Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study ☆

Renaud Mazeron [a,*], Lars U. Fokdal [b], Kathrin Kirchheiner [c], Petra Georg [c], Noha Jastaniyah [c], Barbara Šegedin [d], Umesh Mahantshetty [e], Peter Hoskin [f], Ina Jürgenliemk-Schulz [g], Christian Kirisits [c], Jacob C. Lindegaard [b], Wolfgang Dörr [c], Christine Haie-Meder [a], Kari Tanderup [b], Richard Pötter [c], on behalf of the EMBRACE collaborative group [1]

[a] Department of Radiotherapy, Gustave Roussy, University of Paris-Saclay, Villejuif, France; [b] Department of Oncology, Aarhus University Hospital, Denmark; [c] Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna/General Hospital of Vienna, Austria; [d] Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia; [e] Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India; [f] Department of Radiotherapy, Mount Vernon Cancer Centre, United Kingdom; and [g] Department of Radiotherapy, University Medical Center Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 11 April 2016
Received in revised form 23 May 2016
Accepted 3 June 2016
Available online xxxx

Keywords:
Locally advanced cervical cancer
MRI-guided adaptive brachytherapy
Rectal bleeding
Proctitis
Fistula
Rectal morbidity
D_{2cm^3}
Normal tissue complication probability

ABSTRACT

Purpose: To establish dose volume–effect relationships predicting late rectal morbidity in cervix cancer patients treated with concomitant chemoradiation and MRI-guided adaptive brachytherapy (IBABT) within the prospective EMBRACE study.

Material and method: All patients were treated with curative intent according to institutional protocols with chemoradiation and IGABT. Reporting followed the GEC-ESTRO recommendations ($D_{0.1cm^3}$, D_{2cm^3}), applying bioeffect modeling (linear quadratic model) with equieffective doses ($EQD2_3$). Morbidity was scored according to the CTC-AE 3.0. Dose–effect relationships were assessed using comparisons of mean doses, the probit model and log rank tests on event-free periods.

Results: 960 patients were included. The median follow-up was 25.4 months. Twenty point one percent of the patients had grade 1 events, 6.0% grade 2, 1.6% grade 3 and 0.1%, grade 4. The mean D_{ICRU}, $D_{0.1cm^3}$, and D_{2cm^3} were respectively: 66.2 ± 9.1 Gy, 72.9 ± 11.9 Gy, and 62.8 ± 7.6 Gy. Increase of dose was associated with increase in severity of single endpoints and overall rectal morbidity (grade 1–4) ($p < 0.001$–0.026), except for stenosis ($p = 0.24$–0.31). The probit model showed significant relationships between the D_{2cm^3}, $D_{0.1cm^3}$, and D_{ICRU} and the probability of grade 1–4, 2–4, and 3–4 rectal events. The equieffective D_{2cm^3} for a 10% probability for overall rectal grade $\geqslant 2$ morbidity was 69.5 Gy ($p < 0.0001$). After sorting patients according to 6 D_{2cm^3} levels, less favorable outcome was observed in the high dose subgroups, for bleeding, proctitis, fistula, and overall rectal morbidity. A $D_{2cm^3} \geqslant 75$ Gy was associated with a 12.5% risk of fistula at 3 years versus 0–2.7% for lower doses ($p > 0.001$). A $D_{2cm^3} < 65$ Gy was associated with a two times lower risk of proctitis than $D_{2cm^3} \geqslant 65$ Gy.

Conclusions: Significant correlations were established between late rectal morbidity, overall and single endpoints, and dose–volume (D_{2cm^3}, $D_{0.1cm^3}$) and dose-point (D_{ICRU}) parameters. A $D_{2cm^3} \leqslant 65$ Gy is associated with more minor and less frequent rectal morbidity, whereas a $D_{2cm^3} \geqslant 75$ Gy is associated with more major and more frequent rectal morbidity.

© 2016 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology xxx (2016) xxx–xxx

Brachytherapy is a crucial component in the treatment of locally advanced cervical cancer [1,2]. During the last 20 years, image guided adaptive brachytherapy (IGABT), a high precision radiation technique has been developed through progress in afterloaders, applicators and computer software which enable the integration of 3D images such as MRI into treatment planning. This approach includes accurate delineation of tumor and targets and

☆ These results were partly presented as an oral communication at last ESTRO forum, held in Barcelona April 2015. The current study has been presented at the World Congress of Brachytherapy, held in San Francisco, June 2016.

* Corresponding author at: Department of Radiotherapy, Gustave Roussy Cancer Campus, 114, rue Edouard Vaillant, 94805 Villejuif Cedex, France.
E-mail address: Renaud.mazeron@gustaveroussy.fr (R. Mazeron).

[1] See Appendix A for EMBRACE collaborative group.

http://dx.doi.org/10.1016/j.radonc.2016.06.006
0167-8140/© 2016 Elsevier Ireland Ltd. All rights reserved.

Please cite this article in press as: Mazeron R et al. Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.06.006

the organs at risk (OAR), as well as optimized 3D treatment planning based on dose–volume histograms. Recent monocentric series showed high local control rates with promising results and only limited to moderate morbidity in regard to classical outcomes from historical cohorts [3–10].

In 2000, in a will of harmonizing contouring and reporting in image guided cervix cancer brachytherapy, the GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiation Oncology) launched a Gynaecologic working group which finally led to publish recommendations to define clinical target volumes (low, intermediate and high risk CTV) for response-adaptive brachytherapy and consensual dosimetric parameters (D_{100} and D_{90} for the CTV, $D_{0.1cm^3}$, D_{1cm^3} and D_{2cm^3} for OAR) in 2005–06 [11,12]. In the aftermath, the GEC-ESTRO launched a prospective multicentric study, EMBRACE (an intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer) in 2008, aiming to evaluate the outcome and morbidity of MRI-guided brachytherapy [13]. At that time, little evidence was available on dose constraints for organs at risk and most clinicians were used to refer to data based on 2D experience and monoinstitutional reports [14,15]. In EMBRACE, the participants were free to apply their institutional protocols, but had to perform contouring and to report their data following the GEC-ESTRO recommendations. Among secondary study aims, aim #6 was to establish dose–volume effects correlations between morbidity and dose–volume parameters. The objective of this work was to establish dose–volume correlations between volumetric dosimetric parameters (D_{2cm^3} and $D_{0.1cm^3}$, minimal dose delivered to a maximally exposed volume of an OAR) and the occurrence of rectal morbidity.

Material and methods

Patients

The EMBRACE study included prospectively patients with histologically proven cervical carcinomas from 24 centers located in Europe, Asia, and North America. Centers went through a dummy run before being accepted in the study [16]. The complete study protocol is available on the study website [13]. Briefly, to be eligible, patients should have no history of cancer except carcinoma in situ of the cervix or basal cell carcinoma of the skin, and no total or partial hysterectomy. An MRI at diagnosis was required. Patients were included prior to treatment initiation (EBRT). Their treatment had to combine pelvic or extended-fields external beam radiotherapy with concomitant chemotherapy when not contra-indicated and MRI guided brachytherapy, and to be led with curative intent. Patients with involvement of the para-aortic lymph nodes could be included provided pathological nodes were located below the level of L1–L2. The study was approved by local ethic committees and patients consent was obtained if required according to institutional rules.

Treatment

The study was prospective and observational. However, the EBRT technique was harmonized with standard fractionation (1.8–2 Gy, once a day, 5 times a week), prescribed doses ranging from 45 to 50 Gy, and delivery of 4 field conformal EBRT or IMRT/VMAT. Midline block during EBRT was not allowed. Nodal boosts could be sequential or performed with simultaneous integrated boost technique. Parametrial boosts were also allowed. Concomitant chemotherapy was foreseen for all patients, except for those with major comorbidity. Neo-adjuvant or adjuvant treatment was not allowed. Patients could be treated either with high dose rate (HDR) or pulsed-dose rate (PDR) brachytherapy. No planning aims were imposed, but the reporting had to follow the GEC-ESTRO recommendations including the $D_{0.1cm^3}$ and D_{2cm^3} for OAR [11,12].

Morbidity

Outcomes and morbidity were assessed at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months after treatment completion. Morbidity was evaluated using the Common Toxicity Criteria for adverse events (CTC-AE), version 3.0. Late morbidity was defined as any toxicity event occurring or lasting over 90 days after treatment initiation (first fraction of EBRT). Therefore, patients with follow-up less than 90 days were not eligible for this subgroup analysis. Four types of rectal events were reported in EMBRACE: rectal bleeding, proctitis, stenosis, and fistula (Additional material: Table 1). They were analyzed independently, and together as overall rectal morbidity. Patients with persistent disease after completion of the treatment were not eligible for morbidity assessment. Patients who experienced relapses were excluded from morbidity analysis from the date of their recurrence. Morbidity was censored if present at the same time of any local and/or regional and/or systemic evidence of disease.

Dose–volume parameters

Dose volume parameters ($D_{0.1cm^3}$ and D_{2cm^3}) and rectal D_{ICRU} (dose to the rectal International Commission for Radiation measurements and Units point, ICRU, report 38 were reported and converted in 2 Gy equivalent (EQD2) using the linear quadratic model with $\alpha/\beta = 3$ Gy and a half-time repair of 1.5 h [17]. In cases of multiple brachytherapy fractions, doses were summed by adding the dose from each fraction, assuming that the most exposed area of the rectum remained stable in succeeding brachytherapy fractions. Brachytherapy doses were summed with the EBRT prescribed dose converted into EQD2, using the same model, assuming that studied volumes (points) were located in the 100% isodose of the EBRT prescribed dose.

Data collection

Data were extracted from the study database in August 2015. For the purpose of this analysis, patients who completed their treatment at least 12 months before (August 2014) were retained.

Statistics

Prevalence and cumulative incidence were calculated. Times to onset were defined from treatment initiation to the date of event occurrence. For crude incidence, as well as for dose effect correlations, the maximal graded event was considered for analyses. In case of equally graded events in the same patients, the earliest was considered for analyses. For patients with rectal symptoms at baseline, treatment related morbidity was defined as an increase in the score. As D_{ICRU}, $D_{0.1cm^3}$, and D_{2cm^3} did not follow normal distributions (positive Shapiro Wilk and Kolmogorov–Smirnov tests), mean doses were compared using Kruskal–Wallis tests while comparing three or more variables and Mann–Whitney–*U* tests for analyses limited to 2 variables. Dose–volume effects were analyzed using two methods. First, dose effect correlations were tested using the logistic regression analysis with the probit model, without assumption of a threshold dose. Second, log rank tests were performed on Kaplan–Meier event-free period curves sorting patients according D_{2cm^3} levels, by steps of 5 Gy. Statistical significance was considered for $p \leqslant 0.05$. All statistics were performed using XLSTAT 2014 (Addinsoft SARL, Paris, France).

Please cite this article in press as: Mazeron R et al. Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.06.006

Download English Version:

https://daneshyari.com/en/article/8459497

Download Persian Version:

https://daneshyari.com/article/8459497

Daneshyari.com