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Interstitial brachytherapy as a boost to patients with anal carcinoma and poor response to chemoradiation: Single-institution long-term results

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ABSTRACT

PURPOSE: To analyze the efficacy of a protocol-based brachytherapy (BT) boost after external beam radiation therapy (EBRT) with simultaneous chemotherapy in patients with anal carcinoma.
METHODS AND MATERIALS: About 190 patients have been analyzed. Around 143 patients were identified with a good clinical response at the end of EBRT. Another 47 patients received an additional BT boost to the residual tumor at 6 weeks after end of chemoradiation.
RESULTS: The 5-year incidence of local recurrence was 24% in patients with BT boost and 19% in patients without BT boost ($p = 0.238$). The 5-year disease-free survival rate, overall survival rate, and colostomy-free survival rate were 64% and 75% and 76.1% in the BT group and 69% ($p = 0.212$), 72% ($p = 0.924$), and 82.7% ($p = 0.488$) in the non-BT group. We found no differences in late toxicity between the groups.
CONCLUSIONS: For patients with anal cancer with not a good response to 50−59 Gy EBRT with simultaneous chemotherapy, the further dose escalation using the BT boost up to a mean of 67.5 Gy seems to improve the clinical outcome to the same level as observed in patients with a good response to ERBT, without an increase in late side effects.

Keywords: Anal cancer; Brachytherapy; Boost; Chemoradiation

Introduction

Concurrent chemoradiation is a long-established standard treatment for anal cancer (1) typically using drugs, such as 5-fluorouracil and mitomycin (2, 3). The introduction of intensity-modulated radiotherapy techniques led to a significant reduction in acute and late toxicity (4, 5). After external beam radiation therapy (EBRT) of the primary tumor area and including nodal regions, a boost to the gross tumor volume (GTV) is often necessary. Of the boost techniques apart from EBRT, the brachytherapy (BT) technique in particular has been widely used since the 1940s (6), primarily because of the high versatility and precision of interstitial BT associated with a reduction in late side effects (7−9). Nevertheless, there is no broad agreement on which boost technique should be given preference (10), and unfortunately randomized trials comparing EBRT boost with BT boost are not available.

The strategy of radiation therapy for anal cancer has shifted in recent years. The former concept of a split-course EBRT with a mandatory break during EBRT has been abandoned. As a prolonged break and overall treatment time (OTT) were shown to worsen the clinical outcome (11, 12), the recommendation ‘‘that boost should follow primary therapy immediately’’ has been widely accepted (12). Nevertheless, the regression time of anal carcinoma after EBRT remains long (up to 12 weeks and more) (13), and the most opportune point in time for evaluation of clinical response remains uncertain.

An optimum radiation dose still needs to be found. In very early Tumor Stage T1, a good clinical outcome can

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be achieved with total radiation doses of 40−50 Gy (3, 14, 15). With increasing T stage, higher radiation doses are recommended to meet the increasing risk of local failure. Despite good complete response rates of up to 92% after a dose of 45−50.4 Gy, the high 5-year local recurrence rates (LRRs) of 17−60%, as seen in the Radiation Therapy Oncology Group (RTOG) 98-11 study (14), remain at a level that calls for further improvement. Consequently, further dose escalation found broad acceptance (16). Importantly, Peiffert *et al.* (17) demonstrated a highly increased risk of death for patients with less than 50% tumor response after initial therapy. In our view especially for those patients with inadequate response to primary radiation, a further optimal conservative therapeutic strategy as an alternative to the mutilating abdominoperineal resection should be considered. Here, it seems that the use of interstitial multicatheter BT for further escalation of the radiation dose to reach definitive tumor control is at least promising. Recently, Lestrade *et al.* (8) reported that an 18 Gy or more boost dose with interstitial BT could significantly improve colostomy-free survival (CFS) as compared with lower boost doses. It is worth noting that other authors demonstrate that with interstitial BT, high total radiation doses of up to 70 Gy can be safely applied for anal cancer (7). In our treatment protocol, we therefore specified performing a further escalation of the radiation dose using interstitial BT for a selected and not sufficiently responding group of patients (nonresponders) after simultaneous chemoradiation. Here, we present the long-term results of our protocol-based dose escalation using interstitial BT in patients with persistent anal cancer after simultaneous chemoradiation.

Methods and materials

We analyzed the clinical records of 190 patients with anal cancer treated from February 1980 to November 2014 in our hospital with EBRT, in curative intention. We analyzed individual risk factors, tumor status, therapy outcome, and therapy-related toxicity. Eligibility criteria for involvement in statistical evaluation were if age at diagnosis was older than 18, histologically confirmed cancer of the anal canal, radiation therapy as part of the concept for primary therapy, and the absence of distant metastases at date of diagnosis (for details, see Table 1). All patients received EBRT of the anal canal and pelvic lymph nodes and a boost with EBRT to the region of the anus. Most analyzed patients also received simultaneous chemotherapy with 5-fluorouracil and mitomycin (Table 1). In case of good tumor response (no tumor measurable at the end of treatment), the patients crossed over to followup (nBT group) according to the national guidelines. In case of a persisting and/or measurable tumor at the end of therapy and also at the time of 6 weeks after the end of EBRT, interstitial BT was applied as a second boost (BT group). In 1 patient, the BT boost was given before EBRT because of acute tumor−based bleeding. In 1 other patient, the interstitial BT was performed as the sole treatment method because of previous radiation therapy for prostate cancer (BT with iodine-125 alone).

EBRT was performed typically with 20 MV X-rays initially to the anal region with surrounding structures and regional lymph nodes up to a total dose 50.4 Gy (dose per fraction, 1.8 Gy). The total EBRT dose was prescribed in relation to the tumor size. Thus, T1 tumors received a 5.4 Gy boost and T2 or bigger tumor received 9 Gy boost in addition to the pelvic irradiation with 50.4 Gy.

Subsequently, a boost with EBRT limited only to GTV up to a total dose of 55.8−59.4 Gy was completed. As a radiation technique most frequently used, a CT-based three-dimensional EBRT has been performed (171 of 190, 90%); only in 17 patients, two-dimensional EBRT and in 2 patients intensity-modulated radiotherapy techniques were also used.

For most patients (169 of 190, 89%), simultaneous chemotherapy during first and fifth weeks of EBRT was implemented as well, preferably with 5-fluorouracil 1000 mg/m^2 Day 1−5/29−34 and mitomycin-C 10 g/m^2 Day 2 and 30 (Table 1).

Poor tumor response was defined as residual tumor 6 weeks after the end of EBRT and clinically identified by digital rectal examination, anuscopy, and transrectal ultrasound. In patients with a measurable tumor 4−6 weeks after chemoradiation, typically a pulsed-dose-rate interstitial brachytherapy (PDR-BT) as a second boost was used. For 1 patient, high-dose-rate BT with 1 × 6 Gy was undertaken because of limited compliance. All interstitial implants were done under general or spinal anesthesia using titanium or steel needles and respecting the rules of the Paris system and International Commission on Radiation Units and Measurements 58 (Fig. 1). We used the Papillon template and inserted the needles of appropriate length typically in only one row in 36 of 47 patients (80%). In remaining patients, the needle insertion was done free hand. In average, we used seven needles (range, 3−18) with typical active length of 2 cm, related to the typical tumor length of 3 cm and typical tumor thickness of <1 cm. In no patient, more than half of the circumference of anal canal has been involved by persisting tumor.

The clinical target volume and organs at risk were defined on the basis of palpation, inspection, ultrasound, and CT. MRI was not used. We defined clinical target volume as identifiable tumor (GTV) with safety margins of 5 mm in all directions. For treatment planning, a CT scan and ultrasound were used. The dose calculation was performed by the Oncentra Brachytherapy Planning System (Nucletron, an Elekta Company, Veenendaal, The Netherlands), using geometrical and manual optimization. For dose specification and prescription, rules according to the Paris system and International Commission on Radiation Units and Measurements 58 were used.