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CLINICAL INVESTIGATION

Overall Severe Morbidity After Chemo-Radiation Therapy and Magnetic Resonance Imaging-Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancer: Results From the EMBRACE-I Study

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Purpose: To evaluate overall severe late morbidity (grade ≥3) in patients with locally advanced cervical cancer treated with chemo-radiation therapy and magnetic resonance image guided adaptive brachytherapy within the prospective EMBRACE-I study, and to compare the results with published literature after standard radiograph based brachytherapy (BT).

Methods and Materials: From 2008 to 2015 the EMBRACE-I study enrolled 1416 patients. Morbidity was assessed (Common Terminology Criteria for Adverse Events version 3.0) every 3 months the 1st year, every 6 months the second and third year, and yearly thereafter and 1251 patients had available follow-up on late morbidity. Morbidity events (grade 3-5) were summarized as the maximum grade during follow-up (crude incidence rates) and actuarial estimates at 3 and 5 years. To compare with the published literature on standard radiograph based BT, Common Terminology Criteria for Adverse Events scores from the EMBRACE-I study were retrospectively converted into a corresponding score in the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer system.

Results: In total, 534 severe events occurred in 270 patients; 429 events were grade 3 and 105 were grade 4 events. Actuarial estimates for grade ≥3 gastrointestinal (GI), genitourinary (GU), vaginal and fistula events at 5 years were 8.5% (95% confidence interval [CI], 6.9%-10.6%), 6.8% (95% CI, 5.4%-8.6%), 5.7% (95% CI, 4.3%-7.6%), and 3.2% (95% CI, 2.2%-4.5%), respectively. The 5-year actuarial estimate for organ-related events (GI, GU, vaginal, or fistula) was 18.4% (95% CI, 16.0%-21.2%). The 5-year actuarial estimate when aggregating all G≥3 endpoints (GI, GU, vaginal, fistulas, and non-GI/GU/vaginal) was 26.6% (95% CI, 23.8%-29.6%). Thirteen patients had a treatment-related death, 8 of which were associated with GI morbidity.

Conclusions: This report assesses severe morbidity from the largest prospective study on chemo-radiation therapy and image guided adaptive brachytherapy for locally advanced cervical cancer to date. Severe late morbidity was limited per endpoint and organ category, but considerable when aggregated across organs and all endpoints. The late morbidity results in the EMBRACE-I study compare favorably with published literature on standard radiograph based BT for GI morbidity, vaginal morbidity, and fistulas.

Introduction

The gold standard for the treatment of locally advanced cervical cancer (LACC) is chemo-radiation therapy (CRT) followed by brachytherapy (BT).[1] Approximately 2 decades ago BT evolved from a standard radiograph-based technique with dose prescription to point A, to image guided adaptive brachytherapy (IGABT). This step forward contributed to improved local control and survival.[2-6] A recent meta-analysis based on 24 studies compared standard point A radiograph-based BT and volume-based brachytherapy in LACC and showed a significant improvement in 3-year disease-free survival from 67% to 79%, a 3-year local control from 86% to 92%, and nonsignificant increase in 3-year overall survival from 72% to 79%.[7] For IGABT specifically, 5-year overall survival is now approximately 75%.[3] Consequently, a large cohort of LACC survivors is at risk of being affected by late morbidity.

The adaptive target concept introduced by GEC-ESTRO (Groupe Européen de Curiethérapie- European Society for Radiation therapy and Oncology) considers both tumor size and location at diagnosis and the tumor shrinkage caused by CRT. It allows for an increase of high dose volumes in large or poorly responding tumors and a reduction of high dose volumes in small or well-responding tumors, and therefore has the inherent potential to both increase and decrease late morbidity. A previous report comparing isodose surface volumes in IGABT with standard radiograph based BT showed an average considerable reduction of V85 Gy, V75 Gy, and V60 Gy for IGABT plans compared with standard 85 Gy point A based plans.[8] This suggests the possibility of an overall decrease in late morbidity. Although there was an average reduction of treated volume, there was also significant variation between patients depending in particular on the size of the high-risk clinical target volume (CTV_{HR}) at the time of BT. In 21% of patients, the treated volume was increased, in 41% of patients there was a reduction, and for the remaining 38% of patients volumes remained similar to 85 Gy point A based standard plans.[8] Furthermore, while the BT approach has evolved, external beam radiation therapy (EBRT) has also advanced with new techniques such as intensity modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT) and image guided radiation therapy.

Previous reports on late morbidity after IGABT have primarily been based on retrospective series or smaller prospective cohorts. However, to avoid the risk of underestimation that comes with retrospective assessment and to reliably assess rare events, a large prospective study is essential.

In 2008 the EMBRACE-I study was initiated, the first large-scale prospective study with a focus on IGABT for LACC. The primary endpoints of the study were local control and late morbidity. The EMBRACE-I collaborative group has previously published organ-specific reports on mild, moderate and severe morbidity.[9-14] This report aims to provide a comprehensive overview of physician-assessed severe morbidity events (grade ≥3) across organs in the EMBRACE-I cohort and benchmark it to the literature on standard radiograph based BT.

Methods and Materials

Study design and patients

The EMBRACE-I study (NCT00920920) is a prospective observational multi-institutional study that started accrual in 2008 with patients included from 24 centers worldwide and finished accrual in 2015 (www.embracestudy.dk). The protocol is registered with ClinicalTrials.gov, and may be viewed online at https://clinicaltrials.gov/ct2/show/NCT00920920. The study was approved in all institutions according to local ethics requirements and written informed consent was obtained from all patients. Patients eligible for definitive CRT with IGABT for biopsy verified International Federation of Gynecology and Obstetrics (FIGO) stage IB-IVB LACC were candidates for inclusion. Information on study design, patient selection, and treatment has been provided in more detail in a previous publication.[3] This analysis was based on data extracted on July 15, 2019.

Treatment

Treatment consisted of EBRT with concomitant chemotherapy and IGABT. EBRT was delivered as either 3-dimensional conformal radiation therapy (3D-CRT), IMRT, or VMAT. The prescription dose to the elective pelvic target volume was according to institutional practice and ranged from 45 to 50 Gy. Para-aortic irradiation and lymph node boosts (simultaneously integrated or sequential) were administered according to institutional criteria. Cisplatin was administered weekly (40 mg/m^2 body surface) during treatment. IGABT was delivered as either pulsed dose rate (PDR) or high-dose-rate, and dose prescription was according to institutional practice. MRI was required for at least the first brachytherapy fraction. The aim for overall treatment time (OTT) was 50 days as maximum. GEC-ESTRO recommendations were followed for contouring and reporting of doses to target volumes and organs at risk (OAR).[15,16] Normal tissue constraints were according to institutional practice. Total equieffective doses (EBRT and BT) in 2 Gy per fraction (EQD2) were calculated assuming an α/β ratio of 3 Gy for organs at risk ($EQD2_3$) and 10 Gy for tumor ($EQD2_{10}$) and for PDR a half-time for sublethal damage repair of 1.5 hours.[16,17]

Assessment and quality assurance of morbidity

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used for grading physician-assessed morbidity.[18] Morbidity assessments were performed at baseline and every 3 months in the first year of follow-up, every 6 months in the second and third year, and yearly thereafter. Physical and gynecologic examinations were performed at each follow-up and pelvic MRI were performed at 3 and 12 months as a minimum. In case of a suspected recurrence a complete patient workup was performed, including gynecologic examination in general anesthesia with biopsy if possible/relevant, MRI of the pelvis, CT thorax and abdomen, and ultrasound-guided fine needle aspiration in case of suspected lymph nodes. Assessments were censored at the time of recurrence in patients with evidence of local, nodal, or systemic relapse. All organ-related severe morbidity events (grade 3-5) were reviewed to confirm the correct grading. In unclear cases, the center was contacted for additional information.[19]

Conversion of Common Terminology Criteria for Adverse Events version 3.0 morbidity into Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer morbidity scale

In the standard radiograph based BT era, late morbidity was often graded according to the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC).[20] To compare CTCAE scores from the EMBRACE-I study were retrospectively converted into a corresponding score in the RTOG/EORTC system to the best of ability. The RTOG/EORTC system does not include bladder fistulas in the scoring of bladder morbidity. However, because this was the practice in the publications used for comparison, CTCAE scorings were converted into an RTOG/EORTC bladder grade encompassing bladder fistulas.

Statistical analyses

The morbidity endpoints in this analysis derived from 2 sources: preselected endpoints described in the study case report form and morbidity endpoints compiled from free-text fields in the case report form.

Morbidity endpoints were analyzed separately and aggregated as an overall per organ and an overall of all endpoints. As fistulas involve more than one organ they were reported outside the organ categories to avoid counting them twice. Crude incidence rates and actuarial estimates were used as statistical summary measures. Crude incidence rates were calculated using the maximum scoring during follow-up. Actuarial estimates were calculated with the Kaplan-Meier method and 95% confidence intervals were calculated. Time was calculated from the end of treatment to the first grade $\geq$3 event. Censoring occurred at the last follow-up or at the time of any first local, nodal, or systemic recurrence. Treatment-related deaths were often complex and were reported descriptively as a case story for each patient, instead of attributed to a single grade 5 event. All grade 3 to 4 morbidity events preceding treatment-related deaths are reported.

Endpoints were divided according to FIGO stage (2009 edition[21]). FIGO stage 4B patients were allocated to a local FIGO stage based on the clinical examination at baseline.

Actuarial time to event curves (Kaplan-Meier) for the different stages were compared with the log-rank test. The significance level was set at 0.001 due to multiple testing according to the Bonferroni adjustment (39 endpoints).

The development of morbidity after the occurrence of a grade ≥3 event was analyzed for preselected endpoints. To have sufficient events for providing descriptive analysis, only endpoints occurring in ≥10 patients were analyzed. For each endpoint, patients with ≥3 follow-up assessments after the occurrence of a severe event were included in the analysis. Patients were divided into 4 groups: patients with a median grade of 0 (resolves), patients with a median grade between 0.5 to 1.5 (improves), patients with a median grade of ≥2 (persists), and patients where further assessment was not possible due to altered organ function after an intervention not related to the endpoint in question (eg, incontinence after ileal conduit urinary diversion. IBM SPSS statistical software for Windows (IBM Corp., version 26.0; Armonk, NY) was used for all statistical analyses.

Results

The EMBRACE-I study enrolled 1416 patients. Seventeen patients were registered in the database without any further information, 21 patients did not fulfill the inclusion criteria, and 34 patients did not receive treatment as per protocol (Fig. E1). Three patients were excluded from follow-up by individual centers as the aim for OTT was exceeded. This reason for exclusion from follow-up was not per protocol and was not enforced in other patients with extended OTT. Of the remaining 1341 patients, 68 patients did not reach assessment of late morbidity at 3 months due to local, nodal, systemic recurrence or disease-related death and 22 patients had no available information on late morbidity, leaving 1251 patients with available follow-up on late morbidity (3 months and onwards) which were chosen for further analyses. The median follow-up was 48 months (interquartile range, 20-62). Patient, disease, and treatment characteristics are shown in Table 1.

Table 2 shows baseline incidence, crude incidence rates, and actuarial estimates for grade ≥3 morbidity. In total, 534 severe events occurred in 270 patients; 429 events were grade 3 (80.3%) and 105 were grade 4 events (19.7%). The 5-year actuarial estimate when aggregating all endpoints was 26.6% (95% confidence interval [CI], 23.8%-29.6%). For organ-related morbidity (gastrointestinal [GI], genitourinary [GU], vaginal, or fistula) 330 grade ≥3 events occurred in 183 patients. Actuarial estimates for grade ≥3 GI, GU, vaginal, and fistula events at 5 years were 8.5% (95% CI, 6.9%-10.6%), 6.8% (95% CI, 5.4%-8.6%), 5.7% (95% CI, 4.3%-7.6%), and 3.2% (95% CI, 2.2%-4.5%), respectively. The actuarial estimate for G≥3 organ-related events (GI, GU, vaginal, or fistula) at 5 years was 18.4% (95% CI, 16.0%-21.2%). In total, 98 out of 117 (84%) GI morbidity events, 92 out of 112 (82%) GU morbidity events, 41 out of 59 (69%) vaginal morbidity events, and 27 out of 34 (79%) fistulas events occurred within the first 3 years of follow-up. The most common single endpoints (5-year actuarial estimates) were fatigue (6.5% [95% CI, 5.1%-8.4%]), insomnia (4.8% [95% CI, 3.6%-6.5%]), vaginal stenosis (4.0% [95% CI, 2.8%-5.7%]), fistulas (3.2% [95% CI, 2.2%-4.5%]), GI stenosis (2.8% [95% CI, 1.9%-4.2%]), GI bleeding (2.2% [95% CI, 1.4%-3.4%]), ureteral strictures (2.9% [95% CI, 2.1%-4.2%]), urinary incontinence (2.2% [95% CI, 1.4%-3.3%]), and hot flashes (2.1% [95% CI, 1.4%-3.2%]). Five out of 10 patients with ileus also had severe GI stenosis. For bowel perforation, 2 events were likely not treatment-related (one occurred in relation to drainage of an abscess and the other was a perforated appendicitis).

The cumulative actuarial risk of fistulas grade ≥3 at 5 years when dividing patients according to local FIGO stage was 1.6% (95% CI, 0.5%-4.8%) for stage I, 1.3% (95% CI, 0.6%-2.7%) for stage II, 10.2% (95% CI, 6.3%-16.2%) for stage III, and 18.6% (95% CI, 7.8%-40.6%) for stage IVA (P <.001). For ureteral strictures grade ≥3 the risk was 0.0% for stage I, 1.0% (95% CI, 0.4%-2.1%) for stage II, 10.8% (95% CI, 6.9%-16.8 %) for stage III, and 21.3% (95% CI, 9.8%-42.9%) for stage IVA (P <.001), and for urinary incontinence grade ≥3 the risk was 1.2% (95% CI, 0.3%-4.7%) for stage I, 1.5% (95% CI, 0.8%-2.9%) for stage II, 4.5% (95% CI, 2.3%-8.8%) for stage III, and 9.7% (95% CI, 3.2%-27.2%) for stage IVA (P <.001). The remaining endpoints had P values above the adjusted significance level (Table E1).

The cumulative actuarial risk of suffering a treatment-related death was 1.2% (95% CI, 0.7%-2.2%) at 5 years. Table 3 shows case stories for the 13 patients with treatment-related deaths. One patient died at the end of EBRT likely due to sepsis secondary to neutropenia. For the remaining 12 patients, the median time from the end of treatment to death was 44 months (interquartile range, 27-67). In 6 patients the clinical conclusion on the cause of death was attributed to more than one CTCAE organ category. In total, 8 were related to GI events, 5 were related to infection, 4 were related to GU events, and 4 were related to fistulas. The most common occurring single grade 3 to 4 endpoints preceding death were sepsis (5 patients), bowel perforation (4 patients), bowel necrosis (4 patients), diarrhea (4 patients), fistulas (4 patients), GI bleeding (3 patients), renal failure (3 patients), and ureteral stricture (3 patients).

Table 4 shows disease characteristics and doses to OAR for 34 patients with grade 3 to 4 fistula events and fistula events divided into groups according to organ involvement. Among the 42 fistula events, the most frequent were vesicovaginal (15 events) and rectovaginal (10 events). Of patients with vesicovaginal/rectovaginal fistulas, 47%/50% had involvement of bladder/rectum or middle or lower vagina at baseline. Eight of the 68 patients (12%) with bladder involvement at baseline (mucosa involvement at cystoscopy or bladder involvement on MRI) developed a fistula involving the bladder. Two of the 12 patients (17%) with rectal involvement at baseline (rectum involvement directly

Table 1 Patient, disease, and treatment characteristics at diagnosis (n = 1251)

Patient and disease characteristics		
Age	Median (range), y	49 (21-92)
WHO performance status	0	911 (73%)
	1	314 (25%)
	2-3	26 (2%)
Comorbidity		360 (29%)
Smoker status	Yes	375 (30%)
	No	818 (65%)
	Missing	58 (5%)
Local FIGO2009 tumor stage*	1B	237 (19%)
	2A	68 (5%)
	2B	701 (56%)
	3A	15 (1%)
	3B	195 (16%)
	4A	35 (3%)
Histology	Squamous cell carcinoma	1031 (83%)
	Adenocarcinoma	174 (14%)
	Adenosquamous carcinoma	45 (4%)
Lymph node status (CT, PET-CT, or histologic confirmation)	Node positive	635 (51%)
	Node negative	616 (49%)
Invasive lymph node staging		339 (27%)
Tumor involvement of the bladder†		68 (5%)
Tumor involvement of the rectum‡		12 (1%)
Tumor involvement of the vagina§	Upper	557 (45%)
	Middle	77 (6%)
	Lower	34 (3%)
Treatment characteristics		
EBRT technique	3D-CRT	739 (59%)
	IMRT/VMAT	511 (41%)
EBRT CTV-E prescribed dose	Median dose in Gy (IQR)	45 (45-46)
EBRT CTV-E nodal regions	Pelvic	1034 (83%)
	Pelvic + PAN AND/OR inguinal	216 (17%)
EBRT treated volume 43 Gy	Median cm^3 (IQR)	2450 (2057-2944)
	Missing	30 (2%)
EBRT lymph node boost	No lymph node boost	817 (65%)
	Lymph node boost	433 (35%)
EBRT treated volume 57 Gy in LN boost patients (n = 433)	Median cm^3 (IQR)	102 (5-322)
	Missing	11 (3%)
Brachytherapy dose rate	Pulsed dose rate	530 (42%)
	High-dose-rate	719 (58%)
Brachytherapy technique	Intracavitary	726 (58%)
	Intracavitary/interstitial‖	525 (42%)
CTV_{HR} volume for the 1 brachytherapy fraction	Median cm^3 (IQR)	28 (20-40)

(*Continued*)

Table 1 (*Continued*)

Patient and disease characteristics		
Overall treatment time	Days (IQR)	46 (42-50)
CTV_{HR} D90 in $EQD2_{10}$	Median dose in Gy (IQR)	90 (85-94)
Rectum $D_{2\ cm3}$ in $EQD2_3$	Median dose in Gy (IQR)	62 (57-68)
ICRU rectovaginal point dose in $EQD2_3$	Median dose in Gy (IQR)	65 (60-71)
	Missing	26 (2%)
Bowel $D_{2\ cm3}$ in $EQD2_3$	Median dose in Gy (IQR)	57 (48-67)
Bladder $D_{2\ cm3}$ in $EQD2_3$	Median dose in Gy (IQR)	76 (69-83)
ICRU bladder point dose in $EQD2_3$	Median dose in Gy (IQR)	65 (56-76)
	Missing	28 (2%)
Sigmoid $D_{2\ cm3}$ in $EQD2_3$	Median dose in Gy (IQR)	64 (59-69)
	Missing	13 (1%)
Isodose surface volume 60 Gy in $EQD2_3$	Median cm^3 (IQR)	223 (177-290)
	Missing	4%
Isodose surface volume 75 Gy in $EQD2_3$	Median cm^3 (IQR)	114 (90-146)
	Missing	4%
Isodose surface volume 85 Gy in $EQD2_3$	Median cm^3 (IQR)	87 (69-111)
	Missing	4%
Concomitant chemotherapy (including reduced cycles)	0 cycles	97 (8%)
	1-4 cycles	288 (23%)
	≥5 cycles	866 (69%)

Missing information was below 1% unless otherwise stated.

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; CT = computed tomography; CTV-E = clinical target volume of elective field; CTV_{HR} D90 = dose received by 90% of the high-risk clinical target volume; $D_{2\ cm3}$ = minimum dose in the maximally exposed 2 cm^3; EBRT = external beam radiation therapy; $EQD2_3$ = equal dose in 2 Gy fractions with α/β of 3 for normal tissue; $EQD2_{10}$ = equal dose in 2 Gy fractions with α/β of 10 for tumor; FIGO = International Federation of Gynecology and Obstetrics; ICRU = International Commission on Radiation Units; IMRT = intensity modulated radiation therapy; IQR = interquartile range; PAN = para-aortic nodes; PET-CT = positron emission tomography-computed tomography; VMAT = volumetric arc therapy; WHO = World Health Organization.

* Eighty-seven patients with FIGO stage 4B were allocated to a local FIGO stage based on the clinical examination at baseline.

† Mucosa involved at cystoscopy or bladder involvement on magnetic resonance imaging.

‡ Rectum involvement directly palpable at clinical examination, mucosa involved at rectoscopy or rectum involvement on magnetic resonance imaging.

§ Vaginal involvement at clinical examination or magnetic resonance imaging.

‖ At least 1 fraction with intracavitary/interstitial treatment.

palpable at clinical examination, mucosa involved at rectoscopy or rectum involvement on MRI), developed a fistula involving the rectum. Eight of the 111 patients (7%) with middle or lower vaginal involvement at baseline (vaginal involvement at the clinical examination or MRI) developed a fistula involving the vagina.

Figure 1 shows the 177 patients with grade ≥3 GI, GU, or vaginal events (14%) divided into groups according to the CTCAE categories involved (fistula events are not included). In total, 148 patients (11.8%) had grade ≥3 events restricted to one CTCAE category (GI, GU, or vaginal), while 29 patients (2.3%) had grade ≥3 events from more than one category. Patients with both GI and GU events (groups B and D) had more grade ≥3 events within each CTCAE category compared with the other groups.

Figure 2 shows the development of morbidity scoring after the occurrence of a grade ≥3 event. Resolution varied from 0% (vaginal stenosis) to 74% (GI bleeding), improvement varied from 0% (vaginal stenosis) to 54% (hot flashes), and persistence varied from 5% (GI bleeding) to 100% (vaginal stenosis).

The crude incidence of RTOG/EORTC converted late morbidity grade ≥3 for small/large bowel and bladder were 6.1% and 3.5%, respectively. The actuarial estimates for RTOG/EORTC grade ≥3 late small/large bowel, bladder and vaginal morbidity were 6.4% (95% CI, 5.0%-8.1%), 3.7% (95% CI, 2.7%-5.1%), and 4.3% (95% CI, 3.2%-5.8%) at 3 years, and 8.0% (95% CI, 6.4%-10.0%), 4.2% (95% CI, 3.1%-5.8%) and 6.5% (95% CI, 5.0%-8.5%) at 5 years.

Table 2 Crude incidence rates and Kaplan-Meier estimates of grade ≥3 events (CTCAE version 3.0) in patients with at least one follow-up assessment (n = 1251)

	Baseline	Absolute numbers and crude incidence rates during follow-up			Actuarial estimates G≥3 (95% CI)	
	G≥3	G3	G4	G≥3	3 y	5 y
CTCAE GI category						
Diarrhea	1 (0.1%)	19 (1.5%)	1 (0.1%)	20 (1.6%)	1.7% (1.1-2.7%)	1.9% (1.2-3.0%)
Incontinence	0 (0.0%)	4 (0.3%)	1 (0.1%)	5 (0.4%)	0.4% (0.2-1.1%)	0.5% (0.2-1.3%)
Proctitis	0 (0.0%)	6 (0.5%)	0 (0.0%)	6 (0.5%)	0.6% (0.3-1.4%)	0.6% (0.3-1.4%)
Bleeding	0 (0.0%)	20 (1.6%)	2 (0.2%)	22* (1.8%)	2.2% (1.4-3.4%)	2.2% (1.4-3.4%)
Stenosis	0 (0.0%)	15 (1.2%)	11 (0.9%)	26 (2.1%)	2.0% (1.3-3.2%)	2.8% (1.9-4.2%)
Other GI						
Ileus	0 (0.0%)	7 (0.6%)	3 (0.2%)	10 (0.8%)	0.7% (0.4-1.6%)	1.2% (0.6-2.2%)
Bowel perforation	0 (0.0%)	2 (0.2%)	8 (0.6%)	10 (0.8%)	0.6% (0.3-1.3%)	1.1% (0.6-2.1%)
Bowel necrosis	0 (0.0%)	1 (0.1%)	5 (0.4%)	6 (0.5%)	0.5% (0.2-1.3%)	0.7% (0.3-1.5%)
Radiation enteritis	0 (0.0%)	2 (0.2%)	1 (0.1%)	3 (0.2%)	0.3% (0.1-0.9%)	0.3% (0.1-0.9%)
Abdominal pain	0 (0.0%)	5 (0.4%)	1 (0.1%)	6 (0.5%)	0.5% (0.2-1.3%)	0.7% (0.3-1.5%)
Constipation	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0.1% (0.0-0.7%)	0.1% (0.0-0.7%)
Peritonitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0.1% (0.0-0.9%)	0.1% (0.0-0.9%)
Total GI events	1	83	34	117		
Total patients w/ GI events	1 (0.1%)	54 (4.0%)	27 (2.0%)	81 (6.5%)	7.0% (5.6-8.8%)	8.5% (6.9-10.6%)
CTCAE GU category						
Frequency	8 (0.6%)	19 (1.5%)	NA†	19 (1.5%)	1.6% (1.0-2.6%)	1.8% (1.1-2.8%)
Incontinence	3 (0.2%)	18 (1.4%)	6 (0.5%)	24 (1.9%)	1.9% (1.2-2.9%)	2.2% (1.4-3.3%)
Cystitis	2 (0.2%)	13 (1.0%)	1 (0.1%)	14 (1.1%)	1.3% (0.8-2.3%)	1.3% (0.8-2.3%)
Bladder spasms	2 (0.2%)	3 (0.2%)	0 (0.0%)	3 (0.2%)	0.3% (0.1-0.9%)	0.3% (0.1-0.9%)
Bleeding	0 (0.0%)	6 (0.5%)	0 (0.0%)	6 (0.5%)	0.5% (0.2-1.3%)	0.8% (0.3-1.8%)
Ureteral stricture	24 (1.9%)	31 (2.5%)	5 (0.4%)	36§ (2.9%)	2.6% (1.8-3.8%)	2.9% (2.1-4.2%)
Other GU						
Renal failure	1 (0.1%)	3 (0.2%)	6 (0.5%)	9 (0.7%)	0.7% (0.3-1.5%)	0.7% (0.3-1.5%)
Total GU events	40	93	19	112		
Total patients w/ GU events	32 (2.6%)	59 (4.7%)	16 (1.3%)	75 (6.0%)	6.1% (4.8-7.7%)	6.8% (5.4-8.6%)
CTCAE vaginal [sub]category						
Stenosis	0 (0.0%)	36 (2.9%)	NA†	36 (2.9%)	2.1% (1.4-3.2%)	4.0% (2.8-5.7%)
Mucositis	0 (0.0%)	11 (0.9%)	3 (0.2%)	14 (1.1%)	1.2% (0.7-2.0%)	1.4% (0.8-2.3%)
Bleeding	37 (3.0%)	3 (0.2%)	2 (0.2%)	5 (0.4%)	0.5% (0.2-1.2%)	0.5% (0.2-1.2%)

(*Continued*)

Table 2 (*Continued*)

	Baseline	Absolute numbers and crude incidence rates during follow-up			Actuarial estimates G≥3 (95% CI)	
	G≥3	G3	G4	G≥3	3 y	5 y
Other vaginal						
Dyspareunia	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.2%)	0.0%	0.2% (0.0-1.3%)
Necrosis	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.2%)	0.2% (0.1-0.8%)	0.2% (0.1-0.8%)
Total vaginal events	37	54	5	59		
Total patients w/ vaginal events	37 (3.0%)	50 (4.0%)	5 (0.4%)	55 (4.4%)	3.6% (2.7-5.0%)	5.7% (4.3-7.6%)
Total fistula events	1	18	24	42		
Total patients w/ Fistulas[‡]	1 (0.1%)	13 (1.0%)	21 (1.7%)	34 (2.7%)	2.6% (1.8-3.8%)	3.2% (2.2-4.5%)
Total GI, GU, vaginal, or fistula events	79	248	82	330		
Total patients w/ GI, GU, vaginal, or fistulas events	72	128 (10.2%)	55 (4.4%)	183 (14.6%)	14.5% (12.5-16.8%)	18.4% (16.0-21.2%)
Non-GI/GU/vaginal symptoms						
Insufficiency fracture						
Pelvic ring	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.2%)	0.2% (0.1-0.9%)	0.2% (0.1-0.9%)
Femoral head	0 (0.0%)	3 (0.2%)	1 (0.1%)	4 (0.3%)	0.5% (0.2-1.2%)	0.5% (0.2-1.2%)
Pelvic fibrosis	0 (0.0%)	11 (0.9%)	0 (0.0%)	11 (0.9%)	0.8% (0.4-1.7%)	1.3% (0.7-2.5%)
Lymphedema						
Lower limb	0 (0.0%)	5 (0.4%)	0 (0.0%)	5 (0.4%)	0.4% (0.1-1.0%)	0.4% (0.1-1.0%)
Trunk or genital	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.2%)	0.2% (0.1-0.8%)	0.2% (0.1-0.8%)
Hot flashes	0 (0.0%)	23 (1.8%)	NA[†]	23 (1.8%)	2.0% (1.3-3.1%)	2.1% (1.4-3.2%)
Fatigue	10 (0.6%)	58 (4.7)	5 (0.4%)	63 (5.1%)	4.7% (3.6-6.2%)	6.5% (5.1-8.4%)
Insomnia	8 (0.6%)	43 (3.5%)	4 (0.3%)	47 (3.8%)	3.6% (2.6-5.0%)	4.8% (3.6-6.5%)
Other non-GI/GU/vaginal						
Pain (lower back/pelvic)	1 (0.1%)	6 (0.5%)	0 (0.0%)	6 (0.5%)	0.6% (0.3-1.3%)	0.6% (0.3-1.3%)
Neuropathy	0 (0.0%)	4 (0.3%)	2 (0.2%)	6 (0.5%)	0.6% (0.3-1.3%)	0.6% (0.3-1.3%)
Lymphocele	1 (0.1%)	2 (0.2%)	0 (0.0%)	2 (0.2%)	0.1% (0.0-0.6%)	0.2% (0.1-1.0%)
Pelvic abscess	0 (0.0%)	4 (0.3%)	2 (0.2%)	6 (0.5%)	0.5% (0.2-1.1%)	0.6% (0.3-1.4%)
Sepsis	1 (0.1%)	3 (0.2%)	5 (0.4%)	8 (0.6%)	0.5% (0.2-1.1%)	0.6% (0.3-1.3%)
Other, not specified above	6 (0.5%)	16 (1.3%)	3 (0.2%)	19 (1.5%)	1.6% (1.0-2.6%)	1.8% (1.1-2.8%)

(*Continued*)

Table 2 (*Continued*)

	Baseline	Absolute numbers and crude incidence rates during follow-up			Actuarial estimates G≥3 (95% CI)	
	G≥3	G3	G4	G≥3	3 y	5 y
Total non-GI/GU/vaginal events	27	181	23	204		
Total patients w/ non-GI/GU/vaginal events	24 (1.9%)	132 (10.6%)	17 (1.4%)	149 (11.9%)	11.7% (9.9-13.8%)	14.5% (12.4-17.0%)
Total events overall	106	429	105	534		
Total patients w/ events overall	90 (7.2%)	203 (16.2%)	67 (5.4%)	270 (21.6%)	21.5% (19.1-24.2%)	26.6% (23.8-29.6%)

Crude incidence rates are given at baseline and as the maximum scoring during the follow-up period.

Abbreviations: CI = confidence interval; CTCAE ver. 3.0 = Common Terminology Criteria for Adverse Events version 3.0, G = grade; GI = gastrointestinal; GU = genitourinary; NA = not applicable.

* In 15 patients the bleeding originated from the rectum.

† Grade 4 was not a possibility in CTCAE ver.3.0.

‡ Twelve out of 36 patients had G≥3 ureteral stricture at baseline. Among these, 5 patients had persistent ureteral stricture until the end of follow-up or resolution without subsequent reoccurrence, whereas in 7 patients the ureteral stricture resolved to reoccur at a later time point. Table 4 contains detailed information on fistulas.

Discussion

This report provides a comprehensive overview of grade ≥3 late morbidity events from 38 endpoints in 1251 patients from the EMBRACE-I study. The overall cumulative actuarial risk for severe morbidity at 5 years was substantial (26.6%). The vast majority of severe events were grade 3 (80.3%). For organ-related endpoints, the cumulative actuarial risk of severe GI, GU, vaginal, and fistula events at 5 years was 8.5%, 6.8%, 5.7%, and 3.2%, respectively, and 18.4% overall. The most frequent organ-related endpoints were ureteral stricture, vaginal stenosis, GI stenosis, and fistulas. The majority of organ-related events occurred within 3 years. The most frequent nonorgan-related endpoints were fatigue and insomnia. Treatment-related deaths were preceded by at least one severe GI morbidity event in 8 out of 13 patients (62%), including bowel perforation (4 patients), bowel necrosis (4 patients), diarrhea (4 patients), and GI bleeding (3 patients). The cumulative actuarial risk at 5 years of grade ≥3 morbidity when aggregating all endpoints increased with higher local FIGO stage (Table E1). The risk for fistulas and aggregated GU morbidity (driven by incontinence and ureteral stenosis) increased with higher local FIGO stage. The same trend was not found for aggregated GI morbidity, vaginal morbidity or non-GI/GU/vaginal morbidity. This report does not cover patient-reported outcome from the EMBRACE-I study which has been reported elsewhere.[11-14,22–24]

The majority of fistulas involving bladder/rectum/vagina were related to tumor involvement of these organs and could thus be considered an expected outcome. This is also reflected by the low risk of fistulas seen for FIGO stages I and II and the increased risk seen with higher FIGO stages. It likely reflects both the tumor involvement at diagnosis and the subsequent increase in doses to OARs necessary to treat organ-involving tumors as seen in Table 4. Significant tumor shrinkage achieved during EBRT broadens the therapeutic window at the time of brachytherapy and thereby allows for sparing of doses to the OARs while the opposite is true in the case of poorly responding tumors. However, it remains uncertain whether the increased risk of late morbidity with increasing FIGO stage can be explained by unfavorable dose-volume histogram parameters alone, or whether a large central fibrotic mass at the original tumor site contributes to functional and structural changes in organ function.[25] It may be possible to further lower doses to the OARs through the introduction of dose constraints, which may lead to a further decrease of the risk of fistulas in patients without involvement of bladder, rectum or mid/lower vagina. Furthermore, in patients with a low risk of local recurrence, it may be possible to dose de-escalate the CTV_{HR} and consequently lower doses to the OAR.[26]

Comparison of late morbidity between IGABT (EMBRACE-I) and standard radiograph based BT is challenging due to several factors. The majority of publications on standard radiograph based BT report on retrospective studies, which could result in underestimation of morbidity. Furthermore, the use of morbidity grading scales was very heterogeneous, and in some cases, morbidity was not graded according to a well-defined scale. Consequently, only

Table 3 Overview of patient, disease and treatment characteristics for patients with treatment-related deaths

Patient	Age	Local FIG0 stage	PS	Comorbidity	Smoking status	EBRT nodal regions	LN boost	Cycles of CC	Time of death in FUP	Development of severe morbidity events	Conclusion on the cause of death (CTCAE categories involved*)
1	52	2B	0	None	Unknown	Pelvic	No	3	0	End of EBRT: G4 sepsis likely due to neutropenia	Sepsis (infection)
2	42	3B	0	Heterozygote prothrombin mutation	Smoker	Pelvic PAN	Yes	4	51	3 mo: G4 diarrhea leading to G4 hypokalemia and admitted to ICU 9 mo: Colostomy due to G3 colon stenosis and G3 colon perforation 18 mo: G4 diarrhea, G3 anal bleeding, G3 renal failure, G3 bladder frequency, parenteral nutrition and IV fluids daily 30 mo: G4 diarrhea, G3 proctitis 36 mo: G3 retrorectal/presacral abscess formation 48 mo: G4 diarrhea, G4 fatigue	Multiple gastrointestinal morbidity events (gastrointestinal)
3	56	2B	0	Bronchial asthma	Smoker	Pelvic	No	5	23	23 mo: G4 small bowel perforations and extensive G4 bowel necrosis	Small bowel perforations (gastrointestinal)
4	67	3B	0	Arthritis, Hemorrhoids	Smoker	Pelvic	Yes	5	6	6 mo: G3 radiation enteritis, G3 diarrhea, G3 cystitis, G4 bowel perforation, and subsequent G4 sepsis	Septic shock due to bowel perforation (infection, gastrointestinal)
5	57	2B	1	Hypertension	Nonsmoker	Pelvic PAN	No	1	74	Pretreatment: Bleeding from vena cava inferior after lymph node staging = laparotomy. Abdominal wound dehiscence and deep vein thrombosis 7 mo: Admitted with G3 diarrhea, bowel pain, and vomiting; colostomy due to abdominal catastrophe with G4 bowel necrosis; ICU and repeated medical interventions due to G3 pelvic abscess formation 60 mo: G3 ureteral stricture 74 mo: G4 renal failure	Multiple gastrointestinal morbidity events and renal failure (gastrointestinal, genitourinary)

(*Continued*)

Table 3 (*Continued*)

Patient	Age	Local FIG0 stage	PS	Comorbidity	Smoking status	EBRT nodal regions	LN boost	Cycles of CC	Time of death in FUP	Development of severe morbidity events	Conclusion on the cause of death (CTCAE categories involved*)
6	77	4A	1	Hypertension	Nonsmoker	Pelvic	No	No	17	6 mo: G3 rectovaginal fistula 12 mo: Stoma; no longer fit for follow-up	Rectovaginal fistula (fistula)
7	53	1B	1	Hypertension, IHD, DM, PVD	Unknown	Pelvic	No	5	65	18 mo: G2 proctitis treated with hyperbaric oxygen 48 months: G4 bowel perforation resulting in a stoma 65 mo: G4 stoma bleeding	Stoma bleeding (gastrointestinal)
8	57	2B	0	None	Nonsmoker	Pelvic	No	3	88	18 months: G3 bleeding sigmoid, G3 vaginal stenosis 88 mo: G4 bilateral ureteral stricture leading to renal failure; deep vein thrombosis; refused further treatment and was discharged against advice	Bilateral ureteral stricture resulting in renal failure (genitourinary)
9	48	3B†	0	None	Nonsmoker	Pelvic	Yes	5	32	9 mo: G4 vesicovaginal and sigmoid-vaginal fistula 24 mo: G4 osteonecrosis in the right femoral head, G4 stress fracture of the right sacroiliac joint; G2 rectal bleeding; general condition did not allow surgery 26 mo: Received hyperbaric oxygen treatment; unable to walk 32 mo: G4 urosepsis	Multiple morbidity events and poor performance status (infection, fistula, gastrointestinal)
10	58	4A	2	Apoplexia cerebri	Smoker	Pelvic PAN Inguinal	No	No	38	24 mo: G3 vaginal stenosis 36 mo: G4 rectovaginal fistula 38 mo: G4 sepsis	Sepsis likely caused by rectovaginal fistula (infection, fistula)

(*Continued*)

Table 3 (*Continued*)

Patient	Age	Local FIG0 stage	PS	Comorbidity	Smoking status	EBRT nodal regions	LN boost	Cycles of CC	Time of death in FUP	Development of severe morbidity events	Conclusion on the cause of death (CTCAE categories involved*)
11	59	2B	0	Fibromyalgia, Hypothyroidism, Psoriasis, Hypertension, Depression	Nonsmoker	Pelvic PAN	Yes	5	50	24 mo: G3 diarrhea, G3 vaginal stenosis, G3 vaginal mucositis, G3 urinary frequency, G3 urinary incontinence, G3 cystitis 36 mo: G3 vesicosigmoid and G3 vesicovaginal fistula; G4 massive pelvic/bowel necrosis and fibrotic changes seen in the entire radiation field; hyperbaric oxygen therapy w/ o effect; suspected hypersensitivity to radiation	Extensive pelvic necrosis causing extensive fistulation (gastrointestinal, fistula, genitourinary)
12	49	2B	0	None	Smoker	Pelvic	Yes	5	28	18 mo: Local and peritoneal recurrence; underwent pelvic exenteration leading to G4 bowel necrosis in the postradiation pelvis	Cancer recurrence, bowel necrosis (gastrointestinal)
13	57	3B	0	None	Nonsmoker	Pelvic	No	5	101	60 mo: Scheduled follow-up ceased; no severe morbidity had occurred so far 101 mo: Nephrostomy placed due to G3 ureteral stricture. Hospitalized due to G4 sepsis.	Sepsis likely due to nephrostomy (infection, genitourinary)

A description of the development of severe morbidity events is provided. Based on a review of each patient's case story a conclusion on the cause of death is given and the CTCAE categories involved are stated in parenthesis. The conclusion was not straightforward for all patients.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; CC = concomitant cisplatin; DM = diabetes mellitus; EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; FUP = follow-up period; G = grade; ICU = intensive care unit; IHD = Ischemic heart disease; IV = intravenous; LN = lymph node; PS = performance status at diagnosis; PVD = Peripheral vascular disease.

* Fistulas are reported as a separate category.

† Later review of the diagnostic magnetic resonance indicated tumor penetration into the bladder and rectosigmoid colon.

Table 4 Fistulas

				Tumor involvement at baseline					Local FIGO stage				Median $D_{2\ cm3}$ in $EQD2_3$ (IQR)		
		Grade				Vaginal[‡]									
	No.	3	4	Bladder[*]	Rectum[†]	Upper	Middle	Lower	I	II	III	IVA	Bladder	Rectum	Sigmoid
Patients with G≥3 fistulas	34	13	21	11 (33%)	4 (12%)	17 (50%)	5 (15%)	3 (9%)	3 (9%)	8 (24%)	17 (50%)	6 (18%)	80 (77-88)	70 (64-73)	65 (59-69)
Patients w/o G≥3 fistulas	1217			57 (5%)	8 (1%)	539 (44%)	72 (6%)	31 (3%)	234 (19%)	769 (61%)	196 (16%)	29 (2%)	76 (69-83)	62 (57-67)	64 (59-69)
5-y risk of G≥3 fistulas				16.8%	39.4%	3.6%	9.6%	6.0%	1.6%	1.3%	10.2%	18.6%			
G≥3 fistula events (n = 42)															
Vesicovaginal	15[§]	10	5	7 (47%)	1 (7%)	6 (40%)	1 (7%)	3 (20%)	0 (0%)	5 (33%)	6 (40%)	4 (27%)	83 (78-90)	70 (65-75)	65 (59-69)
Rectovaginal	10	2	8	3 (33%)	2 (20%)	5 (50%)	3 (33%)	1 (10%)	0 (0%)	1 (10%)	6 (60%)	3 (30%)	79 (76-87)	72 (69-77)	65 (56-67)
Sigmoid to vagina	4	1	3	2 (50%)	1 (25%)	2 (50%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	2 (50%)	1 (25%)	78 (68-80)	68 (65-72)	73 (70-79)
Other fistulas[‖]	13	5	8	3 (23%)	1 (8%)	9 (69%)	1 (8%)	0 (0%)	2 (15%)	4 (31%)	7 (54%)	0 (0%)	80 (69-89)	69 (60-73)	65 (59-70)

At the top: disease characteristics and doses to OAR for patients with fistula grade ≥3 events (n = 34) and patients without fistula grade ≥3 events (n = 1217). In the middle: the 5-year cumulative actuarial risk of developing a fistula according to disease characteristics. At the bottom: the 42 fistula events are divided according to organ involvement.

Abbreviations: $D_{2\ cm3}$ = minimum dose in the maximally exposed 2 cm^3; $EQD2_3$ = equal dose in 2 Gy fractions with α/β of 3 for normal tissue; FIGO = International Federation of Gynecology and Obstetrics; G = grade; IQR = interquartile range; MRI = magnetic resonance imaging; OAR = organs at risk.

[*] Mucosa involved at cystoscopy or bladder involvement on MRI.

[†] Rectum involvement directly palpable at clinical examination, mucosa involved at rectoscopy or rectum involvement on MRI.

[‡] Vaginal involvement at clinical examination or MRI.

[§] 3 patients had vesicovaginal fistulas at baseline (grade ≥1).

[‖] Types: Small bowel to the vagina (2), ureterovaginal (2), sigmoid to an abscess (2), vesicosigmoid (1), colovesical (1), sigmoid to the skin (1), sigmoid to ileal conduit urinary diversion (1), involved organs unclear (3).

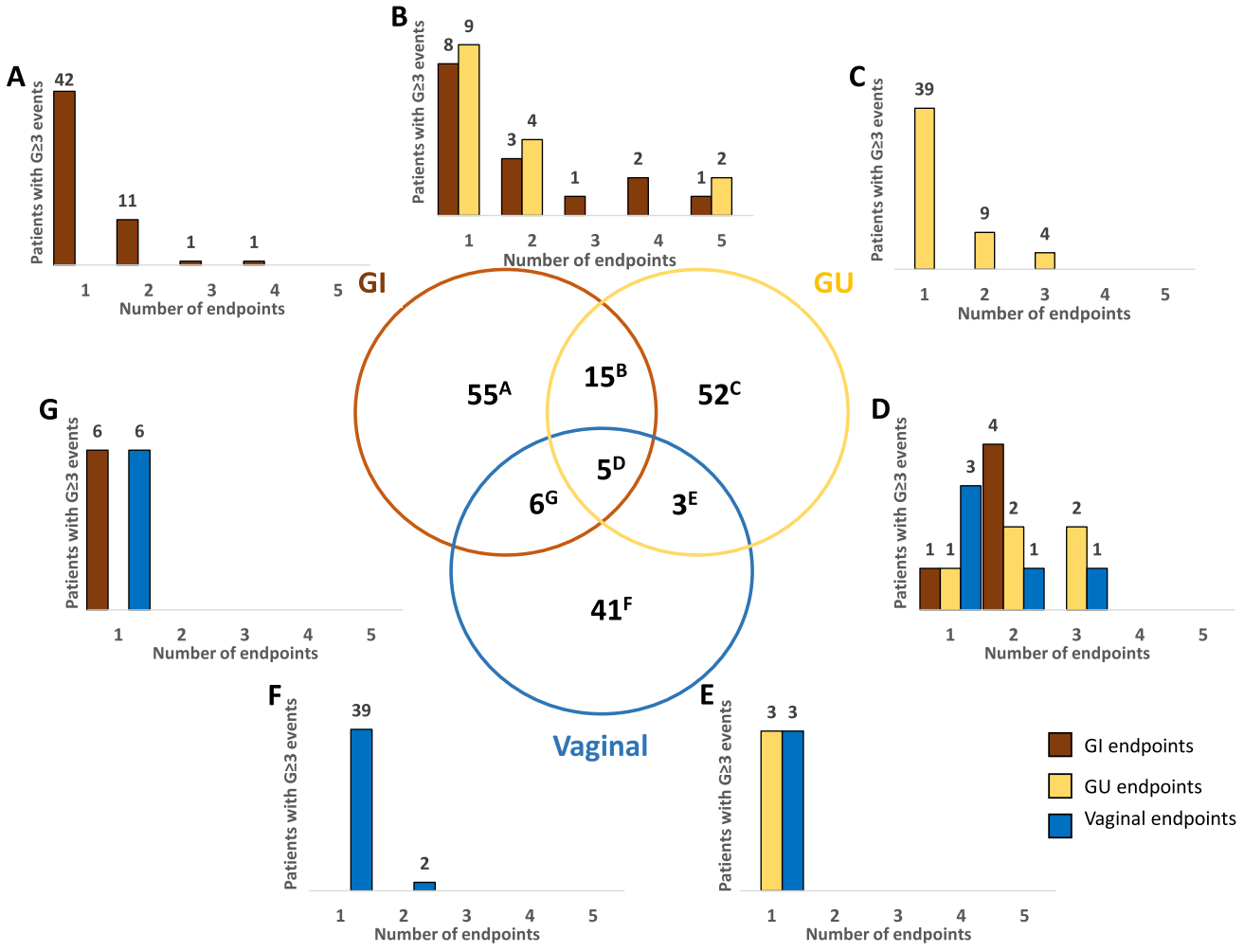

Fig. 1. Venn-diagram and bar charts depicting GI, GU, and vaginal grade ≥3 events. Fistulas events are not included in the Common Terminology Criteria for Adverse Events categories. An overlap represents patients with grade ≥3 events from more than one Common Terminology Criteria for Adverse Events category. The bar charts show the number of endpoints with severe events per patient for each organ system. The letters A-G indicate the corresponding groups in the Venn diagram and bar charts. *Abbreviations*: G = grade; GI = gastrointestinal; GU = genitourinary.

publications on prospective studies where morbidity was graded according to CTCAE or the RTOG/EORTC grading scale were considered for comparison (4 publications). However, even publications on prospective studies have been shown to suffer from missing data, as illustrated by a meta-analysis on randomized clinical trials comparing chemoradiotherapy versus radiation therapy where the comparison of late morbidity was abandoned due to insufficient data.[27] A heterogenic use of summary statistics, and a different practice for reporting either single endpoints or endpoints aggregated per organ also challenges comparison. Aggregated endpoints from the same organ are often not directly comparable, due to a large variety of the number and type of endpoints included per organ.[28] Nonorgan-related endpoints such as fatigue were generally not reported, and could therefore not be compared.

The nonrandomized prospective French STIC trial (2005-2007) compared standard radiograph based BT versus 3D-BT in LACC stage IB-IIIB and reported on 3 groups.[4] Morbidity was graded using CTCAE version 3.0 and aggregated by organ. It was not defined which endpoints contributed to the organ categories. Group 3 was treated with EBRT and concomitant chemotherapy followed by BT (n = 118), and thus comparable to the EMBRACE-I cohort. EBRT was administered as 45 Gy in 25 fractions to the pelvic and delivered as a 4-field technique in 92% of patients. Due to paraaortic lymph node involvement, 22% of patients received an extended field. For standard radiograph based BT they reported actuarial estimates of GI, urinary and gynecologic at 2 years of 9.2%, 9.0%, and 15.4%. The EMBRACE-I results compare favorably with 3-year actuarial estimates for GI, GU, and vaginal severe morbidity of 7.0%, 6.1%, and 3.6%, respectively.

In the RTOG trial 90-01 (1990-1997), women with IB-IVA cervical cancer were randomized between pelvic radiation therapy with chemotherapy versus extended-field

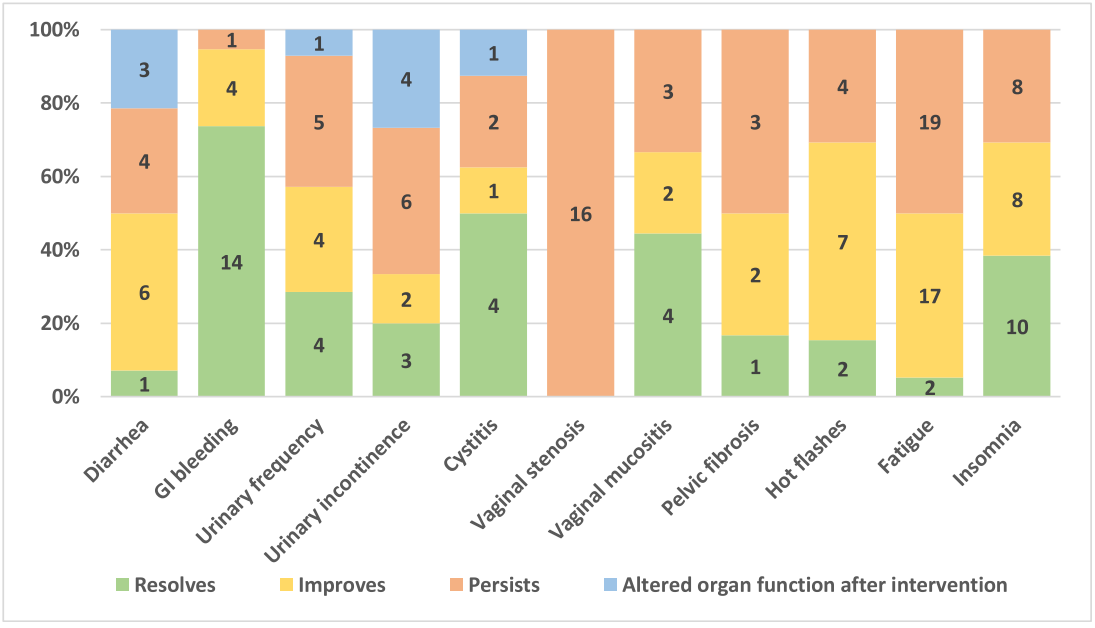

Fig. 2. Development of morbidity scoring after the occurrence of a grade ≥3 event. Endpoints with less than 10 grade ≥3 events and endpoints where the grade definition is closely linked to a surgical intervention were not analyzed (eg, fistulas). For each endpoint patients with ≥3 follow-up assessments after the occurrence of the grade ≥3 event were analyzed. Patients were divided into 4 groups: patients with a median scoring of 0 (resolves), patients with a median scoring between 0.5 to 1.5 (improves), patients with a median scoring of ≥2 (persists), and patients where further assessment was difficult due to altered organ function after intervention for another reason. *Abbreviation*: GI = gastrointestinal.

radiation therapy covering the para-aortic region.[29] Standard radiograph based BT was administered in both groups. EBRT was delivered either as opposed beams (anteroposterior-posteroanterior) or as a 4-field technique. As more than 90% of patients in the EMBRACE-I study received concomitant chemotherapy and less than 20% were treated with an extended field, the pelvic radiation therapy with chemotherapy group (n = 191) was chosen for comparison. Crude incidences of grade ≥3 RTOG/EORTC late morbidity for small bowel and large bowel/rectum were 3.7% and 8.9%, respectively. The RTOG/EORTC converted results grade ≥3 late morbidity for small/large bowel from the EMBRACE-I study were lower (6.1%). For bladder, the RTOG 90-01 trial reported a crude incidence of 3.5%, similar to the RTOG/EORTC converted results from the EMBRACE-I study with a crude incidence of 3.1%. For fistulas, they reported a crude incidence of 5.2%, nearly 2-fold of the 2.7% seen in the EMBRACE-I study.

In the prospective The Nordic Cervical Cancer trial (1994-2000) women with LACC stage IIB-IVA were treated with EBRT (3D-CRT) followed by standard radiograph based BT with a planning aim to reach 80 Gy cumulative dose to point A. Concomitant chemotherapy was not administered. Nordic Cervical Cancer was never published, but single-institution reports from Aarhus (n = 99) and Oslo (n = 91) have been published.[6,30] Cumulative actuarial estimates of RTOG/EORTC G≥3 late morbidity for GI, urologic and vaginal were reported to 8%, 2%, and 9% at 3 years in the Aarhus cohort, and 15%, 13%, and 23% at 5 years in the Oslo cohort. Actuarial estimates for the RTOG/EORTC converted EMBRACE-I results for GI, GU and vaginal severe morbidity were 6.4%, 3.7%, and 4.3% at 3 years, and 8.0%, 4.2%, and 6.5% at 5 years and thus compare favorably, especially for GI and vaginal morbidity.

Overall, the comparison with the literature on standard radiograph based BT shows a considerable decrease in severe GI, fistula and especially vaginal morbidity. GU morbidity showed the same trend; however, the conclusion was less straightforward, with the comparison showing both higher and lower levels of morbidity. The overall decrease in morbidity seen in this report is consistent with previous publications which compared morbidity between cohorts treated with standard radiograph based BT and IGABT.[4,6,31]

The level of morbidity is also affected by the doses derived from the EBRT.[32] The evolution of EBRT from 3D-CRT to IMRT/VMAT has achieved a more conformal dose distribution which allows for the sparing of OARs and a subsequent reduction in late morbidity, GI in particular.[33-35] The partial introduction of IMRT/VMAT in the EMBRACE-I study (41% of patients) likely contributes to the lower levels of GI late morbidity because all patients in the standard radiograph based BT publications were treated with 3D-CRT. The randomized PARCER trial compared late morbidity after postoperative radiation in cervical cancer delivered either as image guided IMRT with 3D-CRT and also found a reduction in late morbidity in the image guided IMRT group.[36] Extending the field to include the paraaortic region and

boosting the doses to involved lymph nodes comes with an increased risk of late morbidity.[37] The clinical outcome of mandatory image guided IMRT/VMAT for LACC is being investigated in the EMBRACE-II study study.[38]

Before EMBRACE-I, the largest study on IGABT was RetroEMBRACE.[5] RetroEMBRACE was a retrospective multicenter cohort study where 731 women with LACC stage IA-IVB were treated with definitive CRT followed by IGABT. CTCAE version 3.0 was used retrospectively to grade morbidity. Morbidity endpoints and follow-up schedules were comparable to the EMBRACE-I study. The cumulative 5-year risk of G≥3 morbidity was 7% for GI, 5% for bladder, and 5% for vagina (organ categories included fistulas), and hereby lower than in EMBRACE-I. These differences are most likely due to the retrospective design of the study, and the results provided by this report are likely a more realistic estimate of severe late morbidity after IGABT.

The development of morbidity scorings after the occurrence of a severe event was analyzed for 11 endpoints. There was a considerable variety in the long-term consequences of a given event. For some symptoms, the majority of patients recovered while for other symptoms, patients would remain permanently impaired. The highest tendency for persistence (≥50%), included endpoints driven by fibrotic changes in the connective tissue (vaginal stenosis and pelvic fibrosis),[39] but also endpoints where the cause is more multifactorial (fatigue). On the other end of the spectrum, GI bleeding either resolved or improved in 95% of patients in line with findings of postradiation therapy sigmoidoscopies.[40] Cystitis, vaginal mucositis, hot flashes, and insomnia also showed a high tendency for either resolution or improvement of 63%, 67%, 69%, and 69%, respectively. Traditionally late radiation effects have been considered irreversible and in general nontreatable.[41] However, the findings in this report clearly show that the occurrence of severe morbidity events does not necessarily mean persistence of the severity. Different endpoints displayed different trajectories over time and in many cases, the severity improved or the symptom resolved. A report on late persistent substantial patient-reported symptoms from the EMBRACE-I study showed similar findings.[24] Improvement in the severity of symptoms could be due to either passive resolution or active management of the symptoms. Progress in the management of gastrointestinal morbidity has shown that it is possible to treat several radiation-induced symptoms.[42,43] However, this report highlights the multitude of different symptoms that patients are at risk of experiencing, and at the moment we are still far from having successful management strategies for all symptoms, making this an important focus for the future. Morbidity management has the potential to alter a symptom's time trajectory skewing the tendency toward improvement/resolution.

Previous publications from the EMBRACE-I study have investigated risk factors for late morbidity. For GI morbidity, risk factors were analyzed for individual endpoints (diarrhea, flatulence, incontinence, proctitis, and bleeding) and pooled morbidity based on the location within the GI tract (anus/rectum, sigmoid, and colon/small bowel). Anus/rectum morbidity included bleeding, stenosis, fistula, incontinence and proctitis, while sigmoid and colon/small bowel morbidity included bleeding, stenosis, and fistula.[10,32,44] Baseline morbidity and smoking were risk factors for most endpoints, and increasing age was a risk factor for incontinence and bleeding. Treatment-related risk factors were higher EBRT prescription dose, larger lymph node boosts (V57 Gy >165 cm^3) and extended elective fields including the para-aortic nodes. Furthermore, doses to bowel D_{2cm3}, rectum D_{2cm3}, and ICRU recto-vaginal point were risk factors for multiple endpoints. For GU morbidity risk factors were analyzed for ureteral stricture, frequency, incontinence, bladder fistulas, cystitis, and bleeding.[45-47] Baseline urinary morbidity was a risk factor for all endpoints, and overweight/obesity and smoking were risk factors for most endpoints. For treatment-related factors bladder D_{2cm3} was a risk factor for bladder fistulas, bleeding, and cystitis while dose to the ICRU bladder point was a risk factor for incontinence. For vaginal stenosis risk factors were the extent of vaginal wall infiltration, doses to the ICRU recto-vaginal point, and EBRT prescription dose.[9] Risk factors for persistent fatigue were fatigue at baseline, obesity, younger age and larger lymph node boosts (V57 Gy >169 cm^3).[48] Based on the results described above the following suggestions were made: to keep the EBRT prescription dose to 45 Gy, to apply a soft constraint of 65 Gy EQD2 (combined EBRT + BT dose) to the ICRU recto-vaginal point and rectum D_{2cm3}, and to apply a soft constraint of 80 Gy EQD2 (combined EBRT + BT dose) to bladder D_{2cm3}.[9,10,32,45]

The primary limitation of the EMBRACE-I study is the observational design, and thus the lack of a randomized standard radiograph-based BT comparison arm. However, one could question whether a randomized study between standard radiograph based BT and MRI-based IGABT would have been ethical based on the indications of improved efficacy available before the initiation of the study.[31] Management of morbidity was not recorded in the EMBRACE-I study. Consequently, it was not possible to determine whether a symptom resolved spontaneously or due to a successful medical intervention. Grading of morbidity is affected by subjectivity; however, the degree of subjectivity is reduced when grading is done according to a well-defined grading scale as the CTCAE. Comparison with previous literature comes with a risk of bias. Sources of bias come from the heterogeneity in study design (retrospective/prospective), morbidity grading scales, summary statistics, and practice for aggregating endpoints. Furthermore, the past 2 decades have seen other changes in the treatment of LACC than the shift from standard radiograph based BT to IGABT (eg, in the EBRT technique and use of concomitant chemotherapy). These biases were addressed by choosing studies/cohorts with design and treatment as similar as possible to the EMBRACE-I study for comparison. To enhance comparability, CTCAE morbidity from the EMBRACE-I study was transformed into RTOG/EORTC scorings.

The EMBRACE-I study also benefits from several strengths. It is the largest prospective study with

longitudinal morbidity assessment of LACC after IGABT to date. All organ-related severe morbidity events underwent quality assurance. The study covers a broad spectrum of late morbidity endpoints, including less frequently reported endpoints (eg, fatigue), and morbidity from free-text fields, which allows for a comprehensive overview of severe late morbidity.

Perspectives

Risk factor analyses for late morbidity have been published, linking the risk of morbidity endpoints with doses to the OARs and hereby establishing dose-effect relationships.[9,10,32,44-48] Such analyses facilitate the process of establishing the relevant dose-volume parameters for each endpoint (eg, $D_{2\ cm3}$ [minimum dose in the maximally exposed 2 cm^3] for fistulas) and help set dose constraints.

In 2016, the prospective interventional EMBRACE-II study was initiated. Several interventions within the study aim at reducing treatment-related morbidity, including an introduction of soft and hard constraints for OARs, reduction in vaginal source loading, consistent definition of the lower target border, more focus on the use of interstitial needles, and a requirement for the use of IMRT/VMAT and daily image guided radiotherapy.[38] De-escalation in patients with low-risk LACC could be considered with the aim of reducing late morbidity without compromising local control. However, such de-escalation needs to be addressed in future prospective studies. Primary preventive initiatives as listed above have the potential to reduce the risk of severe late morbidity after radiation therapy. However, to effectively help the patients who have late morbidity, there is a need to focus on secondary prevention through early detection and active management of morbidity.

Conclusions

EMBARCE-I is the largest study with prospective morbidity assessment after CRT and IGABT to date and can serve as a benchmark for future studies on the treatment of LACC. Late morbidity from the EMBARCE-I study compares favorably with published literature on standard radiograph based BT, especially for GI morbidity, vaginal morbidity, and fistulas. However, when unfolding the full spectrum of prospectively assessed morbidity endpoints as done in this report, substantial levels of severe late morbidity are still revealed.

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