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Original article

Bowel morbidity following radiochemotherapy and image-guided adaptive brachytherapy for cervical cancer: Physician- and patient reported outcome from the EMBRACE study

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ABSTRACT

Background/Purpose: This study describes late bowel morbidity prospectively assessed in the multi-institutional EMBRACE study on MRI-guided adaptive brachytherapy in locally advanced cervical cancer (LACC).

Materials/Methods: A total of 1176 patients were analyzed. Physician reported morbidity (CTCAE v.3.0) and patient reported outcome (PRO) (EORTC QLQ C30/CX24) were assessed at baseline and at regular follow-up.

Results: At 3/5 years the actuarial incidence of bowel morbidity grade 3–4 was 5.0%/5.9%, including incidence of stenosis/stricture/fistula of 2.0%/2.6%. Grade 1–2 morbidity was pronounced with prevalence rates of 28–33% during follow-up. Diarrhea and flatulence were most frequently reported, significantly increased after 3 months and remained elevated during follow-up. Incontinence gradually worsened with time. PRO revealed high prevalence rates. Diarrhea ≥"a little" increased from 26% to 37% at baseline to 3 months and remained elevated, difficulty in controlling bowel increased from 11% to 26% at baseline to 3 months gradually worsening with time. Constipation and abdominal cramps improved after treatment.

Conclusion: Bowel morbidity reported in this large cohort of LACC patients was limited regarding severe/life-threatening events. Mild-moderate diarrhea, flatulence and incontinence were prevalent after treatment with PROs indicating a considerable and clinically relevant burden. Critical knowledge based on the extent and manifestation pattern of treatment-related morbidity will serve future patient management.

Major developments in the treatment of locally advanced cervical cancer (LACC) have emerged during the last two decades. With the introduction of Image-Guided Adaptive Brachytherapy (IGABT) in combination with radiochemotherapy (RCHT), significant improvement in disease outcome has been demonstrated and in parallel, IGABT studies have indicated reduction of severe treatment-related morbidity compared to historical series [1–8]. The international study on MRI-guided Brachytherapy in locally Advanced Cervical cancer (EMBRACE) [9] was initiated in 2008 to introduce MRI-based 3D-4D brachytherapy (BT) in LACC in a multi-institutional setting within the frame of a prospective observational study. The general aim of EMBRACE was among others to establish a benchmark for clinical outcome with IGABT regarding local control, survival, morbidity and quality of life (QoL).

With improvements in disease outcome and an increasing cohort of cancer survivors, it is necessary to identify and manage the clinically relevant burden and long-term consequences of the cancer treatment. Traditionally, focus has been on severe treatment-related morbidity [10–13], but recent studies indicate, that mild and moderate morbidity affects daily life in cancer survivors [14–17], and that application of patient reported outcome (PRO) is useful in detecting the patients' symptom burden [18–20].

During pelvic RCHT various parts of the gastrointestinal (GI) tract are being exposed, consequently causing radiation-induced toxicity and risk of persistent morbidity. Permanent changes in

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bowel habits are often a result of changes throughout the GI-tract, and results in a variety of symptom profiles [21].

The aim of present EMBRACE report is to provide a descriptive overview of late bowel morbidity reflecting the different symptoms in addition to what has been published so far for vagina and rectum [15,22] following IGABT for LACC including both physician reported morbidity and PRO.

Materials and methods

Patients

From July 2008 to December 2015 patients from 24 institutions were registered in EMBRACE, supported by the GEC-ESTRO (Groupe Européen de Curiethérapie – European SocieTy of Radiotherapy and Oncology) Gynaecologic Group. Patients with histologically proven cancer of the uterine cervix, FIGO stage IB-IVB considered suitable for curative treatment with definitive RCHT and IGABT were included. Patients with metastatic disease beyond the level of L1-L2 at time of diagnosis were excluded. All patients signed informed consent, and the study [9] was approved by the respective National Ethics Committees.

Treatment

Treatment included external beam radiotherapy (EBRT) delivered either as 3-dimensional conformal radiation therapy (3DCRT) or intensity modulated radiotherapy (IMRT)/volumetric arc therapy (VMAT). Concomitant chemotherapy with cisplatin was administered ideally for 5–6 cycles. The clinical target volume (CTV) for EBRT encompassed the gross tumor volume at diagnosis (GTV-T_D), uterus, parametria, the proximal part of vagina and the pelvic lymph node regions. EBRT dose prescription was 45–50 Gy in 1.8–2.0 Gy fractions, 5 fractions per week with boosting of pathological lymph nodes performed with sequential or simultaneous integrated techniques. Para-aortic irradiation was applied according to institutional practice. IGABT was delivered as high-dose-rate (HDR) BT or pulsed-dose-rate (PDR) BT with MRI at least for the first fraction. Dose prescription was performed according to institutional practice, whereas contouring and reporting was done according to the GEC-ESTRO recommendations [23,24] and the EMBRACE protocol.

Assessment of outcome

The Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) was used including five single symptoms (diarrhea, flatulence, incontinence (anal), stenosis/stricture and fistula) and a free text option to report other GI events. In this analysis GI bleeding was not included as a specific endpoint. Rectal morbidity including bleeding has been previously analyzed [22].

PRO was assessed according to The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 and the cervical cancer module CX24, comprising 4 bowel-related single items of diarrhea, constipation, abdominal cramps and difficulty in controlling bowel. Patients rated the intensity of symptoms with the categories "not at all", "a little", "quite a bit" and "very much". The percentage of patients reporting any burdens of symptoms were summarized in $\geq$ "a little", and patients reporting "substantial" burden of symptoms as described in previous literature [25,26] summarized in $\geq$ "quite a bit".

Assessments were performed at baseline (BL) prior to treatment and at regular follow-up every 3 months the first year, every 6 months the second and third year and yearly afterward. Patients with BL information and at least one follow-up were included in the study.

Statistical methods

Single bowel symptoms were analyzed separately, and for the CTCAE analysis the symptoms were also combined in an overall bowel morbidity score including other GI events. Crude incidences with maximum grading per patient during follow-up were calculated. Actuarial analysis with Kaplan–Meier estimates was performed for CTCAE scorings, and time to event calculated from end of treatment to the date of occurrence of first adverse event or last follow-up. Events were defined in patients with any bowel morbidity ($G \geq 1$), grade 2 and higher ($G \geq 2$), and grade 3 and higher ($G \geq 3$). Temporal patterns of the symptoms were analyzed through prevalence proportions at each follow-up and compared by nonparametric statistics using the Wilcoxon matched pairs signed rank test. CTCAE diarrhea and incontinence scores were associated with PRO categories of diarrhea and difficulty in controlling bowel by including every observation per se (over all time points).

No imputations were done and single missing datum was eliminated from analyses and handled as missing-at-random. The 95% confidence interval (CI) was given, and statistical significance was assigned at a level of $p < 0.05$ (two-sided). The SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. was used.

Results

From the 1416 patients registered in the database at closure for this analysis (Aug. 2016), patients not meeting selection criteria or not receiving treatment as planned ($n = 61$), with suspicion or evidence of disease at 3 months ($n = 69$), and missing BL morbidity and/or any follow-up information were excluded ($n = 110$), leaving a total of 1176 patients evaluable for morbidity analysis, and 914 patients evaluable for PRO analysis (Appendix A). Median follow-up time was 27 months (range 1–85). Patient, disease and treatment characteristics are provided in Table 1.

Physician reported morbidity and PRO at baseline

The physician reported symptoms at BL were limited with crude incidences $G \geq 1$ of 5.0%, $G \geq 2$ of 2.9% and only one G3 event registered (Table 2). No $G \geq 2$ bowel stenosis/stricture or fistula was present at BL. Constipation and abdominal cramps were the most frequently reported among the PROs at BL and substantially present in 11.5% and 12.6%, respectively. Substantial patient reported diarrhea and difficulty in controlling bowel were 6.5% and 1.9%, respectively.

Physician reported morbidity and PRO during follow-up

Overall bowel morbidity is shown in Table 2 with crude incidences of G1 symptoms reported by physicians in 42.9%, G2 symptoms in 14.9% and G3-4 symptoms in 3.6% of the patients. One patient died due to a small bowel necrosis. In absolute numbers a total of 51 $G \geq 3$ events were reported in 43 patients, 12 being other GI events reported as abdominal pain (5 events), perforation and ileus (6 events) and colitis (1 event). The corresponding actuarial estimates are shown in Fig. 1, revealing 3/5-years estimates $G \geq 3$ of 5.0%/5.9% (CI: 3.4%–6.6%/3.9%–7.9%).

Diarrhea was the most frequent single bowel symptom with crude incidence $G \geq 1$ of 42.3%, 8.7% for $G \geq 2$, and 1.5% for $G \geq 3$, followed by flatulence (40.8% $G \geq 1$ and 8.2% G2) and incontinence (13.5% $G \geq 1$, 2.4% $G \geq 2$, and 0.4% $G \geq 3$). Crude incidences of stenosis/stricture and fistula $G \geq 2$ were 1.3% ($n = 19$ events in 16 patients) and 0.5% ($n = 7$ events in 6 patients), from which $G \geq 3$ was 1% ($n = 12$ events in 12 patients) and 0.4% ($n = 6$ events in 5 patients), respectively.

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