Sentinel lymph node biopsy in anal cancer: A review

Biopsie du ganglion sentinelle dans le cancer anal

M. Mistrangelo*, M. Morino

Department of Surgery, Centre of Minimal Invasive Surgery, Molinette Hospital, University of Turin, C.so A.M. Dogliotti 14, 10126 Turin, Italy

Available online 4 March 2009

Introduction

Anal cancer is a rare disease. An estimated 5070 new cases (2020 men and 3050 women) of anal cancer (involving the anus, the anal canal, or the anorectum) occurred in the United States in 2007, accounting for approximately 1.85% of digestive system cancers. It has been estimated that 680 deaths due to anal cancer occurred in the US alone in 2007 [1]. Published data suggest that its incidence is rising and that the risk factors for anal cancer include human papilloma virus (HPV) infection, cervical dysplasia or cancer, human immunodeficiency virus (HIV) seropositivity, low CD4 count, cigarette smoking, anoreceptive intercourse, and immunosuppression following solid organ transplant [2].

Since 1974, the management of epidermoid carcinoma of the anal canal has changed from abdominoperineal resection to a combination of radiation and chemotherapy [3]. This approach allows sphincter preservation in most patients and achieves high rates of survival: the reported overall five-year survival rate with combined treatment is 58–92% [4].

Approximately 12% of patients will eventually develop distant metastases, most commonly in the liver and the lung [5], while lymph node metastases occur in 10–25%. The presence of inguinal lymph node metastases in anal cancer reduces overall survival to 30–58% [6]. In general, lymphatic drainage occurs through passive processes (osmotic and hydrostatic pressure) and active muscular contraction that cause centripetal lymph flow. Neoplastic lymph flow in the anal region is bidirectional: proximal to the dentate line, two-thirds of the lymph fluid is drained along the inferior rectal artery to the origin of the inferior mesenteric artery; while distal to the dentate line the main pathway is to the inguinal lymph nodes along the femoral artery [6].

Although the standard treatment for anal cancer is defined, the ideal approach to inguinal lymph nodes remains debated. The true incidence of inguinal node involvement is difficult to determine; clinical examination and radiological imaging each has a sensitivity of 50% [7]. Since 2001 [8] sentinel lymph node (SLN) biopsy in patients with anal cancer has improved the accuracy of inguinal staging and planning for radiotherapy, preventing the need for inguinal radiotherapy and eliminating its related morbidity in patients without metastasis at SLN biopsy. The literature has described 161 patients who have undergone this technique to date.

This study presents our experience and a review of the published data to assess the feasibility of SLN biopsy in anal cancer.
cancer and determines its impact on treatment in these patients [9—12].

**Sentinel lymph node history**

Lymphatic mapping with SLN biopsy is one of the most interesting recent developments in surgical oncology. This approach allows patients with lymph node metastases to be treated in an early phase and prevents unnecessary regional lymph node dissection or treatment in those without. Direct lymphoscintigraphy of the breast was the indirect predecessor of the idea of SLN. In 1970, Kett demonstrated that one node, the “Sorgious node”, usually received drainage from the breast first, before it progressed through to the remaining axillary lymph nodes. Coined by Gould in 1960, the term “sentinel node” refers to the anatomical position of a lymph node found during radical neck dissection during parotidectomy. Cabanas, however, is generally considered to have discovered the SLN. In 1977, he described the existence of a specific lymph node centre that drained the penis. Based on lymphangiograms of more than 100 patients, he called the first draining lymph node the “SLN” [13]. In the late 1980s, Morton proposed the innovative concept of lymphatic mapping with SLN biopsy for melanoma [14]. The exact definition of a sentinel node is the subject of debate. The sentinel node is neither a “blue node” nor a “node with a certain amount of radioactivity”. These characteristics simply reflect the technology applied to understand the physiology of lymphatic drainage. Morton’s original definition of a sentinel node as “the first lymph node that receives afferent lymphatic drainage from a primary tumor” best illustrates the concept of the stepwise spread of cancer through the lymphatic system [15]. The sentinel node acts as the main barrier for the spreading of tumor cells, being it the most likely node to harbor metastatic deposits. If the sentinel node is free of metastases at histological examination, it is highly probable that other lymph nodes in the region will also be disease free. Although skip metastases have been reported in some neoplasms, this event has not been described in anal cancer. The standard of care for patients with anal melanoma or breast cancer is SLN biopsy, which could probably become the procedure of choice in anal cancer as well.

**Sentinel lymph node biopsy in anal cancer: review of the literature**

In 2000, Spratt suggested that prophylactic groin dissection is not required in all patients with anal cancer, but only for those with enlarged nodes or in the presence of a positive SLN; it may be curative in many cases and palliative in all [16]. This was the first report to suggest the use of the sentinel node in anal cancer, but no patients treated with this technique were presented. Since then, several case reports have been published [8,9,17]. Larger series have confirmed the utility of SLN detection as a guide towards a more selective approach to patients with anal cancer. The technique has been found to be safe and highly effective for sampling the inguinal lymph node and has also proved useful for detecting micrometastatic deposits in clinically normal nodes [6,18—21].

Bobin et al., in a study on 33 patients with a median follow-up period of 18 months and a detection rate of 100%, concluded that the sentinel node technique in anal cancer is mini-invasive and permits accurate exploration of inguinal lymph node status. Inguinal radiotherapy was only performed in N+ patients, preventing the morbidities associated with this procedure (inguinal fibrosis, external genitalia edema, lower limb lymphedema, and femoral fracture, which occurs in 6.4% of menopausal women) [11].

In 2003, Damin et al., in a study on 14 patients treated with a combined technique (blue dye and 99mTc dextran 500), reported a detection rate of 100% and occurrence of lymph node metastases in 7.1% of patients. They observed that the tumors located either on the right or the left side of the anal canal without extension to the midline (6 patients) showed SLN only in the isilateral groin, whereas tumors involving the midline of the anal canal (16 patients) resulted in bilateral inguinal nodes in 94% of cases (15 patients) [18]. In their later review of the literature [10], they evaluated 84 patients by SLN sampling: the detection rate was between 66 and 100% and metastases were found in 7.1—42% of cases. No major complications were reported.

After this review and our recent report [22], Gretschel et al. described their experience in 40 patients [12]. In contrast to their previous reports [6,19], they obtained a detection rate of 56% in inguinal lymph nodes (76% in a previous series), with 30% of inguinal node metastases (42% previously). They suggested that SLN biopsy in anal cancer can be used to appropriately select patients for inguinal irradiation, especially in T1 and T2 tumors. These patients receive either additional treatment or are spared from unnecessary radiation. In their opinion, SLN biopsy is not currently recommendable for larger (T3/T4) tumors or in patients who have undergone prior surgery of the anal or inguinal region. These conclusions contrast with previous reports in which SLN biopsy was indicated in all patients. Table 1 reports the results of the published series and our updated series.

**The sentinel lymph node biopsy technique**

The procedure starts with a radioisotope injection between 3 and 24 h before surgery preferably in a nuclear medicine department in compliance with radiation-safety precautions. The radiopharmaceutical product we use is Nanocoll®, characterized by particles which are 80 nm in diameter, and perfect for adequate migration. Other centres use 99mTc sulfur colloid or dextran 500. Our protocol calls for injection of 37 MBq of nanocoll-Tc-99m dextran 500 at a total volume of 0.4 ml, divided into four insulin syringes, with a total volume of 0.1 ml per syringe. The injection is made at four cardinal points around the neoplasm using a 22 G needle. The injection can be performed directly when a neoplasm is perianal points to their previous reports [6,19], they obtained a detection rate of 56% in inguinal lymph nodes (76% in a previous series), with 30% of inguinal node metastases (42% previously). They suggested that SLN biopsy in anal cancer can be used to appropriately select patients for inguinal irradiation, especially in T1 and T2 tumors. These patients receive either additional treatment or are spared from unnecessary radiation. In their opinion, SLN biopsy is not currently recommendable for larger (T3/T4) tumors or in patients who have undergone prior surgery of the anal or inguinal region. These conclusions contrast with previous reports in which SLN biopsy was indicated in all patients. Table 1 reports the results of the published series and our updated series.

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Lymphoscintigraphy is performed 2—3 h postinjection. Images are taken with a G.E. Millennium gamma camera equipped with a high-resolution collimator and a rectangu-
Table 1

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Place</th>
<th>Patients (no.)</th>
<th>Tumor site</th>
<th>Palpable nodes</th>
<th>Technique</th>
<th>MTS (%)</th>
<th>Detection rate (%)</th>
<th>Tumor site</th>
<th>Palpable nodes</th>
<th>Technique</th>
<th>MTS (%)</th>
<th>Detection rate (%)</th>
</tr>
</thead>
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<tr>
<td>Vajda, 2001</td>
<td>Kecskemet</td>
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<td>Not specified</td>
<td>Not specified</td>
<td>Combined</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Combined</td>
<td>0</td>
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<tr>
<td>Keshtgar, 2001</td>
<td>London</td>
<td>1</td>
<td>Anal verge</td>
<td>No</td>
<td>Combined</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Combined</td>
<td>29</td>
</tr>
<tr>
<td>Perera, 2003</td>
<td>Adelaide</td>
<td>12</td>
<td>5 anal canal</td>
<td>Not specified</td>
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<td>67</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Combined</td>
<td>9</td>
</tr>
<tr>
<td>Bobin, 2003</td>
<td>Lyon</td>
<td>33</td>
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<td>No</td>
<td>Combined</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Combined</td>
<td>9,1</td>
</tr>
<tr>
<td>Damin, 2006</td>
<td>Porto Alegre</td>
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<td>Not specified</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>Combined</td>
<td>10</td>
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<tr>
<td>Gretschel, 2008</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Combined</td>
<td>1</td>
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<tr>
<td>Mistrangelo, 2008</td>
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<td>Anal canal or verge</td>
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<td>Combined</td>
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<td>100</td>
<td>Combined</td>
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</tr>
</tbody>
</table>

MTS denotes metastases.

The inguinal SLN biopsy procedure is performed in the operating room and begins with localization of the SLN by a manual portable gamma probe (Scintiprobe MR 100, Politech®, Carsoli Italy). To read the signal the probe is directed away from the anus to remove the signal originating from the injection site. When the positive signal is identified, the skin is marked to identify the point of the surgical incision. Surgery is performed under local or spinal anesthesia. The SLN is biopsied under signal guidance. A signal is only considered positive when the node to background radioactivity signal ratio is greater than or equal to 5:1. As pointed out by Testori et al., the gamma probe permits safe, minimal dissection of the SLN. They used the gamma probe immediately after incision of the superficial fascia to reduce the surgical dissection required to locate the sentinel node [23]. We measure the radioactivity of the resected node to confirm that it is positive after removal; and we evaluate persistent radioactivity in the inguinal area to locate other possible sentinel nodes. The procedure is bilateral when lymphoscintigraphy or the intraoperative signal is positive for bilateral migration. Postoperative complications are rare and generally include inguinal lymphorrhea which resolves with ambulatory drainage. In our experience, one monolateral lymph edema of the lower limb occurred and was treated conservatively in one patient and an inguinal lymphocele developed in another patient and was treated surgically (4.6% of cases) [22].

The specimens are then sent to the pathology department for microscopic evaluation; in nodes greater than 5 mm, 5–10 microsections at representative levels of each SLN are obtained by a step sectioning technique. The sections are stained with hematoxylin and eosin (H&E). If the SLN is found to be free of metastases after routine H&E staining, immunohistochemical analysis using an antipancytokeratin antibody (AE1/AE3) is performed to identify micrometastases or isolated tumor cells.

We have used the patent blue dye in only one patient, because Nanocoll® failed to migrate. In many of the other published series, the two techniques were applied to identify the SLN. Patent blue dye is injected just before surgery. Damin et al. have suggested that the concomitant use of radiomarkers and blue dye tends to result in higher rates of SLN detection than the use of either one alone. In our experience, slow migration of Nanocoll® was observed in certain cases, which only identified a positive node several hours after injection. We believe that good detection rates can generally be obtained with Nanocoll®, while patent blue dye should be used when migration does not occur.

Although SLN sampling should not be performed in patients presenting with clinically positive lymph nodes in other tumor types, this rule is not always true in anal cancer. In our experience the palpable lymph node often did not correspond to the SLN. While palpable lymph nodes are...
generally superficial, the real inguinal SLN is a deep node, usually located in a medial site close to the pubis. We therefore advise against using this technique in patients with massive groin invasion by metastatic lymph nodes or in those with multiple nodes, where diagnostic biopsy is indicated instead.

Discussion

Carcinoma of the anal canal is a rare neoplasm, accounting for less than 5% of all carcinomas of the colon, rectum and anus. As stated by de Parades et al., preoperative work-up is mandatory to establish correct therapeutic indications based on results of locoregional staging, evidence of visceral metastases, and details of the patient’s medical history [24].

Current primary therapy includes radiochemotherapy and radical surgery; abdominoperineal resection is indicated as salvage therapy for persistent disease or recurrence. According to multivariate analysis in phase III of the European Organization for Research and Treatment of Cancer (EORTC) trial, synchronous inguinal lymph node metastases are an independent prognostic factor for local failure and overall mortality [25]. Conversely, the presence of concurrent perirectal lymph nodes does not significantly affect prognosis.

Nevertheless, consensus on treatment of the inguinal zone is still lacking. Inguinal treatment is, in fact, mostly empirical and based on institutional routines. Some centers follow a protocol that calls for prophylactic inguinal irradiation, while others reserve inguinal irradiation for patients with histologically confirmed inguinal metastases.

Inguinal irradiation has a 48% rate of acute and late morbidity: acute toxicity requiring major medical or surgical intervention is seen in 15% of patients, especially those with a previous history of pelvic surgery. Late toxicity (e.g., small bowel injury, soft tissue injury, neurogenic bladder, osteonecrosis of femoral head with fracture which occurs in 6.4% of menopausal women, inguinal fibrosis, external genitalia edema, lower lymph edema) develops in 33% of cases [26].

Gerard et al. advise against systematic irradiation of the groin. In their study on 270 patients, late inguinal node metastases was only observed in 7.8% of patients [27]. Similarly, in a study on 223 patients treated with radiochemotherapy avoiding inguinal fields, Papillon et al. observed metachronous metastases in only 7.4% [28]. The results of these studies suggest that most patients (92%) submitted to routine inguinal irradiation are actually being overtreated. Nevertheless, since the conservative treatment advised by Papillon and Gerard, is associated with late inguinal metastases in some cases, early detection of metastatic inguinal lymph nodes is key to selecting patients for inguinal irradiation.

Wade et al. demonstrated that lymph node size is not a reliable parameter for predicting the presence of metastases. They reported that 44% of all lymph node metastases found in a series from the Roswell Park Cancer Institute using a “clearing technique” were less than 5 mm in diameter [29]. At present there is no imaging test to detect metastases in lymph nodes this small. And in many cases, clinical examination and imaging studies (computed tomography (CT), magnetic resonance imaging, and endosonography) cannot detect the presence of inguinal lymph node metastases.

In recent years, the use of SLN biopsy in anal cancer has improved staging of the inguinal status in these patients. Metastases were not found during follow-up in non-irradiated patients who underwent SLN biopsy in any of the studies reviewed. In the absence of skip lymph node metastases, this demonstrates the value of this technique and its utility in planning the fields of irradiation for radiotherapy.

Some investigators have found PET-CT to be useful for staging patients with anal cancer. Nguyen et al. reported that PET scan resulted in upstaging in up to one-fifth of the cases because it identifies nodal and distant disease involvement [30]. Cotter et al. reported that PET-CT detects the primary tumour more often than CT and detects substantially more abnormal inguinal lymph nodes than standard clinical staging with CT and physical examination [31]. However, in our initial experience comparing PET-CT and SLN biopsy in staging inguinal nodes, the results of the latter technique was better, considering the high percentage of false positives observed with PET-CT [32]. No other comparative studies have confirmed our results so far.

Conclusion

Inguinal SLN biopsy in patients with anal cancer should be considered the procedure of choice for staging inguinal lymph nodes. It is easy to perform, has no serious morbidity, and can help detect occult inguinal metastatic disease. Currently, there is no standard management for the treatment of the inguinal areas in N- patients and routine elective irradiation of the bilateral inguinal areas may not be advisable. Inguinal SLN biopsy could help identify patients with negative SLN who should be spared prophylactic radiotherapy and its associated morbidity and those who could benefit from inguinal irradiation. Further larger scale multicenter studies with long-term follow-up data are needed to validate these results.

References