Anal Cancer: Surgery Does Not Influence Prognosis When Performed Prior to Concurrent Radiochemotherapy

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Abstract. Background: Concurrent radiochemotherapy (cRCT) is the standard-of-care for patients with locally advanced anal cancer. There is a subgroup of patients however, vastly with small tumors, which undergo local excision before combined modality treatment. It was suggested that local excision prior to cRCT might improve the local control in comparison with cRCT. We evaluated local excision in comparison to incisional biopsy in this setting. Patients and Methods: Between 2000 and 2005, 84 patients were included in the study. In the majority of patients, only incisional biopsy (INC) was performed for the histopathological verification. Other patients underwent surgery prior to the RCT course as excisional biopsy (EXC). The chemotherapy consisted of 5-fluorouracil (800/1000 mg/m²/d, 4 consecutive days, w 1, five) and mitomycin C (2 times 10 mg/m²). Radiotherapy was prescribed 45 at Gy. Results: All patients (T1-2) were available for analysis. 14% of patients had node-positive disease. For the entire series, at five years and eight years, the actuarial OAS rates were 71% and 54%, respectively; the DSS rates were 74% and 68%, respectively; and the DFS rates were 54% and 54%, respectively. The actuarial control rate achieved by the EXC group was 80% after five years, better than the one for the INC group at 64%. Univariate analysis showed that tumor stage T3-T4 (p=0.04), tumor size ≥6 cm (p<0.001), and nodal stage N1-3 (p<0.00) and OTT >40 days (p=0.05) are significantly correlated with poorer local disease control. Local excision in comparison with INC did not prove to be significant for local disease control (p=0.45). No significance was found for pre-therapeutic prognostic factors age, gender, histological type and grading. Multivariate analysis showed that tumor size as continuous variable (p=0.02) and OTT (p=0.04) remained significant when adjusted for T-stage and nodal stage. Conclusion: According to this highly qualitative trial, surgical excision prior to cRCT, did not improve results. cRCT was confirmed as the standard-of-care.

Anal cancer is relatively uncommon, accounting for only 4% of all cancers of the lower gastrointestinal tract (1). Major prognostic factors for anal cancer are tumor site, tumor size, and nodal status. This condition has posed a challenge for clinicians since a long time. Until the 1980s, surgery was the only available treatment modality. Since then, RTOG 98-11 (2), ACT II (3), and other large clinical trials have evaluated the roles of chemotherapy and radiation therapy in the treatment of this disease. The combined results of several clinical trials have shown that concurrent radiochemotherapy (cRCT) is the first-line therapy of choice for patients with anal carcinoma. This therapy is efficacious and, additionally, often allows sphincter preservation, which has a considerable positive impact on quality of life (4-7). Accordingly, anal carcinoma has become a generally curable disease.

Surgical treatment is generally limited to abdominoperineal resection of tumors that have already destroyed the sphincter or to salvage therapy following recurrence of anal carcinoma. However, some patients—mostly those with localized tumors—could reasonably undergo local excision before combined-modality treatment. In practice, excision is sometimes performed instead of incisional biopsy, an option that combines standard diagnostic investigation with removal of the gross tumor, aiming to improve the overall therapeutic result. Local excision followed by RCT has been suggested to improve local control compared to incisional biopsy followed by RCT and local excision for the residual tumor. In 1999, a team from the Memorial Sloan-Kettering Cancer Center reported on a subset of patients with invasive anal cancer who underwent excision before combined-modality therapy. The objective of that study was to determine whether these patients could be adequately treated with a low dose of radiation therapy. Encouraging results were found with regard to the role of surgery before combined-modality therapy (8).
Because these first results appeared reliable and important, we decided to re-examine and validate them in a controlled clinical setting. Consequently, we designed a controlled, non-randomized phase II clinical trial in order to examine the role of surgery performed before combined-modality therapy for anal cancer. More specifically, we investigated whether therapeutically intended, local excision prior to cRCT could improve the prognosis of patients with localized, non-metastatic anal carcinoma.

Patients and Methods

Setting. Between 2000 and 2005, a total of 84 patients underwent primary treatment for anal carcinoma with cRCT following either incisional biopsy or surgical excision. We received approval from our institutional Review Board based on a prospective, non-randomized phase II protocol (2000/8). Included patients provided informed consent.

Patients received radiotherapy at a mean total dose of 45 Gy (range=43-47 Gy). A dose of 30-36 Gy in 17-20 fractions of 1.8 Gy, five days per week, was administered for noninvolved nodal sites at risk. Using 3-dimensional conformal radiotherapy, the tumor and lymph nodes of the true pelvis were treated with a radiation dose of 45 Gy, with shrinking fields applied after 30 Gy. Chemotherapy consisted of a continuous infusion of 5-fluorouracil (1000 mg/m²/d1-45 Gy, with shrinking fields applied after 30 Gy. Chemotherapy consisted of a continuous infusion of 5-fluorouracil (1000 mg/m²/d) on five days, during weeks 1 and 5) together with a short infusion of mitomycin C (2×10 mg/m²).

In all cases, surgery was performed prior to cRCT. For most patients (n=61) incisional biopsy (INC) was performed on the basis of intraoperative findings. For other patients (n=22), surgical excision (EXC) of the tumor was performed in an attempt to remove the gross cancer; however, a residual tumor load was noted in most cases.

Patient eligibility. Eligibility criteria included histologically-proven squamous cell and basaloid carcinoma of the anal canal, age of 18 years or older, a Karnofsky performance status of ≥60, T2-4 category cancer with any N category (pelvic or inguinal), adequate organ function, and written consent. Patients were excluded if they had T1 or M1 cancer, severe comorbid conditions (including acquired immunodeficiency syndrome), or other major malignancies (unless they had been successfully treated and were disease-free more that five years).

Evaluations. Before treatment, patients underwent baseline proctoscopy or sigmoidoscopy, chest radiography, and computed tomography or magnetic resonance imaging of the abdomen/pelvis to establish the disease stage. Adequacy of hepatic, renal, and bone marrow function was evaluated on the basis of blood and serum chemistry studies. After treatment completion, patients underwent the same procedures performed for baseline evaluation and were then followed-up every three months for four years and yearly thereafter.

All included patients were evaluable, and their data were analyzed with regard to prognostic factors.

Statistical methods. Overall survival (OAS) was defined as the time from treatment to death from any cause. Locoregional failure (LRF) was defined as persistence of the tumor or early recurrence, positive biopsy findings, or involvement or early recurrence in lymph nodes.

Death, LRF, distant metastasis (DM), and a second primary tumor were considered for (DFS) evaluation. OAS, DFS, and disease-specific survival (DSS) were estimated using the Kaplan-Meier method (9), and the treatment arms were compared using the log-rank test (10). Time-to-relapse (LRF or DM) was estimated according to the cumulative incidence method (11), and results for each treatment arm were compared using the Gray’s test (12). Univariate analysis with respect to local control was performed for a variety of factors: age, gender, histology, tumor grade, performance status, tumor size, tumor stage, nodal status, overall treatment time, and extent of surgery. Multivariate analyses were performed using the Cox proportional hazards model (13) to test for treatment differences (incisional biopsy plus cRCT versus excision plus cRCT), while adjusting for tumor size (T1-2 versus T3-4), clinical nodal status (N0 versus N1-3), maximum tumor diameter (<6 cm versus >6 cm), overall treatment time (OTT, <40 days versus >40 days), and extent of surgery (incisional biopsy versus excision).

Results

Patient and tumor characteristics. Our analyses were conducted on all 84 patients who met the eligibility criteria. Table I presents an overview of patients’ characteristics. The median age was 58 years (range: 36-76 years). Most treated patients were women (female-to-male ratio: 2.1:1). Squamous cell carcinomas were more frequent than basaloid carcinomas (ratio of 2.5:1). All cases but one were of T1-2 tumors. Only 14% of patients were node-positive. Tumor sizes ranged from 1 to 5 cm, with median and mean tumor sizes of 3 and 3.1 cm, respectively. The 2 groups did not differ with regard to age, gender, or histology. Tumor stage
was significantly lower \((p=0.08)\), median tumor size was smaller and nodal stage was significantly lower \((p=0.02)\) in the EXC group than in the INC group.

**Treatment characteristics.** An overview of treatment parameters is presented in Table II. Radiation therapy was approximately uniform across patients. In the INC and EXC groups, the mean total dose was 44.9 and 44.8 Gy, respectively; the mean single dose per fraction was 2.0 and 1.9 Gy, respectively; and the median OTT was 39 days.

**Survival results.** For the entire series, at five years and eight years, the actuarial OAS rates were 71% and 54%, respectively; the DSS rates were 74% and 68%, respectively; and the DFS rates were 54% and 54%, respectively (Figure 1). At five years, the EXC group had better actuarial control rate achieved by initial treatment (80% versus 64%) than the INC group (Figure 2).

In univariate analysis, tumor stage T3-T4 \((p=0.04)\), tumor size \(\geq 6\) cm \((p<0.00)\), nodal stage N1-3 \((p<0.00)\), and OTT >40 days \((p=0.05)\) were significantly correlated with poor local control. Extent of surgery (INC versus EXC) was not associated with local control \((p=0.45)\). Furthermore, the pre-therapeutic prognostic factors of age, gender, histologic type, and grade were not significantly associated with local control. Table III presents an overview of all investigated parameters.

Along with extent of resection, factors significant for local control in univariate analysis were entered into multivariate analysis. Tumor size (treated as a continuous variable; \(p=0.02)\) and OTT \((p=0.04)\) retained significance as factors associated with local control after adjustment for T-stage and nodal stage (Table IV).

**Discussion**

Many prospective controlled randomized trials (2-6, 14) have established cRCT as the preferred first-line treatment for most patients with anal carcinoma. cRCT facilitates sphincter preservation in many patients, and surgery is used as salvage therapy for patients with persistent or recurrent tumors (15, 16). Post-cRCT surgery is standard treatment for patients with residual tumor.

For anal carcinoma, the role and clinical significance of local excision as a prognostic factor in anal cancer patients treated with combined-modality treatment is poorly documented. Some case series have shown that smaller anal carcinomas require lower radiation doses than do larger carcinomas (17). It may follow that successful local excision (with no residual gross tumor) would facilitate the same level of local control with a lower dose of radiation and, consequently, fewer side effects. Alternatively, better local control might be achieved after local excision with standard radiation doses.

Hu et al. (11) reported on improved local control after cRCT following local excision of the primary tumor. In this study, patients underwent initial excision followed by cRCT with 30–34 Gy (EX/30 group) or 45–50.4 Gy (EX/45 group). The comparison group received first-line cRCT with 30 Gy followed by excision (30/EX group). For the entire series, the five-year actuarial DFS rate was 78%, the OS rate was 86%, the colostomy-free survival (CFS) rate was 91%, and the local control rate was 82%. Whereas the radiation dose did not affect local control, among patients who received 30–34 Gy, the sequence of the excision (before or after cRCT) appeared to have a borderline significant impact on...
local control: the five-year actuarial local control rate was 100% in the EX/30 group but only 67% in the 30/EX group ($p=0.08$). The authors concluded that an initial excisional procedure followed by cRCT (30 Gy) was associated with better local control. A dose of 45 Gy seemed appropriate for our group of patients. In our study, we were unable to confirm the effect of extent of surgery (incisional biopsy versus excision) on local control. The better local control seen in the EXC group might be attributable to the relatively small tumor size and low tumor stage compared to those of the INC group.

There is an international consensus regarding the chemotherapy regimen for anal carcinoma in locally advanced stages. The most recent UK trial ACT II (3), which is the largest phase III clinical trial published to date, applied a 2×2 factorial design to compare mitomycin (12 mg/m² on day 1) or cisplatin (60 mg/m² on days 1 and 29) with fluorouracil (1000 mg/m² per day on days 1-4 and 29-32) and radiotherapy (50.4 Gy in 28 daily fractions), with or without 2 courses of maintenance chemotherapy (fluorouracil and cisplatin at weeks 11 and 14). These recent results are based on 940 patients and a median follow-up period of 5.1 years (interquartile range=3.9-6.9 years). At 26 weeks, complete response was noted in 391 of 432 patients (90.5%) in the mitomycin group and in 386 out of 431 patients (89.6%) in the cisplatin group (95% confidence interval (CI): 4.9-3.1; $p=0.64$). Both groups exhibited similar toxicity. The most common grade 3-4 toxic effects were skin reactions ([228/472 (48%) versus 222/468 (47%)), pain [122/472 (26%) versus 135/468 (29%)], hematological toxicity [124/472 (26%) versus 73/468 (16%)], and gastrointestinal toxicity [75/472 (16%) versus 85/468 (18%)]. The 3-year progression-free survival rate was 74% (95% CI=69.77%) with maintenance chemotherapy and 73% (95% CI=68.77%) without maintenance chemotherapy (hazard ratio: 0.9; 95% CI=0.75-1.21; $p=0.70$). The authors concluded that radiotherapy (50 Gy) with fluorouracil and mitomycin should be retained as standard treatment. Our findings confirmed that 5-fluorouracil and mitomycin applied concurrently with 45 Gy radiotherapy is a safe and effective regimen and may be seen as the standard-of-care.

The long-term update of the US GI Intergroup RTOG 98-11 phase III trial (n=682) reported a comparison of radiotherapy combined with 5-fluorouracil plus mitomycin with induction 5-fluorouracil plus cisplatin followed by RT combined with 5-fluorouracil plus cisplatin (2). The 5-year DFS (67.8% versus 57.8%; $p=0.006$) and OS (78.3% versus 70.7%; $p=0.026$) rates were statistically better with radiotherapy combined with 5-fluorouracil plus mitomycin than with radiotherapy combined with five-fluorouracil plus cisplatin. The former group tended to have better CFS ($p=0.05$), LRF ($p=0.087$), and colostomy failure ($p=0.074$), but these findings were not statistically significant. Multivariate analysis showed that treatment and clinical node status were significantly associated with DFS and OS; tumor diameter, with DFS; and sex, with OS. The authors concluded that radiotherapy combined with 5-fluorouracil plus mitomycin has a statistically significant, clinically meaningful impact on DFS and OS compared with induction chemotherapy followed by concurrent radiotherapy and 5-fluorouracil plus cisplatin and that the former regimen has borderline significance for CFS, colostomy failure, and LRF. The superiority of cRCT, which includes radiotherapy and 5-fluorouracil plus mitomycin, is supported by this large phase III trial, even though the experimental arm included induction chemotherapy as an additional factor.
In this qualitative trial, additional therapeutic intervention did not improve outcomes, as was the case in our study on surgical excision prior to cRCT. Nevertheless, radiotherapy combined with 5-fluorouracil plus mitomycin (without surgery) remains the standard-of-care for patients with locally advanced anal cancer. Therefore, we have confirmed the standard-of-care in this study—future research should focus on other, novel therapies and combinations.

Conclusion

Our data suggest that for patients with anal carcinoma treated by cRCT with a radiation dose of 45 Gy, local excision prior to cRCT does not confer an additional benefit with regard to local control compared with incisional biopsy.

Conflicts of Interest

All Authors confirm that there are no conflicts of interest with regard to any financial and personal relationships with other people or organization.

References


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