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Determinants for local tumour control probability after radiotherapy of anal cancer

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ABSTRACT

Background and purpose: Anal squamous cell carcinoma is primarily treated with radiotherapy (RT), but the optimal RT dose for anal tumours of different sizes is not known. The purpose of this study was to identify determinants for local tumour control probability (LTCP).

Material and methods: From a large Nordic database 901 patients who received RT for anal cancer between 2000 and 2007 were selected. LTCP was analysed in a series of uni- and multivariable regression analyses.

Results: Higher RT dose, female gender and addition of chemotherapy were associated with higher LTCP whereas increasing tumour size, tumour invasiveness (stage T4) and lymph node metastases (N+) were associated with lower LTCP. Male patients needed approximately 10 Gy higher RT dose than female patients for similar LTCP. The addition of chemotherapy corresponded to 5–10 Gy RT dose.

Conclusions: Our results basically support current guidelines recommending: (1) lower RT dose in small tumours (<4 cm), (2) higher RT dose larger tumours and in stages T4 and /or N+, (3) Chemo should be used in combination with RT. These results will hopefully constitute the basis for future trials, aiming at individualized RT dosing in patients with anal cancer.

 Radiotherapy and Oncology xxx (2018) xxx–xxx

Anal squamous cell carcinoma is primarily treated with radiotherapy (RT), often combined with chemotherapy. Radical chemoradiotherapy (CRT) results in 60–80% cure rates, depending on tumour stage [1,2]. Recurrences occur in 10–30%, most of them locally at the site of the primary tumour. Some patients with local relapse can be rescued with salvage surgery, usually abdominoperineal resection with a permanent colostomy. Many patients that are cured from their anal cancer suffer from late sequelae after the pelvic irradiation. Therefore RT optimization in the treatment of anal cancer remains a very important issue, aiming at good local control and minimizing the late side-effects.

International guidelines recommend RT to the primary tumour to a total doses usually ranging from 45 to 60 Gy, combined with 5-fluorouracil (5FU) and mitomycin C (MMC) [3]. These guidelines generally advocate a lower RT dose to smaller tumours than for larger tumours, but the optimal RT dosage for tumours of different sizes is not known.

Several studies have shown that high age, male gender, poor performance status, high T stage, lymph node metastases, and distant metastases are associated with a poor prognosis [4–8], whereas determinants for local control are less clear.

From a large Nordic database, 901 patients who received RT for anal cancer between 2000 and 2007, with or without concomitant chemotherapy, were selected. The primary aim was to establish the relations between RT dose and local tumour control in tumours of different sizes. Secondarily the impact of other prognostic factors, e.g. gender, tumour invasiveness (stage T4), lymph node metastases and the addition of chemotherapy on the local tumour control probability (LTCP) was investigated.

Material and methods

NOAC database

The NOrdic Anal Cancer (NOAC) group was established in the late 1990s, with participation from most oncological departments in Sweden, Norway and Denmark. Clinical data from a total of 1266 patients with verified squamous cell carcinoma of the anal canal or anal margin, diagnosed from 2000 to 2007, were retrieved retrospectively and entered into the NOAC database. A majority of these patients (n = 886) received RT alone or CRT according to predefined protocols, whereas 380 patients were not treated according to any of the protocols, but still included in the database,

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that covered >90% of all anal cancers diagnosed in the participating regions during that time period. The study was approved by ethics committees in all three countries. One per cent of the patients had known HIV infections. The human papilloma virus (HPV) status was not analysed.

Treatment schedules

In order to standardize treatments, different treatment schedules were launched in 2000, stratified by tumour stage. The protocols in detail and the overall treatment results from this anal cancer cohort have been reported previously [4]. The main features of these protocols were that small tumours T1-2N0 received either RT alone 64 Gy or CRT with 54 Gy RT combined with one cycle of 5FU/MMC and the vast majority of patients with more advanced tumours, T3-4/N+, had CRT based on cisplatin/5FU, either three cycles before 64 Gy RT or two cycles before and one cycle concomitant with 60 Gy RT, Supplementary Table 1. RT in all regimens was scheduled without gap. Each participating centre could choose one protocol for small tumours and one protocol for advanced tumours. Tumour staging was performed according to institutional standards, with digital rectal examination, anorectoscopy and CT of the abdomen and thorax as a minimum. Early in the study period anal ultrasound was used at many centres, but was gradually replaced by MRI. PET-CT was not used at the time these patients were treated. After completion of RT, the recommended follow-up schedule consisted of clinical examination every three months for two years, then every six months, for a total period of five years.

Patient selection

From the total cohort 1123 patients that had received RT/CRT were selected, Fig. 1. Further criteria for inclusion in this study were: (1) a total RT dose of at least 30 Gy given, (2) at least 6 months follow-up post RT, (3) tumour size reported, (4) no brachytherapy given, (5) not planned for tumour resection post RT. Using these criteria 222 patients were excluded and the subsequent analyses were based on 901 patients.

Patient and treatment characteristics

The patient characteristics are listed in Table 1. The median age was 62 years and 73% were females. A majority (71%) had stage T2-T3 tumours and the median size was 44 mm (range 2–160 mm). The median delivered RT dose was 60 Gy (range 30–70 Gy). Chemotherapy was given to 62% of the patients. Out of these 31% had 5FU/MMC and 69% received cisplatin-based treatment; 29% had all chemotherapy as induction treatment and 71% had at least one cycle chemotherapy concomitant with RT.

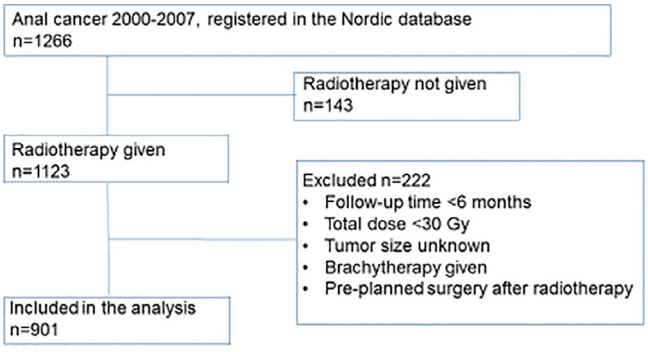

Fig. 1. Flow chart showing the selection process for the study.

Table 1
Patients' and treatment characteristics (n = 901).

Variable	Median (range) n (%)
Age (years)	62 (31–99)
Gender	
Male	248 (27.5)
Female	653 (72.5)
T stage	
T1	96 (10.7)
T2	399 (44.3)
T3	240 (26.6)
T4	166 (18.4)
N stage	
N0/NX	604 (67.0)
N1	89 (9.9)
N2	113 (12.5)
N3	95 (10.5)
M stage	
M0/MX	866 (96.1)
M1	35 (3.9)
Primary tumour size (mm)	44 (2–160)
RT dose (Gy)	60 (30–70)
Chemotherapy given	
No	345 (38.3)
Yes	556 (61.7)
Type of chemotherapy	
5FU/MMC	175 (19.4)
CisPt/5FU before RT	160 (17.8)
CisPt/5FU with RT	187 (20.8)
CisPt/MMC	26 (2.9)
Other	8 (0.9)
Treated according to protocol	
Yes	725 (80.5)
No	176 (19.5)

5FU, 5-fluorouracil; CisPt, Cisplatin; MMC, Mitomycin C.

Primary endpoint

Local failure in the anal region was primary endpoint, either residual tumour after primary treatment or local recurrence during the follow-up period. The median follow-up time was 41 (range 7–103) months. The median time from start of RT to local failure, in patients who developed local failure, was 3.8 (range 0.4–82) months. Local control was defined as absence of local failure. During the follow-up time 48 patients died without local failure and their median survival was 29 (range 7–103) months.

Tumour size

Tumour size can be used in the statistical analysis as a continuous variable, e.g. expressed as the longest diameter, or classified according to T stage. Since tumour size and T stage are strongly correlated only one at a time can be used in the calculations. In the present study we decided to focus on tumour size rather than T stage, for several reasons. In the TNM classification (UICC 4th edition 1997), stages T1-T3 are merely based on size with 2 cm and 5 cm as cut-offs between the T stages. This may not be an optimal division, since several previous studies have indicated that large T2 tumours (>4 cm) harbour a worse prognosis, similar to T3 tumours, and should therefore be considered for more intensive treatment [9]. Moreover, in the clinical setting T3 tumours (>50 mm) is a heterogeneous group where some patients present with very large tumours (>8–10 cm), for whom treatment outcome has not been previously specifically described. Finally stage T4 indicates invasion into adjacent organs, but also a rather small tumour may invade into e.g. the posterior wall of the vagina. From

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