon beam using 3-field isocen-

tric technique. In 1995, three-dimensional CT-planning system was introduced (Helax TMS system). Target volume included the presacral space and the internal iliac and common iliac lymph nodes as well as the dorsal wall of the urogenital organs. After A-P resection, the perineal scar was included in the target volume. With five fractions per week and a daily dose of 1.8 Gray (Gy), a mid-tumor dose (MTD) of 50.4 Gy was delivered. 5-FU as a radio-sensitizer was given in the first (450mg/m²) and last 3 days (300mg/m²) of the radiotherapy. Only 86 patients had postoperative XRT and of those, 63 patients had undergone AR resection.

Pre-operative XRT was started at KCCC in 2001. The pre-operative XRT dose is 45Gy/25 fractions with the same 5-FU radiosensitizer dose as for postoperative XRT. In addition, the target volume remained the same except for the perineal scar, which is included in the postoperative XRT following A-P resection. Only 36 patients received pre-operative XRT. Following pre-operative XRT, AR resection, A-P resection and Hartman procedure was performed on 18, 3 and one patients respectively. The remaining 14 patients were operated on outside KCCC.

As for adjuvant chemotherapy, sixty-eight patients received additional chemotherapy with six courses of 5-FU and Leucovorin. Each course consisted of five daily bolus intravenous injections of 5-FU 500 mg/m²/day and Leucovorin 20 mg/m²/day (Mayo clinic regime).

Post-treatment follow-up was carried out every 3 months for the first 2 years, then every 6 months for the next 3 years then annually. History and physical exam was performed on every visit. Blood tests (including CBC, serum electrolytes, liver and renal function tests and tumor markers CEA and CA19.9) and abdominal ultrasound or CT scan were done every 6 months. Colonoscopy and chest x-ray were done annually. The median length of follow-up was 37 months (range: 13 to 151 months). End points studied included overall survival and disease-free survival.

Statistical analysis

Statistical Analysis was used to determine prognostic factors with significant impact on overall survival and Disease free survival, including age, primary tumor stage, primary tumor location (above vs. below peritoneal reflection), presence of lymphatic vessel invasion, surgical method (A-P Vs AR resection) and XRT dose. Survival rates were calculated and compared using the Kaplan Meier method. Log rank test was used for comparison of survival curves. A significance level of 0.05 was set for this study.

Results

One hundred and ninety three files (59.1 % males, 41.9 % females) were identified, reviewed, and abstracted on a computer ready form.

Median age of patients was 51 years (range: 25 to 96). Kuwaitis represented 98 cases (50.8%) Vs. 95 Non-Kuwaitis. Only 9.3 % had family history of cancer. Moreover, about 21.2% had diabetes and 17.6 had hypertension. The frequency of presenting symptoms was as follow: rectal bleeding (74.1%), pain (33.2%), weight loss (24.9%), constipation (18.1%), diarrhea (14%), and others (less than 10%). Carcino-embryonic antigen (CEA) level was taken pre-operatively for 136 patients (70.5%). One hundred and sixty four patients (85%) had pre-operative colonoscopy or sigmoidoscopy. (Table 1)

Table 1.: Patient and Tumor Characteristics

| | | No. | % |
|---------------------------------------|----------------------|-------|------|
| Age | 20-30 | 9 | 4.7 |
| | 30-40 | 32 | 16.6 |
| | 40-50 | 44 | 22.8 |
| | 50-60 | 44 | 22.8 |
| | 60-70 | 43 | 22.3 |
| | 70+ | 21 | 10.9 |
| | Median Age | 51.0 | |
| Sex | Range | 25-96 | |
| | M | 114 | 59.1 |
| Nationality | F | 79 | 41.9 |
| | K | 98 | 50.8 |
| Positive Family History of malignancy | NK | 95 | 49.2 |
| | | 18 | 13.4 |
| Presenting Symptoms: | | | |
| | Rectal bleeding. | 143 | 74.1 |
| | Pain | 64 | 33.2 |
| | Weight loss | 48 | 24.9 |
| | Constipation | 35 | 18.1 |
| | Diarrhea | 27 | 14.0 |
| | Other | 38 | 19.7 |
| Distance from Anus: | | | |
| | < 2 cm | 1 | 0.6 |
| | 2 – 5 cm | 33 | 17.1 |
| | > 5 cm | 121 | 62.7 |
| Circumference of tumor: | | | |
| | 1/4 | 6 | 3.9 |
| | 1/2 | 22 | 14.2 |
| | 3/4 | 37 | 23.9 |
| | Full | 39 | 25.2 |
| Type: | Ulcerative | 85 | 44.0 |
| | Proliferative | 52 | 26.9 |
| | Infiltrative | 9 | 4.7 |
| | Ultero-proliferative | 35 | 18.1 |
| Investigation: | | | |
| | Proctoscopy | 5 | 2.6 |
| | Sigmoidoscopy | 13 | 6.7 |
| | Colonoscopy | 151 | 78.2 |
| Tumor Markers: | | | |
| CEA: | ≤3 | 36 | 18.7 |
| | >3 | 100 | 51.8 |
| CA 19.9: | ≤30 | 44 | 22.8 |
| | >30 | 88 | 45.6 |
| Stage: | I | 18 | 11.0 |
| | II | 46 | 28 |
| | III | 87 | 53 |
| | IV | 13 | 7.9 |
| Site: | | | |
| | Rectum | 124 | 64.2 |
| | Recto-Sigmoid | 69 | 35.8 |
| Pathology: | | | |
| Grading: | Adenocarcinoma | 172 | 89.1 |
| | I | | |
| | II | 29 | 16.8 |
| | III | 119 | 68.8 |
| Lymph Nodes: | | | |
| | | 25 | 14.5 |
| | 0- | | |
| | 2- | 82 | 58.2 |
| | 4- | 25 | 17.7 |
| | 6+ | 16 | 11.3 |
| | | 17 | 12.1 |

Cancer of the rectum constituted 64.2% while rectosigmoid cancer constituted 35.8% of the cases. About 17.7% had tumor located within 5 cm from anal verge. Locally advanced or metastatic diseases were found in 67.6%. Tumor involving more than $\frac{1}{2}$ of the lumen circumference was found in 49.1% of cases. Liver was the most frequent site (14.5%) of metastasis followed by lung (4.1%). Well, moderately and poorly differentiated adenocarcinoma constituted 16.8%, 68.8% and 14.5% of the cases respectively.

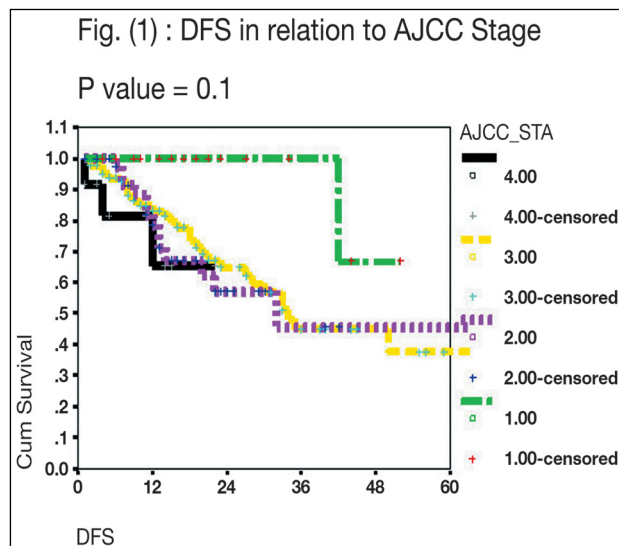
Loco-regional Control

Among our cases, 19.7% had recurrent disease distributed as follow: 18.7% local, 5.7% loco-regional nodes, 8.8% liver metastases, 6.7% lung metastases, 4.7% bone metastases and 1% brain metastases.

The loco-regional control rate was 88.9% in stage I, 69.6% in stage II, 75.9% in stage III. ($P=0.14$).

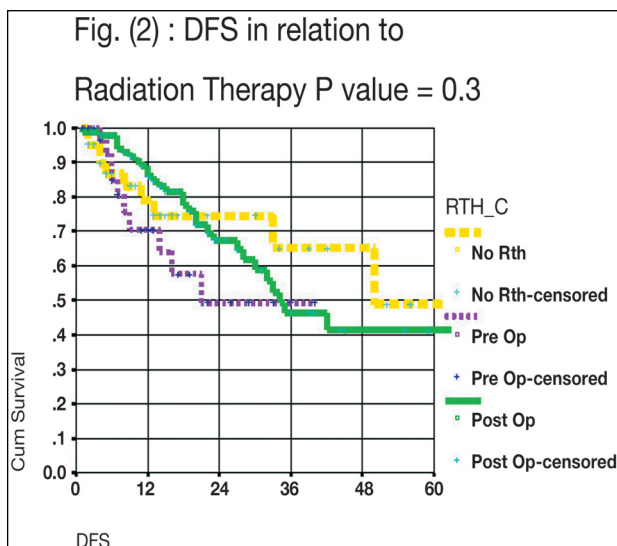
Survival

The calculated 5-year overall survival was 90.04% and $SE=3.5$. While disease free survival (DFS) was 42.7 and $SE=7.4$. Disease free survival did not show significant statistical difference in relation to sex ($P=0.9$) nor nationality ($P=0.56$). DFS was 66.7%, 45.5% and 65.2% for patients with stage I, II and III respectively ($P=0.1$) (Figure 1). Moreover DFS did not show significant statistical difference in relation to type of surgery (P value = 0.47, or tumor site ($P=0.17$). On the other hand, lymph node involvement showed statistical significant effect on DFS (P value = 0.036). Also, the use of Adjuvant Chemotherapy ($P=0.029$) had a statistically significant effect on DFS after 5 years. Comparing pre-operative and postoperative XRT effect on DFS did not show significant statistical effect ($P=0.3$) (Figure 2). (Figure 1),.



Toxicity

The major acute toxicities of treatment were gastrointestinal (21.2%), dermatological (17.6%) and genitourinary (10.9%). Chronic side effects were very rare (4.7%) and as follow: fibrosis (1%), chronic diarrhea (1%), intestinal obstruction (0.5%), impotence (0.5%), and chronic pain (0.5%)



Discussion

Rectal cancer is one of the most frequently diagnosed malignancies of the gastro-intestinal tract in the western world (5). In the United States, cancer of the large bowel is the second most common cause of cancer death after cancer of the lung. (14) The incidence of rectal cancer in USA is less than in Kuwait (3-4).

Our patients were younger at presentation. For instance, the median age of all patients was 51 years compared to the west (1). Also age did not have any significant influence on local control or survival as suggested by some studies. (9). It was surprising to find that there were not more patients, who claimed a family history of rectal cancer in view of high incidence of consanguineous marriage in Kuwait as only 13.4% of positive family history reported among the whole group. Almost 20% of the patients reported were found to have circumferential tumors by colonoscopy and this has not been found to be associated with prognosis.

The duration of symptoms was more than 2 months in 57.8% of patients, suggesting delayed presentation and referral to specialized centers. About 59.1% of patients had locally advanced growths signifying the lack of screening programs as well as delayed diagnosis. Pre-treatment tumor marker (CEA) was not found to be a prognostic factor for survival. The rate of sphincter preservation in this study (61.1%) was comparable to that reported in literature (40-70%) (4) reflecting that most of the tumors (67.8%) were located in the upper part of the rectum (>5 cm from anal verge). Several randomized studies have found lower rates of local failure with pre-operative XRT than with surgery alone. However, only the Swedish Rectal Cancer Trial, which evaluated a short course of pre-operative XRT (25 Gy delivered in five fractions), found an advantage in overall survival (11). The authors of a subsequent meta-analysis also concluded that the combination of pre-operative XRT and surgery, as compared with surgery alone, significantly improves local control and overall survival (2). The Dutch Colorectal Cancer Group reported that the additional of short courses pre-operative radiotherapy to optimal surgery with total mesorectal excision reduced the rate of local recurrence, but did not improve two-year survival (7). The German Rectal Cancer Group randomly assigned 823 patients with clinically

staged T3/T4 or node-positive rectal cancer to the same chemo-radiotherapy regimen administered either pre-operatively or postoperatively: 50.4 Gy in 28 daily fractions to the tumor and pelvic lymph nodes concurrent with infusional 5-FU (1000 mg/m² daily for five days during the first and fifth weeks of XRT). They concluded that pre-operative chemo-radiotherapy, as compared with postoperative chemo-radiotherapy, improved local control and were associated with reduced toxicity but did not improve overall survival (10). Because of such results, pre-operative XRT was started in our center over the past three years.

The disease-free survival (42.6%) for patients treated with radio chemotherapy in our series is slightly lower than that reported from randomized trials recently (8,12-13). Also, pre-operative XRT was not superior in terms of local control in comparison with postoperative XRT. Patients treated with radio-chemotherapy in our series experienced more local recurrence (18.7%) than that reported in the Norwegian trial (12%), the Gastrointestinal Intergroup trial (10%) and the Intergroup 0114 trial (11%) (8, 12-13). This can be

partly attributed to the possible bias effect from such retrospective analyses and to the non-standardized criteria for adjuvant treatment. Since more than 60% of our patients had locally advanced or metastatic diseases as well as late referral to tertiary care centers have contributed significantly to our results.

Conclusions

Rectal and rectosigmoid cancer in Kuwait is different from western countries with a high propensity for locally advanced tumors because of delayed referral and misdiagnosis. Improved local control and survival can be achieved by careful patient selection and judicious use of adjunctive therapy and surgery. Analysis of results is also more meaningful based on clinically staged categories of patients as is routinely done for most other tumors.

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