Inguinal Lymph Nodes Management In Squamous Cell Carcinoma Of The Anal Canal

Corresponding Author:
Dr. Saleh M Abbas,
Surgeon, Surgery - Australia

Submitting Author:
Dr. Saleh M Abbas,
Surgeon, Surgery - Australia

Article ID: WMC001565
Article Type: Review articles
Submitted on: 20-Feb-2011, 06:33:08 AM GMT Published on: 22-Feb-2011, 08:50:03 PM GMT
Article URL: http://www.webmedcentral.com/article_view/1565
Subject Categories: GENERAL SURGERY
Keywords: Carcinoma, Radiotherapy, Inguinal Nodes

How to cite the article: Abbas S M. Inguinal Lymph Nodes Management In Squamous Cell Carcinoma Of The Anal Canal. WebmedCentral GENERAL SURGERY 2011;2(2):WMC001565
Inguinal Lymph Nodes Management In Squamous Cell Carcinoma Of The Anal Canal

Author(s): Abbas S M

Abstract

Current issues in the management of clinically negative inguinal lymph nodes in squamous cell carcinoma of the anal canal. Quality of the available evidence.

Background

The first line of management of squamous cell carcinoma (SCC) of the anal canal is chemo-radiation. The radiation field includes, in addition to the anal region and the perirectal nodes, the iliac and both inguinal triangles to target the inguinal nodes. More recently a selective approach has been investigated in patients with non-palpable inguinal nodes utilizing sentinel node biopsy and PET scan.

Methods

Medline was searched using the keywords, squamous cell carcinoma, anal canal, inguinal lymph nodes, sentinel node and radiotherapy. Relevant articles were reviewed with regard to the management of inguinal nodes in SCC of the anal canal.

Results:

Currently the management of clinically normal inguinal nodes in SCC of the anal canal is prophylactic radiation of both inguinal areas. Clinically involved nodes are included in the radiation field plus a boost of radiation to the groin that harbor involved nodes. The radiation is refined recently by intensity modulation radiotherapy (IMR) to involve the diseased area and minimize radiation exposure of normal adjacent tissues. Alternatively, more recently, a selective approach with utilization of sentinel node biopsy and radiation to microscopically involved nodal areas has been described.

Conclusion:

The treatment of clinically normal inguinal nodes is currently by prophylactic radiation of both inguinal regions. It is possible that in the future radiation of clinically normal inguinal may become more selective with an increasing reliance on sentinel node biopsy. Further studies are needed in this field to assess the efficacy of this approach.

Background

Although Squamous cell carcinoma (SCC) of the anal canal is an uncommon disease it is the most common malignant tumor of the anal canal accounting for 90% of malignant tumors at this site. Survival is determined essentially by two factors; the size of the tumor and lymph node spread. Patients with no clinical evidence of nodal disease have a ten-year survival of 73% compared with 53% in those with nodal disease.1 Historically the treatment of SCC of the anal canal was abdominoperineal resection; this involves wide dissection of the ischiorectal fossa with clearance of pararectal lymph nodes with en bloc excision of the posterior vaginal wall in women 2. The current management of SCC of the anal canal is chemoradiotherapy, which includes infusion of 5-flourouracil with or without mitomycin and radiation fields that include the primary tumor and the pelvic and inguinal lymph nodes.3, 4, 5, Surgery is reserved for patients who have an incomplete response, residual disease and those with later disease recurrence. The lymphatic drainage of tumors of the anal canal is bidirectional and depends on the tumor location in relation to the dentate line. Above the dentate line most of the lymph drains in a cephalad direction along the inferior rectal artery to the origin of the inferior mesenteric artery, also along the territory of the middle rectal artery to the iliac nodes. Below the dentate line it drains to the inguinal nodes along the femoral artery. Hence the lymphatic drainage is to the ipsilateral inguinal lymph nodes. The probability of nodal spread is relative to the tumor size (T stage). 1 When the primary tumor is clearly located laterally, the inguinal metastasis nearly always is homolateral to the primary tumor. Midline tumors and locally advanced lesions usually show bilateral inguinal and pararectal lymph node involvement. In the Lyon series bilateral involvement was seen only when the primary tumor involved the medial part of the anal canal. 6 Overall, inguinal nodal involvement occurs in 10-25% of patients 7, 8, 9, 10. Using bipedal lymphangiography in a group of patients with anal cancer Davey et al demonstrated metastasis to external iliac lymph nodes in 7 out of 28 patients (25%).11 CT detected disease in the external iliac nodes in only one of these patients.
Lymph node involvement is related to the T stage of the tumor with nodal metastases seen in 0-10% of T1 and 2 lesions and 40-50% of T3 and 4 disease (table 1). At the time of diagnosis local tumor extent is T1: 8.5%; T2: 51.1%; T3: 30.4%; T4: 10%. Pelvic lymph node involvement correlates with increasing risk of pelvic relapse and residual disease after definitive radiochemotherapy. Pelvic nodes are routinely targeted within the radiation field of the primary tumor and therefore their involvement or otherwise are unlikely at this stage to change the approach of treatment. However this is not the case for inguinal lymph nodes. Clinical examination and CT scan are not sensitive for detecting inguinal node metastases due to the fact that the size of the lymph node does not accurately predict the likelihood of metastatic disease and 44% of involved nodes are less than 5 mm in maximal diameter.

Currently the treatment of clinically negative inguinal nodes is prophylactic radiation given by inclusion of both inguinal regions in the radiation field with a radiation boost if the nodes are clinically involved. More recently a selective approach has been explored utilizing staging information obtained from sentinel node biopsy and PET scan.

We conducted this review to assess the current strategies for dealing with treatment of clinically negative inguinal lymph nodes.

**Methods**

The literature was searched (Medline and Embase) using the keywords, squamous cell carcinoma, anal canal, inguinal lymph nodes, sentinel node and radiotherapy. The relevant articles were reviewed with regard to the management of clinically negative inguinal nodes in SCC of the anal canal.

**Implications of Lymph node involvement for survival**

The presence of metastatic disease in the inguinal nodes reflects the local extent of the disease and is a marker for advanced disease (T3 and T4). It is also a marker for the presence of systemic disease at gross or microscopic level, which is associated with an increased likelihood of incomplete response to radiochemotherapy, resulting in loco-regional recurrence, systemic metastases and reduced overall survival.

13 Inguinal lymph node metastases may occur later in a metachronous manner after curative chemo-radiotherapy in about 8% of patients, and this is also associated with reduced survival.

6 Treatment failure that manifests as local recurrence or persistent disease is still amenable to treatment, usually by inguinal node dissection, but this event is associated with reduced 5 year overall survival of 40-64%.

Molecular studies have failed to show any possible association between tumor genetics and tumor behavior with regard to nodal metastasis or aggressive behavior and overall survival. Deletion of cancer suppressor genes such as the p53 and Rb genes has no effect on nodal invasion.

In patients with clinically involved inguinal nodes treated with definitive chemo-radiation therapy there is an increased risk of loco-regional failure in the regional lymph nodes, which translates into a 5-year survival of 40% after salvage nodal dissection.

**Options for treatment**

**Chemo-radiotherapy**

SCC of the anus is generally considered a slowly growing disease with a low tendency for systemic dissemination. Therefore loco-regional control assumes great importance in improving disease outcome. Before the advent of curative chemo-radiation the options for inguinal node treatment depended on clinical circumstances and lymph node dissection was performed only for clinically involved nodes.

The management of clinically negative nodes was either wait and watch with node dissection for regional failure that occurs in 5-25% of cases or elective node dissection at the time of original surgery for the anal canal tumor.

Currently, chemo-radiotherapy is usually employed as a definitive treatment for anal canal cancer. The radiation field involves the anal canal, perineum, pelvic lymph nodes and bilateral inguinal lymph nodes.

Chemo-radiotherapy is the treatment of choice for disease in the inguinal nodes with a cure rate of 90%.

The Nigro protocol is widely used. This involves 30 Grays of radiotherapy at 2 Gy per day, five days a week for three weeks to the primary tumor and to the pelvic and inguinal lymph nodes with both inguinal areas involved in the radiation field. Chemotherapy is given in the form of 5-fluorouracil intravenous infusions (1gm/m2) on days 1-4 of the radiation therapy and repeated on days 29-32 of the treatment regimen.

Mitomycin C is given in the form of an intravenous bolus (15 mg/m2) on day 1 of the cycle.

In a modification of the Nigro protocol Gerard et al reported their experience in Lyon, France for 27 patients with clinically involved nodes at the time of original presentation. Patients were treated with lymph node dissection followed by chemo-radiotherapy with 5FU 1gm/m2 for four days of continuous infusion and cisplatinum 80 mg/m2 on Day 2 after standard.
hydration. The radiation treatment was initiated 3 weeks after the end of the first cycle of chemotherapy. The inguinal area was irradiated with a separate direct field using a mixed beam of telecobalt and electrons. The involved inguinal area was irradiated at a dose of 45-50 Gy over 5 weeks through the antero-posterior or postero-anterior field with an additional electron boost. This group of patients was followed up for 6 years. At the end of the treatment, local control of the inguinal area was observed in 25 of the 27 patients (86%). In long-term follow-up, two patients developed contralateral inguinal metastases that were controlled by inguinal dissection and irradiation. An incomplete response was seen in two patients who had fixed inguinal nodes. Other institutions have adopted a similar approach and have achieved similar results.20

Another option is inguinal irradiation with concomitant chemotherapy using 5-Flourouracil and mitomycin or cisplatinum. Radiation of the involved nodes is given according to a protocol that involves a large antero-posterior or postero-anterior field including the inguinal node areas (45 Gy in 25 fractions over five weeks). The clinically involved inguinal fields are boosted up to 65 Gy.19-23 There is no standard recommendation for patients who present with clinically non-involved inguinal nodes. Commonly, such patients receive prophylactic bilateral radiotherapy and elective inguinal dissection is not recommended. Alternatively these patients receive no treatment for the inguinal nodes and are followed up with regular clinical evaluation for inguinal node disease development. Long term follow up studies have shown that 80-90% of those patients will have no inguinal node disease development.1, 6, 23 However, there is approximately a 15% chance of disease recurrence particularly in patients with locally advanced disease (T3 and T4) with clinically non-involved inguinal nodes. In these patients elective irradiation of non-involved inguinal regions may minimize the risk of inguinal nodes disease development. Three recent randomized trials have compared, mitomycin-based chemotherapy with radiotherapy or radiotherapy without chemotherapy, these studies also analyzed elective node radiation versus no radiation in patients with clinically negative nodes; and concluded that prophylactic irradiation of bilateral inguinal regions in normal inguinal nodes reduced the development of lymph node disease to less than 5%.20; however that part of the study was not randomized and was only a subgroup analysis. For those who develop metachronous metastases, which usually happen within six months of initial treatment, chemo-radiotherapy is the treatment of first choice. Inguinal node dissection is reserved for those who fail to respond or relapse after initial response.8 None of the available studies had considered the inclusion of the inguinal region in the field of radiation stratified by the T stage of the disease, given the fact that the higher the T stage the more likely would be a microscopic disease in the clinically non-palpable inguinal nodes.

Complications of Radiation
Radiation therapy to the inguinal region with concomitant chemotherapy as part of the protocol for anal canal cancer has proven to be safe and effective in preventing local recurrence. Death is a rare event as a complication of chemoradio toxicity and has been reported to occur in approximately 2% of patients.21; but that is not related to inguinal radiation, rather a complication of the whole treatment. With the increasing use of intensity modulation radiotherapy (IMR), the radiation dose is focused on the target area to avoid normal adjacent tissues. Still systemic complications of chemotherapy are significant. However radiotherapy to the inguinal region is not without its risks. Recognized complications specific to inguinal node radiation that have been reported by various centers are femoral neck fracture, radionecrosis of the femoral head, iliac artery stenosis and inguinal fibrosis leading to lymphedema of the leg. Cicchini et al reported a single case of penile shaft necrosis following inguinal irradiation due to radiation-induced thrombosis.24 These complications are rare; usually occur when therapeutic doses given rather than elective doses, but they can be serious in nature.

The Role of Surgery
The role of surgery is controversial. Currently lymph node dissection is usually reserved for disease recurrence in the inguinal region.13, 14. Alternatively, as noted above, some centers provide elective node dissection for patients with clinically involved nodes at the time of first presentation.6

Selective Approach
Since it is desirable to avoid irradiation of lymphatic fields that are not involved in macroscopic or microscopic disease, a selective approach for the management of the inguinal nodes has been evaluated in more recent studies. A selective approach to management of inguinal lymph nodes in anal SCC depends on accurate staging. A number of methods have been utilized to achieve this.

Sentinel Lymph Node Biopsy
Sentinel node biopsy has been studied by Bobin et al 25 who evaluated 35 patients with clinically N0 disease using a combination of blue dye and Tc99 radiocolloid mapping and followed patients for 18
months. None of the patients, who had a pathologically negative sentinel node, had disease recurrence. Sentinel node biopsy proved to be a sensitive and safe procedure. As noted above it has been demonstrated that midline tumors usually have bilateral lymphatic drainage.

Perera et al performed the procedure on 12 patients and advocated sentinel node biopsy as a safe technique for detecting metastatic disease in the inguinal nodes in patients with anal SCC26. It also proved to be useful as a useful technique to detect micrometastatic deposits in clinically normal inguinal nodes. There are no clinical studies that managed inguinal nodes with no radiation based on the results of the sentinel node biopsy; therefore it is not possible to estimate the possibility of nodal recurrence if this form of treatment is utilized.

Therefore these results suggest that sentinel lymph node biopsy may have a role in guiding a more selective approach for patients with anal cancer although plainly studies with larger numbers are required. 27, 28. The role of sentinel node biopsy role is still in its early stages and may play an important role in the future to manage clinically non-palpable inguinal nodes.

PET scanning:
PET scanning is an established modality that is useful in the clinical management of SCC of the head and neck and esophagus. PET scanning for anal SCC provides accurate staging of disease and may alter treatment planning by identifying inguinal node involvement not apparent on clinical examination. In one study with clinically negative nodes at presentation 66% of inguinal nodes identified by PET scan were FNA positive for metastatic disease. 33 In another study FDG-PET/CT detected abnormal nodes in 20% of groins that were normal by CT, and in 23% without abnormality on physical examination. Furthermore, 17% of groins negative by both CT and physical examination showed abnormal uptake on FDG-PET/CT. PET upstaged 17% with unsuspected pelvic/inguinal nodal disease. 29 Currently PET scan is effective in monitoring disease response to treatment and in detection of recurrence.

An important pitfall of using PET scan is the false positive detection of inguinal nodes, typically these nodes turn out to have reactive follicular hyperplasia as confirmed on histopathology of the removed nodes. Since the uptake and retention of 18F-FDG (Fluorine-18-flourodesoxy-glycose) depends on the metabolic activity of the tissue. 30 This problem is especially important in assessing patients with HIV who have generalized lymphadenopathy as part of their HIV infection; such nodes are potentially positive on PET scan and mostly turn out to be reactive hyperplasia.

Conclusions

The current treatment options for inguinal lymph nodes in patients with SCC of the anal canal vary according to local protocols and preferences. The most widely used approach is prophylactic bilateral inguinal radiation for those with clinically negative nodes and for patients with clinically positive nodes a radiation boost of the involved nodes is added. This approach is associated with good results. Although there is some evidence to support the routine irradiation of the clinically negative inguinal lymph nodes, the issue has not been addressed in the context of the T stage of the disease and there are no randomized trials to answer the question. That should be interpreted carefully taken into consideration the complications of radiotherapy and the consequence of disease recurrence in the inguinal nodes, which would require further radiotherapy or inguinal nodes dissection.

Metachronous metastases are amenable to chemo-radiotherapy with good responses in particular when this occurs within six months of the initial treatment. Surgical lymph node dissection is reserved for primary failure of chemo-radiation (residual disease) and for recurrent disease.

It is possible that in the future a selective approach will be adopted more often for patients with clinically negative inguinal nodes, particularly in patients with early stage disease. This will likely depend on the wider application of sentinel node sampling and PET scanning to detect nodal disease. Such treatment is desirable, as patients with negative inguinal nodes can avoid potential complications of inguinal node radiation. More work is required to prove the efficacy of sentinel node sampling and PET scan evaluation for selection of clinically node negative patients who will benefit from radiation therapy. Meanwhile prophylactic radiation of clinically negative nodes remains widely practiced to prevent inguinal nodes recurrence, which would require further radiation or surgery.

References

2. Clark J, Petrelli N, Mittelman A. Epidermoid
Illustrations

Illustration 1

Table 1

TNM Staging of Squamous Cell Carcinoma of the anal canal

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T1: Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>• T2: Tumor more than 2 cm but not more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>• T3: Tumor more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>• T4: Tumor of any size that invades adjacent organ(s),</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N0: No regional lymph node metastasis</td>
</tr>
<tr>
<td>• N1: Metastasis in perirectal lymph node(s)</td>
</tr>
<tr>
<td>• N2: Metastasis in unilateral internal iliac and/or inguinal lymph node(s)</td>
</tr>
<tr>
<td>• N3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• M0: No distant metastasis</td>
</tr>
<tr>
<td>• M1: Distant metastasis</td>
</tr>
</tbody>
</table>
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepulation peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.