Brachytherapy quality assurance in the PORTEC-4a trial for high-intermediate risk endometrial cancer

Wortman, B.; Astreinidou, E.; Laman, M.; Lutgens, L.; Van der Steen-Banasik, E.; Slot, A.; Westerveld, H.; De Winter, K.; Van den Berg, H.; Bloemers, M.

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[1]*University Medical Centre Groningen UMCG, Radiotherapy, Groningen, The Netherlands*

Purpose or Objective

Sarcopenia, defined as the loss of skeletal muscle mass and strength, is emerging as an adverse prognostic factor for both survival and complication risk in cancer patients. The aim of this study was to determine the impact of sarcopenia on several survival parameters and late toxicity in a large cohort of patients with head and neck squamous cell carcinoma (HNSCC) treated with primary radiotherapy (RT).

Material and Methods

Patients with HNSCC who were treated with definitive RT with or without systemic treatment from January 2007 to June 2016 were included. Prospectively collected variables were retrospectively analysed. The planning CT-scan was used to measure the cross-sectional area (CSA) of skeletal muscles at the level of the third cervical vertebra (C3). The prediction rule by Swartz et al. was used to estimate CSA at the third lumbar vertebra (L3). L3 skeletal muscle index (SMI) was calculated.

The impact of sarcopenia on overall survival (OS) and disease-free survival (DFS) was investigated using univariate (Kaplan Meier) and multivariate (Cox proportional hazards regression) analysis. To analyse the association of sarcopenia with physician-rated grade ≥2 toxicity (i.e. xerostomia and dysphagia) and with moderate-to-severe patient-rated xerostomia, multivariable logistic regression analyses were performed to create association models.

Results

The study population was composed of 750 patients with HNSCC. The cut-off value of sarcopenia was set at SMI <42.4 cm^2/m^2 (men) and <30.6 cm^2/m^2 (women) corresponding with the lowest gender specific quartile. Patients with sarcopenia had significantly poorer survival rates than others. The 3-year OS in sarcopenic patients was 53% compared to 73% in non-sarcopenic patients (p<0.001) and the 3-year DFS was resp. 59% and 76% (p<0.001). However, sarcopenia was only significantly associated with OS and DFS in patients with WHO performance score (WHO-score)>0 (resp. p<0.001 and p=0.003) and in those with locally advanced disease (stage III-IV) (both p<0.001) (**Figure 1** OS stratified by stage of disease). The multivariate analysis showed that sarcopenia was an independent adverse prognostic factor for OS (p=0.004), next to age, WHO-score, tumour stage and primary tumour site and for DFS (p=0.013), next to age, WHO-score and tumour stage (**Table 1**).

In the univariate analysis, sarcopenia was associated with more radiation-induced xerostomia and dysphagia at six and twelve months after treatment, but no such association was found in multivariate analysis after correcting for confounders.

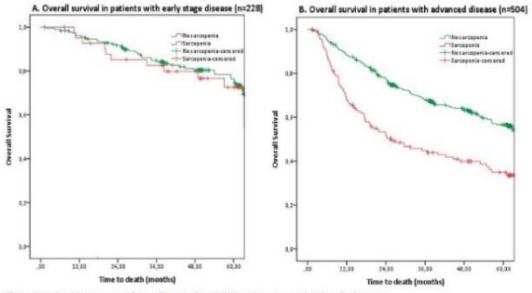

Figure 1 Kaplan Meier curves of overall survival in HNSCC patients treated with radiotherapy.
A. OS of patients with early stage disease (I-II) (p=0.590) **B.** OS of patients with locally advanced disease (III-IV) (p<0.001)
HNSCC = head neck squamous cell carcinoma; OS = overall survival

Table 1 Cox regression analysis of overall survival and disease-free survival in HNSCC patients treated with radiotherapy

	Overall survival (n=729)		Disease-free survival (n=641)	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
Univariate analysis				
Gender (male vs. female)	1.103 (0.853 – 1.425)	0.456	1.058 (0.794 - 1.409)	0.700
Age	1.014 (1.003 – 1.025)	0.011	1.024 (1.012 - 1.037)	<0.001
WHO-score (0 vs. 1 - 3)	0.374(0.299 – 0.467)	<0.001	0.426 (0.333 - 0.546)	<0.001
Sarcopenia (no vs. yes)	0.533 (0.421 – 0.675)	<0.001	0.566 (0.433 - 0.740)	<0.001
Smoking history (never vs. ever)	0.758 (0.520 – 1.105)	0.150	0.950 (0.644 - 1.402)	0.797
Tumour stage (I-II vs. III-IVb)	0.472 (0.360 – 0.617)	<0.001	0.629 (0.479 - 0.827)	0.001
Primary tumour site (larynx vs. other)	0.521 (0.412 – 0.659)	<0.001	0.662 (0.515 - 0.851)	0.001
Treatment modality (RT alone vs. RT with systemic treatment	0.663 (0.531 – 0.828)	<0.001	0.852 (0.662 - 1.096)	0.214
Technique (conventional vs. IMRT)	0.593 (0.417 – 0.843)	0.004	0.695 (0.484 - 0.997)	0.048
Multivariate analysis				
Age	1.020 (1.009 – 1.032)	0.001	1.024 (1.011 - 1.038)	<0.001
WHO-score (0 vs. 1 - 3)	0.442 (0.352 – 0.556)	<0.001	0.501 (0.387 - 0.647)	<0.001
Sarcopenia (no vs. yes)	0.697 (0.545 – 0.892)	0.004	0.705 (0.535 - 0.930)	0.013
Tumour stage (I-II vs. III-IVb)	0.601 (0.440 – 0.821)	0.001	0.624 (0.467 - 0.835)	0.001
Primary tumour site (larynx vs. other)	0.674 (0.515 – 0.883)	0.004		

HNSCC = head neck squamous cell carcinoma; HR = hazard ratio; 95% CI = 95% confidence interval; WHO-score = WHO performance score; RT = radiotherapy; IMRT = intensity modulated radiotherapy

Conclusion

In this prospective cohort study, sarcopenia was significantly associated with poorer OS and DFS, for patients with lower performance (WHO-score >0) and locally advanced disease (stage III-IV), with similar prognostic value as WHO-score, tumour stage and primary tumour site. Given that the SMI can be easily assessed on planning-CT scan, clinical introduction is easy and adds important and clinically relevant information to assess patient outcome.

Proffered Papers: BT 5: Optimising dose distribution

OC-0394 Brachytherapy quality assurance in the PORTEC-4a trial for high-intermediate risk endometrial cancer

B. Wortman[1], E. Astreinidou[1], M. Laman[1], L. Lutgens[2], E. Van der Steen-Banasik[3], A. Slot[4], H. Westerveld[5], K. De Winter[6], H. Van den Berg[7], M. Bloemers[8], T. Stam[9], J. Mens[10], L. Zwanenburg[11], S. Bijmolt[12], I. Jürgenliemk-Schulz[13], A. Snyers[14], C. Creutzberg[1], R. Nout[1]

[1]Leiden University Medical Center LUMC, Radiation Oncology, Leiden, The Netherlands ; [2]Maastricht Radiation Oncology Clinic, Radiation Oncology, Maastricht, The Netherlands ; [3]Radiotherapiegroep, Radiation Oncology, Arnhem, The Netherlands ; [4]Radiotherapy Institute Friesland, Radiation Oncology, Leeuwarden, The Netherlands ; [5]Amsterdam University Medical Center, Radiation Oncology, Amsterdam, The Netherlands ; [6]Institute Verbeeten, Radiation Oncology, Tilburg, The Netherlands ; [7]Catharina Hospital Eindhoven, Radiation Oncology, Eindhoven, The Netherlands ; [8]Netherlands Cancer Institute, Radiation Oncology, Amsterdam, The Netherlands ; [9]Haaglanden Medical Center, Radiation Oncology, Leidschendam, The Netherlands ; [10]Erasmus MC-Cancer Institute, Radiation Oncology, Rotterdam, The Netherlands ; [11]Isala, Radiation Oncology, Zwolle, The Netherlands ; [12]University Medical Center Groningen, Radiation Oncology, Groningen, The Netherlands ; [13]University Medical Center Utrecht, Radiation Oncology, Utrecht, The Netherlands ; [14]Radboud University Medical Center, Radiation Oncology, Nijmegen, The Netherlands

Purpose or Objective

The international multicenter PORTEC-4a trial investigates molecular-integrated risk profile guided adjuvant treatment for women with high-intermediate risk (HIR) endometrial cancer (EC). As part of the quality assurance (QA) program, all participating centers had to pass a mandatory vaginal brachytherapy (VBT) dummy run procedure before site activation. Subsequently, QA review of one VBT treatment plan is done annually for each site to verify protocol adherence. Aims of the current study

were to evaluate VBT planning quality and protocol adherence.

Material and Methods

Each participating center was asked to provide anonymised CT or MRI scan data used for a VBT plan for a randomly selected case. Quality review included the delineation of organs at risk (OAR) and clinical target volume (CTV), applicator reconstruction, dose plan, DVH parameters and printouts of the dose plan including the dose to the reference points (see Figure 1). In an additional questionnaire, changes in type of afterloader, applicator set and software used were recorded. Data was imported into Oncentra Brachytherapy at Leiden University Medical Center. A local expert panel reviewed all information and scored the compliance of plans according to a QA item checklist. After the review, feedback was sent to the study PI and physicist of each participating site.

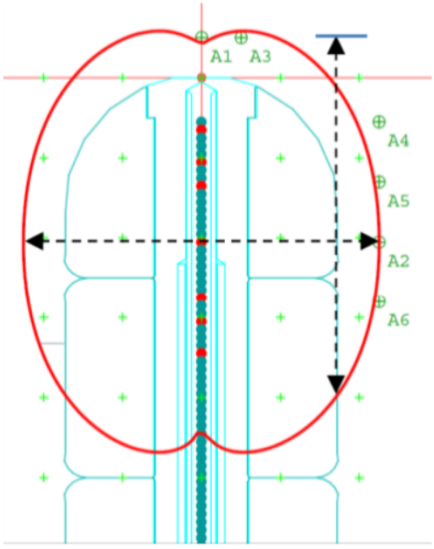

Figure 1. Dose distribution for a vaginal cylinder diameter 3.5cm. 100% isodose line (red). Dose is specified to point A2; average dose of A1+A3 should be approximately 100%; dose to A1 >90% and A3<110%; A4-6 aim for dose reporting with the aiming to reach 100%. Reference length/width (dotted arrows), reference length should aim for 4.5 cm.

Results

Currently a total of 152 patients have been included in the PORTEC-4a trial and 14 sites are actively recruiting. In total, 21 cases were requested for the annual QA review, five in the first and eight in the second round were evaluated; eight data requests are pending. 12 centers used CT planning, two used MRI planning. Three different treatment planning systems and HDR afterloaders were used. During the trial, two centers changed to a different cylinder applicator and two centers changed their planning software. Compliance results of the QA checklist are shown in Table 1. Seven out of thirteen evaluable plans were fully compliant. Most common reasons for feedback were related to target (CTV was not a ring structure or too long) and OAR delineation, and applicator positioning (applicator not horizontal or in optimal contact). Feedback concerning the symmetry of the loading pattern and the reference length (when > 5cm) was provided for six plans (mean reference length 5.0cm, range 4.3 - 5.6; Figure 1). The mean % dose (7Gy = 100%) in A2 was 100.7% (SD 2.4, range 99.3-108.7); in A1: 90.4% (SD 7.1, 67.8-95.7); and in A3: 105.3% (SD 7.7, 81.7-110.0).

Table 1. Checklist QA

Items	Fully compliant	Partly compliant
Applicator positioning		
Position and angle of cylinder	8	5
Contact of cylinder to vaginal mucosa	10	3
Delineation		
CTV delineation	6	7
OAR delineation	9	4
Treatmentplanning		
Reconstruction	10	3
Position of A points	9	4
Prescribed dose in point A2	12	1
Symmetry of loading pattern	7	6
Evaluation of dose distribution		
Average dose in A1+A3 = 100%	8	5
Dose in point A1 $\geq$ 90% and A3 $\leq$ 110%	10	3
Reference length/width	7	6
CTV D90/D98	11	2
OAR D2cm^3	13	0

Conclusion

Most feedback during the continuous QA of VBT planning in the PORTEC-4a trial was related to target and OAR delineation, applicator positioning, symmetry of the loading pattern and reference length. Changes in type of afterloader, applicator and planning software were recorded and can affect VBT protocol compliance. Annual QA contributes to protocol compliance, to ensure uniform high quality VBT in all participating centers.

OC-0395 Bi-objective optimization of dosimetric indices for HDR prostate brachytherapy within 30 seconds

A. Bouter[1], T. Alderliesten[2], B.R. Pieters[2], A. Bel[2], Y. Niatsetski[3], P.A.N. Bosman[1]

[1]Centrum Wiskunde & Informatica, Life Sciences and Health, Amsterdam, the Netherlands ; [2]Amsterdam UMC-University of Amsterdam, Radiation Oncology, Amsterdam, The Netherlands; [3]Elekta, Physics and Advanced Development, Veenendaal, the Netherlands

Purpose or Objective

In clinical practice, plan quality is judged based on dosimetric indices. However, for the purpose of efficiency, typical automated planning methods do not directly optimize dosimetric indices. This creates a mismatch between what is optimized and what is evaluated. A bi-objective optimization approach was recently proposed that directly optimizes dosimetric indices, finding many high-quality plans with different trade-offs between target coverage and organ sparing. This allows for insightful comparison of high-quality plans and patient-specific plan selection. We now aim to accelerate this approach to the extent that it can be used in clinical practice by applying parallelization on a Graphics Processing Unit (GPU).

Material and Methods

The two objectives of our bi-objective optimization are the dosimetric indices having the largest deviations from the clinical protocol (see Table 1) in terms of aspired target coverage and organ sparing, the Least Coverage Index (LCI) and Least Sparing Index (LSI), respectively. Optimization is done using the Gene-pool Optimal Mixing Evolutionary Algorithm (GOMEA). The main acceleration is obtained by calculating dosimetric indices on an NVIDIA Titan Xp GPU, programmed in CUDA.

We perform bi-objective planning for 18 HDR prostate brachytherapy cases. Prior to acceleration, results for these cases after 1 hour of optimization were found to be clinically superior to manually optimized plans. We optimize on 20,000 dose calculation (DC) points, whereas typical planning methods (e.g., IPSA, HIPO) use in the order of 5,000 DC points for the purpose of efficiency. All