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Original article

Physician assessed and patient reported urinary morbidity after radio-chemotherapy and image guided adaptive brachytherapy for locally advanced cervical cancer

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ABSTRACT

Background and purpose: The EMBRACE study is a prospective multi-institutional study on MRI guided adaptive brachytherapy (IGABT) in locally advanced cervix cancer (LACC). This analysis describes early to late urinary morbidity assessed by physicians and patients (PRO).

Material and methods: A total of 1176 patients were analysed. Median follow up (FU) was 27 (1–83) months. Morbidity (CTCAE v.3) and PRO (EORTC QLQ-C30&CX24) was prospectively assessed at baseline (BL), and during FU.

Results: The most frequent symptoms were frequency/urgency, incontinence, and cystitis with grade 2–4 prevalence rates of 4.3%, 5.0% and 1.7% and grade 1–4 prevalence rates of 24.5%, 16.1% and 5.8% at 3-years. The most frequent PRO endpoints were "urinary frequency" and "leaking of urine". Prevalence of "Quite a bit" or "very much" bother fluctuated from 14.0% to 21.5% for "frequency", while "leaking of urine" increased from 4.6% at BL to 9.3% at 3-years.

Actuarial 3-year incidence of grade 3–4 urinary morbidity was 5.3% with most events being urinary frequency, incontinence and ureteral strictures. Grade 3–4 fistula, bleeding, spasm and cystitis were all <1.0% at 3/5-years. No grade 5 toxicity occurred.

Conclusion: Urinary grade 3–4 morbidity with IGABT was limited. Urinary morbidity grade 2–4 comprises mainly frequency/urgency, incontinence and cystitis and has considerable prevalence in PRO. Various urinary morbidity endpoints have different patterns of manifestation and time course.

Introduction of image-guided adaptive brachytherapy (IGABT) with repetitive imaging has improved disease outcome and generally reduced toxicity in locally advanced cervical cancer (LACC) [1–9]. IGABT is based on assessment of the tumour extent at diagnosis and at time of brachytherapy preferably with magnetic resonance imaging (MRI). Dose optimisation can be performed according to predefined dose planning aims and constraints leading to an individually sculpted isodose tailored to targets and organs at risk (OAR) [10–13]. Introduction of IGABT has resulted in development of MRI-compatible applicators for combined intracavitary and interstitial (IC/IS) BT [14–16]. These technical developments make it possible to further optimise the dose with improved target coverage and reduced dose to surrounding OAR resulting in improved outcome [17].

Assessment of treatment related morbidity is important in radiotherapy. Knowledge of morbidity (together with the therapeutic effect) is necessary to define the therapeutic ratio and to determine the specific benefit of a given treatment.

Reports on urinary morbidity following IGABT have so far mainly included retrospective series of patients with physician-assessed morbidity [1,3–9].

The EMBRACE study (www.embrace.dk) is a prospective multi-institutional longitudinal study with focus on IGABT in LACC. One of the specific aims for the study is to establish a benchmark for clinical outcome with respect to local control, survival, morbidity and QoL.

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This EMBRACE study investigation provides a comprehensive and detailed description of late urinary morbidity assessed by the physician and the patient following IGABT for LACC.

Material and methods

Patients

The EMBRACE study opened in July 2008 and finalised accrual in December 2015 with 1416 patients from 24 centres. Patients eligible for inclusion in the EMBRACE study were previously untreated, biopsy proven cervical cancer, FIGO stage IB-IVA (and stage IVB with metastatic nodes below L1 only) treated with curative definitive radio (chemo)therapy and IGABT.

For this urinary morbidity analysis, patients were excluded when: not meeting the selection criteria or not receiving treatment as planned ($n = 61$), having suspicion or evidence of disease at 3 months ($n = 69$), or missing morbidity data at baseline (BL) or all follow up ($n = 110$). This left a total of 1176 patients with BL information and at least one follow up. For the PRO, baseline registration and at least one follow up was available in 914 patients.

The study was approved by the local ethics committee in each participating centre [18].

Treatment

Treatment included external beam radiotherapy (EBRT) and concomitant chemotherapy followed by IGABT aiming for a maximum overall treatment time of 50 days. EBRT was delivered as conformal radiotherapy or as intensity modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT). The clinical target volume (CTV) for EBRT included the primary gross tumour volume at diagnosis (GTV-T_D), uterus, parametria and vagina at least 2 cm below the GTV-T_D and pelvic lymph node regions. Prescribed dose to the CTV was 45–50 Gy in 25–30 fractions. Lymph node boosting to pathological lymph nodes was performed as a simultaneous integrated boost or as post-boost after whole pelvis irradiation (Table 1). Concomitant chemotherapy was administered mainly by use of weekly cisplatin. IGABT was delivered with high dose rate (HDR) BT or pulsed dose rate (PDR) BT. MRI was required for first BT fraction, and 3-dimensionel imaging (CT or MRI) was required for the remaining BT fractions. Dose prescription for BT was performed according to institutional practice in all centres.

Doses to the tumour volumes and OARs were reported according to the GEC-ESTRO recommendations [10,18]. This included dose to the ICRU 38 bladder point and the minimum dose to the most exposed 2 cm^3 ($D_{2\ cm^3}$) of the bladder was reported.

Physician assessed morbidity and PRO

Physician assessed morbidity was recorded prospectively according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). Eight individual urinary endpoints (frequency/urgency, incontinence, bladder spasm, bladder stenosis, ureteral stricture, cystitis, bleeding and fistula) were included. Each endpoint was graded as a mild adverse event (AE) (grade 1), moderate AE (grade 2), severe AE (grade 3), life-threatening or disabling AE (grade 4) and death related to AE (grade 5). The PRO was scored according to the EORTC Quality of Life Questionnaires C30&CX24. This system includes 4 possible answers for each item: "not at all", "a little", "quite a bit" and "very much". Morbidity and PRO were assessed at baseline (BL) before treatment, every 3 months within the first year after treatment, every 6 months within the second and third year, and annually thereafter.

Table 1
Patient ($n = 1176$) and treatment characteristics. AC = adenocarcinoma; AdSQ = adenosquamous carcinoma; D2cm^3 = the minimum dose evaluated in the maximally exposed 2 cm^3 of an organ at risk; EBRT = external beam radiotherapy; EQD_2 = equal dose in 2 gray fractions; Gy = gray; HDR = high dose rate; IC = intracavitary; ICRU = International commission on radiation units; IC/IS = intracavitary/interstitial; IMRT = intensity modulate radiotherapy; PCB = post conformal boost; PDR = pulse dose rate; PTV-E = elective planning target volume; SIB = simultaneous integrated boost; SQ = squamous cell carcinoma.

Median age in years (range)		49 (22–91)
Performance status	0–1	98%
	2–3	2%
Chronic disease		29%
Smoker		30%
FIGO stage	IB	19%
	IIA	5%
	IIB	52%
	IIIA	<1%
	IIIB	15%
	IVA	3%
	IVB	5%
Baseline hydronephrosis	Yes	7%
	No	93%
Bladder involvement on imaging	Yes	5%
	No	95%
Histology	SQ	83%
	AC	14%
	AdSQ	3%
EBRT technique	Conformal	63%
	IMRT/VMAT	37%
Median EBRT PTV-E dose		45.0 Gy (41.4–51.0)
Median number of fractions		25 (20–32)
EBRT lymph node boost	SIB	12%
	PCB	21%
Median lymph node boost dose		59.0 Gy (50.0–66.6)
Concomitant cisplatin		95%
Brachytherapy dose rate	HDR	57%
	PDR	43%
Brachytherapy technique	IC	67%
	IC/IS	33%
Mean bladder ($D_{2\ cm^3}$) in EQD2 (±SD)		76.7 Gy ± 10.4
Mean ICRU bladder in EQD2 (±SD)		68.2 Gy ± 14.7

Statistical analysis

Crude incidence of each symptom was evaluated for all CTCAE categories and PRO by calculating the maximum grade for each patient during all follow up (FU). Prevalence rates were calculated for each FU as the proportion of patients with a specific symptom grading in relation to all patients. Prevalence rates were compared by non-parametric statistics by use of Wilcoxon's rank sum test.

Time to event analysis was conducted for the CTCAE-categories using actuarial Kaplan–Meier's estimates. Time to event was calculated from end of treatment, and patients were censored from analysis of morbidity at the date of last FU or disease recurrence. Patients with persisting grade 3–4 events at BL and at succeeding FUs were not scored as events in actuarial analysis. The SPSS statistical software system v.20 (IBM SPSS Statistics for windows, Version 20.0 Armonk; NY: IBM Corp.) was used for statistical analysis.

Results

In the 1176 patients analysed in this study, the median FU was 27 (1–83) months. The patient, disease and treatment characteristics are reported in Table 1.

Physician assessed morbidity

Baseline urinary symptoms

Prevalence of individual urinary symptoms at BL included mainly urinary frequency or incontinence. For other endpoints, few patients had symptoms at BL (Appendix 1).

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