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Original article

Prospective evaluation of acute toxicity and patient reported outcomes in anal cancer and plan optimization

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ABSTRACT

Background and purpose: Chemoradiotherapy (CRT) is the standard therapy for localized anal cancer (AC), but this treatment is associated with substantial toxicity. However, there is a lack of prospectively collected toxicity and patient reported outcome (PRO) data from larger cohorts.

The purpose was to prospectively collect and determine agreement between physician assessed toxicity (CTCAE) and PRO during and after CRT and to compare IMRT, VMAT and proton-based planning in a subgroup of patients.

Material and methods: Patients, treated with CRT for AC, were included between 2015 and 2017. NCI-CTCAE v.4.0, EORTC QLQ-C30 and CR29 data were collected baseline, mid-therapy, end-of therapy and 2–4 weeks posttherapy. Treatment planning with 5- or 6-fixed field IMRT, 2 and 3 arc VMAT, and 3- and 4-field proton plans were compared.

Results: One-hundred patients were included. Both CTCAE and PROs related to acute toxicity reached a maximum at end of therapy. Incidences of PROs were markedly higher with only slight to fair agreement to CTCAE, (κ 13–37). Comparative planning revealed dosimetric equality of IMRT and VMAT plans, but superiority of proton plans.

Conclusions: The high incidence of PRO scores and weak agreement to CTCAE suggest that PROs are important tools complementary to CTCAE in evaluating patient symptoms during and after CRT. Proton therapy has the potential to lower radiation doses to most organs at risk.

Chemoradiotherapy (CRT) is standard treatment for squamous cell anal cancer (AC). The curative and organ preserving effect of CRT is well established [1,2], but the treatment is associated with significant acute and late toxicity.

Development of newer radiotherapy treatment techniques from 3D to intensity modulated radiotherapy (IMRT) has aimed at optimizing conformity and lowering dose to the organs at risk (OAR). The 2013 RTOG 0529 study showed a superior dose distribution, obtained using IMRT compared with conventional radiation (2 or 4-field 3D photon therapy) for AC, which resulted in significantly less gastrointestinal, hematological and dermatological toxicity [3]. Since, IMRT has become the standard radiation technique for AC in many centers. Further developments of radiotherapy techniques have included volumetric modulated arc therapy (VMAT), helical tomotherapy and latest particle therapy [1].

The potential benefits of VMAT compared to IMRT are further reductions in dose to OARs while maintaining target coverage and dose homogeneity, as well as reduction in treatment time and use of less monitor units [4–6] Despite these improvements toxicity to CRT is still significant and a clinical challenge.

In recent years, increasing focus have been on obtaining patient reported outcomes (PROs) in addition to physician scored toxicity, most frequently assessed by common toxicity criteria for adverse events (CTCAE). Prospective studies of PROs during and after CRT for AC are sparse especially after introduction of these newer radiation techniques [6]. Furthermore, PRO agreement with physician assessment of toxicity remains to be determined.

The aim of this study was to: prospectively collect coinciding CTCAE and PRO data during and 2–4 weeks after VMAT planned CRT, secondly to correlate and determine agreement between acute CTCAE and PROs. Finally, plan comparison between fixed field IMRT, 2 and 3 arc VMAT and additional 3-and 4-field pencil beam scanning proton therapy was performed.

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Methods/materials

Patients

During the study period, September 2015–September 2017, consecutive patients with newly diagnosed AC, undergoing curative CRT, were asked to participate in a study collecting prospective toxicity and quality of life data, during and after CRT. Patients were included from two different (Danish) treatment facilities. The project was approved by the Danish Data Protection Agency (2007-58-0010) and the Regional Ethical Committee (1-10-72-79-16), and all patients gave written informed consent. The study complied with the Helsinki declaration.

Treatment: Standard treatment comprised 60–64 Gy in 30–32 fractions, one fraction per day to tumor and pathological lymph nodes and 49.5–51.2 in 30–32 fractions to the nodal clinical target volume (CTV) including: mesorectum, presacral space, ischioanal space, bilateral internal and external iliac and bilateral inguinal regions (Modifications of nodal CTVs were allowed as per local practice). Treatment planning with patients in the supine position was CT-based, merged with therapeutic MRI and PET-CT or diagnostic PET-CT. Delineation of gross tumor volume (GTV) was based on imaging and clinical investigation including endoscopy. Internal target, and planning target volumes (PTV) were applied as per local practice.

Bowel cavity, bladder, femoral heads, and penile bulb were delineated according to RTOG guidelines, in addition sacral bone and female external genitalia. Plan objectives for PTV were D99% >95%, for OARs, bowel bag: V40 Gy <400 ccm/V50 Gy <300 ccm or V45 Gy <300 ccm/V30 Gy <600 ccm, bladder V45Gy <75% or V50 Gy <20%/V30 Gy <75%, femoral heads V50 Gy <5%, sacral bone, penile bulb, and female external genitalia as much as possible <50 Gy. Radiation was delivered with 2 or 3 arc 6 MV VMAT technique (one IMRT) (Varian Eclipse planning system) and concurrent chemotherapy per local practice. According to national guidelines T1 and smaller T2 (<4 cm), N0 tumors could be treated with radiotherapy alone using higher radiation doses (64 Gy).

Toxicity

Evaluation of adverse events and quality of life with NCI-CTCAE v.4.0, EORTC QLQ-C30 and CR29 questionnaires was performed at baseline, mid-therapy, at the end of therapy and 2–4 weeks after completion of CRT. Here we report parameters relevant to acute toxicity: diarrhea, anal and urinary incontinence and urgency, radiation dermatitis, pain, sexuality and quality of life. For most parameters CTCAE, grade $\geq$3 toxicity is reported. However, grade $\geq$2 (indicating daily use of pads) was chosen for incontinence measures and urinary urgency and frequency (since this reflects the presence of either item, or no higher grading is possible). For PROs we report "very much" (grade 4) for all items except incontinence measures, where we report $\geq$ "quite a bit" (grade 3) and for overall quality of life and overall health "average" to "excellent" (grade 4–7).

Comparative planning was performed in a sub-group of 20 patients. Alternative treatment plans were generated using 5- or 6-fixed field IMRT and 2 or 3 arc VMAT (All Varian Eclipse planning system). Four patients with doses exceeding normally applied constraints (high V40 Gy to the bowel) were selected for additional proton therapy planning; both 3- and 4-field plans were generated (The proton PBS plans were optimized using Multi Field Optimization and a PTV similar to the VMAT plans), these plans were compared with 2 arc VMAT which is current standard for treatment planning.

Statistics

Both CTCAE and PRO data are reported as the percentage of patients with a specific grade of toxicity or symptom (outlined above) at each timepoint.

Spearman's Rank correlation was used for PROs correlations to CTCAE. Weighted Kappa-statistics was applied to measure inter-rater agreement. CTCAE grade 0 corresponded to "not at all", grade 1 to "a little", grade 2 "to "quite a bit" and grade 3 to "very much". Weight (measuring the importance of disagreements) were defined as $1 - |i - j|/(k - 1)$, where i and j index the rows and columns of the ratings by the two raters and k is the maximum number of possible ratings. Although arbitrary, values <0 indicates no agreement and 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1 almost perfect agreement [7].

Student's t-test or Wilcoxon rank sum test was applied for dosimetric comparisons. Chi2-test was used for comparisons of gender differences and differences in CRT vs. radiotherapy alone.

Statistical analyses were done using STATA (STATA/IC 13, StataCorp LP, Texas, College Station, USA). P-values <0.05 were considered significant.

Table 1
Baseline characteristics. *31 (combination 5-FU and cisplatin).

Baseline characteristics	*n* (%)
Participating center	
Herlev	46 (46)
Aarhus	54 (54)
Gender	
Female	73 (73)
Male	27 (27)
Age (mean, SD)	62.9 (11.0)
T-stage	
T1	17 (17)
T2	44 (44)
T3	16 (16)
T4	20 (20)
Tx	3 (3)
N-stage	
N0	66 (66)
N1	12 (12)
N2	13 (13)
N3	5 (5)
Nx	4 (4)
P16 status	
Positive	59
Negative	5
Not evaluated	36
Radiation dose	
64/51,2 Gy/32 fx	35 (35)
60/48 Gy/30 fx	3 (3)
60/49,5 Gy/30 fx	44 (44)
Other	11 (11)
Chemotherapy	
Cisplatin*	46
5FU*	34
Neo-adjuvant	11
RT alone	41
Performance status	
0	70 (70)
1	17 (17)
2	5 (5)
Unknown	8 (8)

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