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Extended Abstract

A Comparison of Post-treatment Quality of Life Outcomes for Endoluminal Brachytherapy and Chemoradiation for the Treatment of Localized Rectal Cancer

Azah A Althumairi
Johns Hopkins University School of Medicine, USA

Keywords: Endoluminal brachytherapy (EBT); Neoadjuvant chemoradiation (CRT) Rectal cancer; Quality of life (QOL); EORTC QLQ-C30; EORTC QLQ-CR29

Introduction

The current standard of care established in large randomized phase III trials for locally advanced distal rectal cancer (stage II and III) is neoadjuvant chemoradiation (CRT) with 5-fluorouracil (5-FU) based chemotherapy and external beam radiation with a total dose of 50.4 Gy delivered in 28 fractions over 5-6 weeks. Neoadjuvant treatment is then followed with total mesorectal excision (TME) by either a low anterior resection (LAR) or abdominoperineal resection (APR) in 6 – 8 weeks [1]. This regimen has been shown to be associated with tumor pathological complete response (pCR) rates of 8.0% – 19.0%, and local recurrence (LR) rates and overall survival (OS) rates at 10 years of 6.0% – 11.7% and 50.7% – 68.0%, respectively [2-5]. However, this current approach is associated with significant risk of adverse effects on short-term and long-term quality of life (QOL) [6]. In particular, strong associations with poor social and emotional functioning, poor body image and sexuality, defecatory dysfunction, and pain have been demonstrated following treatment for rectal cancer [7-9]. In an attempt to improve QOL by decreasing treatment side effects, long term effects, and shortening the duration of therapy, investigators at McGill University have investigated high dose rate endorectal brachytherapy (EBT) as a neoadjuvant monotherapy for locally advanced rectal cancer [10]. This treatment consists of 4 fractions of 6.5 Gy given over 4 consecutive days followed by surgery (TME) in 4 - 8 weeks [10]. With this technique, a focused high dose of ionizing radiation is delivered to the tumor only, limiting the dose of radiation to adjacent normal structures including small bowel, bladder, prostate and skin [10,11]. In the McGill series of 47 patients, the pathologic CR rate was 32.0%, the 5 year LR rate was 5.0%, and the DFS was 65.0% [10]. This neoadjuvant monotherapy delivered over short periods of time and resulting in high pCR rates is a very attractive modality but little is known about the treatment related toxicity and its impact on patient related QOL. At our institution, we performed the first prospective trial to examine the changes in symptoms and QOL of rectal cancer patients undergoing EBT for locally advanced disease. Our objectives were to assess post-treatment symptoms and QOL using validated questionnaires given prior to, during and after EBT monotherapy and compare these results to the same QOL questionnaires that were prospectively collected from rectal cancer patients treated with conventional CRT.

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Methods

Study participants (Study group) From 2010 to 2014, patients with histologically proven locally advanced rectal adenocarcinoma within 12 cm from the anal verge were prospectively enrolled in an institutional pilot study of EBT (NCT01226979). This study was approved by the institutional review board and written informed consents were obtained from all participants. Inclusion criteria included age greater than 18, and staging by magnetic resonance imaging (MRI) and / or endorectal ultrasound (EUS) demonstrating T1-3 N0-2. Patients were excluded if they had metastatic disease at the time of enrollment, concurrent other malignancy, tumors that would not allow endorectal probe insertion, or previous pelvic radiation. Endoscopic assessment of the rectal tumor was performed with placement of fiducial markers proximal and distal to the tumor. EBT was performed via insertion of a flexible silicone endorectal applicator that delivered a high, non-uniform dose of RT (6.5 Gy per day on four consecutive days) to the rectal tumor and surrounding mesorectum. The applicator was positioned in the rectum using MRI guidance while in lithotomy position and each fraction was delivered over approximately 15 minutes using a micro Selectron high-dose-rate iridium-192 remote after loading system (Nucletron). Treatment planning was performed using the Oncentra brachytherapy planning system (Nucletron) [10]. The type of surgery performed (LAR vs. APR) was determined at the discretion of the surgeon. Assessment of clinical response rates was performed by comparing direct endoscopic visualization at initial evaluation with inspection prior to resection and by sequential imaging with pelvic MRI and positron emission tomography (PET) / CT scan performed at an average period of one month following the completion of treatment and prior to surgical resection. To determine pathological response, a designated single pathologist examined each surgical specimen. For the designation of pCR, no viable tumor cells could be present within the primary tumor. Following EBT, patients received 5-FU based chemotherapy at the discretion of their oncologist.

Study participants (Control group):

From 2006 to 2010, 50 patients undergoing neoadjuvant CRT for locally advanced rectal adenocarcinoma (T3, T4 or node positive disease on imaging) were enrolled in a prospective study to examine QOL as previously reported [6]. Similar to the study group, patients were evaluated with laboratory studies and staged with appropriate imaging studies. Radiation therapy was administered at 1.8 Gy to 2.0 Gy doses according to the standard 3-field technique. The whole pelvis was treated with 45 Gy followed by a 5.4 Gy boost to the primary tumor and involved lymphadenopathy. Concurrent chemotherapy was given in the form of oral capecitabine 7 days a week for a dosage of 825 mg/m2 twice daily.

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General and colorectal QOL assessment:

The validated QOL instruments included in this study are the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC QLQ-CR29. The QLQ-C30 is general cancer instrument which consists of 30-items that evaluate global QOL, 5 functional scales, (physical, role, cognitive, emotional, and social), and 9 symptom scales (fatigue, nausea / vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) [12]. The EORTC QLQ-CR29 contains 29-items that evaluate 3 functional QOL items (body image, anxiety, weight) and 14 symptom items (urinary frequency, blood and mucus in stool, stool frequency, urinary incontinence, dysuria, abdominal pain, buttock pain, bloated feeling, dry mouth, hair loss, trouble with taste, flatulence, fecal incontinence, sore skin) that are associated with colorectal cancer and its treatment [13]. There are different scales for patients with or without stoma, and different questions to evaluate sexual function for men and women [13]. For both QLQ-C30 and QLQ-CR29, the responses are scored on a Likert scale of 4 response categories. Higher functional and global QOL domain scores indicated increased function and better QOL, and higher symptom scores represent worse symptoms. Both questionnaires were administered to patients undergoing EBT at 3 time points: (1) within 4 weeks before the start of EBT; (2) during the 4 day treatment; and (3) at a 3 – 6 weeks follow-up visit after the end of EBT. For the control group undergoing conventional neoadjuvant therapy, the validated questionnaires were administered (1) within 3 weeks prior to starting therapy, (2) during the 4th week of chemoradiation therapy, and (3) one month following therapy at a follow-up clinic visit. Provider-rated toxicity scores Patients were interviewed by a healthcare provider to determine the presence of the following treatment-related toxicities: urinary frequency, urinary incontinence, bladder spasms, cystitis, diarrhea, stool incontinence, prostatitis, nausea, vomiting, dehydration, vaginal mucositis, and dermatitis. In accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, toxicities were graded 1 – 5 at the same intervals that the QOL surveys were administered.

Discussion:

In our prospective trial of high dose EBT for rectal cancer, we found a primary tumor pCR rate of 28.0% which is comparable to the EBT outcomes demonstrated by Young et al. [10]. Although, intraluminal radiation therapy appeared to be well tolerated by our patients, our data on symptoms and QOL suggested higher patient reported side effects with EBT.Grade 3 toxicity following EBT, although not statistically significant when compared to conventional CRT, was high (31.0%). In EBT patients, the short-term functional QOL and symptoms scores worsened significantly when comparing pretreatment to post-treatment. When the difference in the mean pretreatment baseline scores and post-treatment scores from EBT was compared to similar time points during conventional CRT, several significantly worse reported

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symptoms and functional outcomes were found. Examining all time points evaluated for EBT and CRT (baseline, during treatment, and following treatment) patients undergoing CRT return to baseline scores at 3 – 6 weeks while patients undergoing EBT do not. This may be a function of time since the end of treatment surveys are administered 9 – 12 weeks later in the CRT patients and only 4 weeks later in the EBT patients.

Conclusion:

Although EBT is an effective alternative, rectal cancer patients may experience worse global QOL and significantly more gastrointestinal symptoms following treatment. Efforts should be made to minimize these symptoms during treatment. Further studies are needed to determine the long-term effects of EBT on QOL.

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