Photodynamic therapy for anal cancer

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Photodynamic therapy for anal cancer

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Summary Invasive anal cancers are generally successfully treated by combined chemotherapy with radiation therapy (XRT). For those patients who locally fail this intervention many are salvaged by surgery which generally results in permanent colostomy. We examined the treatment and outcome of Photofrin® based photodynamic therapy (PDT) in a cohort of patients with anal cancer who failed locally despite chemo-radiation (N=6) and two patients with positive margins of resection after excision of small T1 squamous cell anal cancers who refused further surgery or chemo-radiation. PDT consisted of outpatient infusion of Photofrin® at 1.2 mg/kg followed 48 h later by outpatient illumination. Red light (630 nm) illumination was delivered by a 5 cm diffusing fiber, treating transphincterally at 300 J/cm followed by microlens illumination at 200 J/cm² to the perianal tumor bed with 2 cm margin. All patients completed PDT without incident and all have maintained local control of disease in the anal region for the length of follow up (18–48 months). PDT may serve as a new means to salvage local failures and perhaps could be employed as a primary treatment modality in select patients with early stage of disease.

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Introduction

Anal cancer treatment for invasive squamous cell carcinoma has undergone a paradigm shift away from surgery to chemo-radiation [1]. This has allowed for sphincter sparing therapy with equivalent outcomes to the classical approach of radical surgery with resultant permanent colostomy [2].
Table 1  Patient characteristics and outcomes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Male/female</th>
<th>Stage</th>
<th>Initial Tx</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>Male</td>
<td>T₁ (1 cm)</td>
<td>Wide Excision</td>
<td>NED — 48 months</td>
</tr>
<tr>
<td>2</td>
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<td>Female</td>
<td>T₁ (1 cm)</td>
<td>Wide Excision</td>
<td>NED — 36 months</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Male</td>
<td>T₂</td>
<td>Chemo-XRT</td>
<td>NED — 24 months</td>
</tr>
<tr>
<td>4</td>
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<td>T₃</td>
<td>Chemo-XRT</td>
<td>NED — 48 months</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>Female</td>
<td>T₃</td>
<td>Chemo-XRT</td>
<td>NED — 48 months</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>Male</td>
<td>T₃</td>
<td>Chemo-XRT</td>
<td>NED — 18 months</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>Female</td>
<td>T₃</td>
<td>Chemo-XRT</td>
<td>Systemic failure</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>Female</td>
<td>T₃</td>
<td>Chemo-XRT</td>
<td>Systemic failure</td>
</tr>
</tbody>
</table>

Due to the high risk of pelvic and inguinal nodal metastasis, all but the earliest stage anal cancers undergo comprehensive nodal radiation with resultant excellent control of these regions [3]. However, many patients with bulky primary anal tumors fail locally and undergo salvage exenterative types of surgery with loss of a still functioning sphincter [4]. In select patients perhaps further salvage therapy directed to the recurrent anal tumor bed may be possible. However, this option is rarely pursued due to the inherent damage to normal surrounding tissues caused by chemo-radiation with its resultant high risk of wound healing issues. Further, patients with in situ and very early stage disease where the probability of lymphatic metastasis is very low may undergo very aggressive regional treatment needlessly. In these cases, aggressive local therapy to the anal tumor alone may be successful.

Photodynamic therapy is a tumor ablative treatment technique that has achieved high response rates for a myriad of tumors, of various histology's both deep seated and cutaneous in origin [5,6]. During PDT, a photosensitizing agent is applied and then activated by the appropriate wavelength and intensity of light to create a type II redox reaction that creates singlet oxygen. This reactive species lead to rapid vascular shut down as well as tissue necrosis and/or apoptosis. What is relativity unique about PDT is that the commercially available photosensitizer, Photofrin®, does not appear to concentrate in connective tissue, allowing for superior tissue healing even in heavily pretreated anatomy.

We examined the role of photodynamic therapy in a cohort of anal cancer patients who locally failed chemo-radiation at the primary tumor site and two individuals who refused chemo-radiation or additional surgery for early stage anal cancer.

Materials and methods

All patients signed informed consent. Patients with local recurrence following chemo-radiation had biopsy proven invasive squamous cell cancer. Restaging included chest, abdomen, and pelvic CT scan in all cases, which at the time of restaging were without evidence of regional or systemic failure. Patients with T₁ stage anal disease failed wide local excision and also were similarly restaged and found not to have evidence of regional or systemic disease. All patients refused surgical salvage which would have consisted of permanent colostomy and loss of sphincter. The early stage patients with recurrence also refused chemo-radiation as well. Patient characteristics are noted in Table 1.

Figure 1  Home made device for PDT of anal cancer.

PDT consisted of off label outpatient infusion of Photofrin® (Axcan Pharma) at 1.2 mg/kg. After 48 h, the patient was illuminated in an outpatient setting. Illumination was at 630 nanometers via red light generated from a Diomed diode laser. A bowel prep 24 h prior to illumination was done for all patients. Illumination consisted of placing the patient in a lithotomy position with anal insertion of a clear plastic test tube (Fig. 1). There was a 58.7% light attenuation in the test tube which was accounted for in the treatment. The 5 cm diffusing fiber catheter was placed inside the test tube to allow for 2 cm superior and at least 2 cm inferior to the sphincter illumination (Fig. 2). A total of 300 J/cm² was then delivered. Immediately following, a handheld microlens outlying the gross or recurrent region of

Figure 2  Home made device inserted rectally at the time of therapy.
perianal disease was used to illuminate the target with 2 cm margin, delivering 200 J/cm². In all patients, one diffusing and one microlens illumination was accomplished.

Following PDT, patients were observed for 1 h and then discharged with follow up at 24 and 48 h post-PDT. Immediately following PDT, a Medrol dose pack was dispensed as was 1 week worth of Keflex antibiotics. All patients were immediately placed on oral narcotic analgesia. They were also instructed to use ice packs peri-anally and to maintain very soft stool by softeners. When feasible additional narcotic pain relievers were to be used prior to bowel movement.

**Results**

All patients underwent PDT as prescribed with none lost to follow up. The treatment procedure was well tolerated without undue or unexpected morbidity. All therapy was outpatient with no emergency room or hospital admission required from PDT. No morbidity from Photofrin® infusion was recognized and no patient experienced sunlight photosensitivity.

Immediately post-PDT, the tumor bed appeared dusky, erethematous, and began weeping. Interestingly, no patient reported any pain at this point. At 24 h follow up the tumor bed remained dusky but no longer was with fluid loss. Normal tissue appeared clinically unchanged from non-illuminated regions. The treatment sites were very tender to palpation. Similar findings were noted at 48 h (Fig. 3). All patients were in control of their sphincters for gas and bowel movement during this time.

About 6—12 h post-PDT patients experienced an increase in pain in the anal region, most notable on bowel movement and prolonged sitting. By employing additional narcotics for this break-through pain they were able to minimize these discomforts. The intensity of this discomfort diminished dramatically by 72—96 h in all cases. The addition of an ice pack applied to the anal region offered excellent and rapid short-term relief. Narcotic use was intermittent from the end of this break-through pain they were able to minimize these discomforts.

Patients were then followed at monthly or less frequent periods. At the first month follow up gross tumor was necrotic and appeared to have healing at the periphery. No patient had significant pain at this point and all were back to regular routine exams. Each patient had re-biopsy between 3 and 4 months post-PDT with all showing NED. At 6 months all patients were re-staged. None showed local or pelvic recurrence but two patients had evidence of systemic disease and were placed on chemotherapy. At last follow up (18—48 months) no patient had local failure, wound healing issues or sphincter damage from PDT.

**Discussion**

While comprising only 1% of gastro intestinal malignancies, invasive squamous cell anal cancers are unique in that chemo-radiation alone can be curative in a substantial number of individuals with this diagnosis [7]. This finding came about when several anal cancer patients had pathologic complete response on a pre-op chemo-radiation protocol pioneered by Nigro [8]. Subsequent studies confirmed the efficacy of chemo-radiation on squamous lesions of the anal canal region so this approach has become standard of care for several decades.

With further evaluation it has become evident that patients with bulky tumors (T3) treated with chemo-radiation have a local failure rate approaching 10—20% or more [9]. Most of these patients will then undergo radical surgery for salvage with resultant permanent colostomy. While this salvage approach ultimately offers high rates of local control it is a morbid procedure with permanent change in lifestyle. In addition, it has also been described that patients with in situ or early T1 squamous cell lesions may do well with only local treatment to the primary site generally with a sphincter sparing surgical approach [10]. While not necessarily standard of care this treatment avoids the high acute and chronic morbidity associated with chemo-radiation protocols. A small literature exists that shows local surgery may offer a significant control rate without evidence of pelvic or inguinal failure in very select patients with early stage anal cancer.

As most local failures for anal cancer have undergone radical chemo-radiation, the normal tissue tolerance of the sphincter region has been approached [11]. Therefore, further radiation as a means of salvage would be highly morbid and result in functional sphincter loss. As these tissues heal poorly after chemo-radiation, a local sphincter sparing surgical approach to salvage is also generally contraindicated. As such most patients end up with permanent colostomy.

PDT has an excellent track record of tumor ablation with the potential for normal tissue maintenance [12]. This is attributed to the relative lack of photosensitizer accumulation in connective tissue. When tumor is ablated by PDT the normal tissue infrastructure is maintained allowing for wound healing even in heavily irradiated tissue. Therefore, PDT may be an ideal therapy for local salvage of anal cancer failures. Further, if ablation without sphincter loss were possible then this might also be an ideal option for patients with local failure following surgery alone for early invasive/in situ disease.

A pair of publications reported the potential sphincter sparing and excellent cosmetic outcome possible for a small group of five patients who failed local excision of in situ squamous cell or Paget’s disease of the
peri-anal region [13,14]. All patients failed wide local excision and more radical surgery was planned, which may have required colostomy. Instead all patients were infused with 1 mg/kg of Photofrin® and surface illumination at 200–250 J/cm² followed at 24–48 h post-infusion. In this series, patients were treated as inpatients, but the authors concluded that outpatient therapy would have been possible for all. Pain control was needed for 72–96 h post-PDT. Immediate erythema and blister formation was noted in all patients with excellent tissue healing by 2 months. All maintained functioning sphincters. Biopsy proven local control was maintained for several years in three patients.

Subsequently, several case reports on PDT of peri-anal in situ lesions have been published. Hamdan et al. [15] employed topical ALA in two sessions, achieving complete response for intraepithelial neoplasia. Similarly, perianal Paget's disease was treated with success by Li et al. [16]. In an interesting case report Li et al. [17] employed ALA to first fluoresce and then treat an extensive perianal Paget's lesion. In this protocol, topical ALA was placed on the lesion for 3 h and fluorescence was then used to guide the illumination field size for therapy. A second course of ALA and Hiporfin PDT followed 40 days later with the patient achieving complete response. Webber and Fromm [18] employed PDT in HIV positive patients for carcinoma in situ of the anus. These five patients were given ALA orally. About 4 h later the entire anal circumference was illuminated. Local control was excellent but all patients developed temporary abnormalities on subsequent liver function testing, attributed to oral ALA. Van der Snoek et al. [19] reported on the use of topical Foscarn® (FOSGEL) for high grade anal intraepithelial neoplasia. In this series of nine HIV positive patients, topical FOSGEL was applied and illuminated 8 h later at 652 nm with 20 J/cm². A second treatment followed at 7 days. No clinical or histological response was seen and the authors concluded the therapy ineffective.

A small body of PDT literature also shows the potential for PDT salvage of local failures in rectal cancers. PDT alone or as an adjunct to surgery for local recurrence was possible with Photofrin® PDT in an early report by Harlow et al. [20]. Similarly, PDT or other local ablative techniques may be employed for extended palliation by endoscopic based therapy as was outlined by Dohmoto et al. [21]. A review of outcome, showing the potential role of PDT for this indication was recently published by Wang and Liu [22]. The author found excellent control of signs and symptoms of local recurrence with various PDT treatment regimens, however these findings are based on very small series of patients.

The patients in our series were generally chemo-radiation failures at the primary tumor site. The next step for this group was a surgical procedure with permanent colostomy due to the invasive nature of the recurrence. On re-staging none of these patients appeared to have evidence of pelvic or distant failure and as such a sphincter sparing attempt by PDT appeared reasonable. Two patients had early lesions with involved resection margins. Potentially further local excision would have been an option but the location of the re-excision would likely compromise sphincter function. As such PDT was offered since both of these patients refused chemo-radiation. Staging did not reveal any evidence of adenopathy at the time of PDT.

In all cases PDT was delivered by a combination of diffruser and microlens. A clear plastic test tube was slid into the sphincter, closed side first. A diffuser was then slid inside so that about 2 cm of the light diffuser was above the sphincter and 2 cm or more was below. This allowed for easy trans-sphincter illumination. In addition, a microlens was then employed to the local tumor bed and peri-anal skin region at risk with at least 2 cm margins. We employed 300 J/cm² via the diffuser and 200 J/cm² by the microlens.

All patients had clinical response in the treatment region by illuminations end. The tumor or tumor bed was generally dusky and weeping. Normal surrounding tissue did not develop the weeping phenomena. We did not see significant tissue slough from tumor or normal tissue. Rather at 24–48 h post-PDT the tumor bed remained darkened and hypoxic appearing with surrounding normal tissue appeared undifferentiated from untreated areas. All patients maintained normal sphincter function for stool and gas from the immediate treatment period through follow up. The actual PDT session was pain free and easily accomplished as an out patient procedure. However, after 6–12 h all patients experienced moderate peri-anal discomfort so that sitting or bowel movement was of clinical significance. This was made tolerable by narcotic analgesia, which was required round the clock for about 72 h with additional pain medication dispensed prior to bowel movement. Pain medication was required intermittently for at least 4 weeks post-PDT. Patients were placed on stool softeners which made recovery easier. No photosensitivity was reported or seen on clinical exam.

Using this treatment technique and a drug dose of 1.2 mg/kg with illumination at 48 h post-infusion, biopsy proven local control was maintained in all 8 patients. Minimum follow up was 18 months. All patients maintained sphincter function throughout follow up. Of note two patients developed systemic disease, but none developed pelvic or inguinal failure. Both patients with early invasive cancer have remained NED.

Conclusion

Photofrin® Photodynamic therapy appears to be an effective local treatment for recurrent and/or persistent squamous cell cancers of the anal canal. At the drug dose and light dose employed lesion ablation is possible as is retention of a functioning sphincter. Given the good outcomes presented we believe that PDT may be an option for sphincter sparing salvage therapy and perhaps an up front treatment for early stage disease. This should be evaluated in a larger clinical trial.

References

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