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Value of staging squamous cell carcinoma of the anal margin and canal using the sentinel lymph node procedure: an update of the series and a review of the literature

D M Mistrangelo^{*,1}, M Bellò², P Cassoni³, E Milanese⁴, P Racca⁴, F Munoz⁵, G Fora⁴, N Rondi⁵, N Gilbo¹, R Senetta³, U Ricardi⁵ and M Morino¹

¹Digestive and Colorectal Surgical Department, Centre of Minimal Invasive Surgery, University of Turin, Molinette Hospital, Turin, Italy; ²Department of Nuclear Medicine, University of Turin, Molinette Hospital, Turin, Italy; ³Department of Biomedical Sciences and Human Oncology, University of Turin, Molinette Hospital, Turin, Italy; ⁴Oncological Centre for Gastrointestinal Neoplasms, Molinette Hospital, Turin, Italy and ⁵Department of Radiotherapy, University of Turin, Molinette Hospital, Turin, Italy

Background: Inguinal metastases in patients affected by anal cancer are an independent prognostic factor for local failure and overall mortality. Since 2001, sentinel lymph node biopsy was applied in these patients. This original study reports an update of personal and previous published series, which were compared with Literature to value the incidence of inguinal metastases T-stage related and the overall incidence of false negative inguinal metastases at sentinel node.

Methods: In all, 63 patients diagnosed with anal cancer submitted to inguinal sentinel node. Furthermore a research in the Pub Med database was performed to find papers regarding this technique.

Results: In our series, detection rate was 98.4%. Inguinal metastases were evidenced in 13 patients (20.6%). Our median follow-up was 35 months. In our series, no false negative nodes were observed.

Conclusion: Sentinel node technique in the detection of inguinal metastases in patients affected by anal cancer should be considered as a standard of care. It is indicated for all T stages in order to select patients to be submitted to inguinal radiotherapy, avoiding related morbidity in negative ones. An overall 3.7% rate of false negative must be considered acceptable.

Anal cancer remains a rare disease. An estimated 5820 new cases (2140 men and 3680 women) were estimated to occur in the United States in 2011, accounting for approximately 2.1% of digestive system cancers. It has been estimated that 770 deaths due to anal cancer will occur in United States alone in 2011 (Siegel *et al*, 2011).

In recent years, fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG-PET/CT) (Mistrangelo

et al, 2012) and sentinel lymph node biopsy (SLNB) of inguinal nodes have been introduced in clinical practice.

SLNB was proposed in 2000 by John Spratt, who suggested that prophylactic groin dissection is not required, but it may be curative in many cases for enlarged nodes or in the presence of a positive SLNB (Spratt, 2000).

Since 2001, SLNB was applied in patients affected by anal cancer providing inguinal staging and permitting a better planning of

*Correspondence: Dr DM Mistrangelo; E-mail: mistrangelo@katamail.com

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radiotherapeutic planes, avoiding inguinal radiotherapy and related morbidity in patients without metastasis at SLNB (Keshtgar *et al*, 2001).

Up to now, several studies (Vajda *et al*, 2001; Mistrangelo *et al*, 2002; Peley *et al*, 2002; Rabbit *et al*, 2002; Bobin *et al*, 2003; Damin *et al*, 2003; Ulmer *et al*, 2003; Castro *et al*, 2005; Gretschel *et al*, 2008; Mariani *et al*, 2008; Mistrangelo *et al*, 2009a; Hirche *et al*, 2010; De Nardi *et al*, 2011) and two reviews (Damin *et al*, 2006; Mistrangelo *et al*, 2009b) were published in international literature. All reports agree that SLNB for staging inguinal nodes in anal cancer is easy, feasible and can help to detect occult inguinal metastatic disease, in order to select the patients to submit to inguinal radiotherapy. Gretschel *et al* (2008) precised that SLNB is mainly indicated in T1 and T2 tumours and it is not recommendable for larger (T3-T4) tumours, considering the high incidence of inguinal metastases (MTS), and in patients with previous surgical manipulation in the anal or inguinal region.

Therefore, in 2010, De Jong *et al* (2010) reported a limited value of staging squamous cell carcinoma of the anal margin and canal using the sentinel node procedure in a prospective study with long-term follow up. The authors conclude that, because of the occurrence of inguinal lymph node MTS after a tumour-negative SLNB, the introduction of this procedure as a standard of care in all patients with anal carcinoma should be done with caution to avoid undertreatment of patients who otherwise would benefit from inguinal radiotherapy.

Considering these late reports, we revised our series and those reported in literature to value the incidence of inguinal MTS T-stage related and the incidence of false negative (FN) SLNB in order to confirm or exclude indication to SLNB in all T stages for patients affected by anal cancer.

PATIENTS AND METHODS

The study population consisted of 63 patients with anal cancer submitted to SLNB. The study was approved by the local ethics committee. The presenting symptoms were bleeding on defecation, sometimes associated with anal pain or the sensation of an anal mass.

Clinical workup comprised digital rectal examination, anoscopy, rigid proctoscopy, clinical exam of inguinal nodes, total colonoscopy, CT scan, rectal endosonography and PET-CT scan. HIV status and related CD4 count were valued in order to verify if there is a correlation with inguinal MTS. Patients with perianal cancer were excluded from the study.

All patients except those with an important palpable inguinal lymphadenopathy were studied for inguinal MTS with SLNB technique.

All patients were informed about the procedure and gave their written informed consent.

The technique of SLNB was previously described (Mistrangelo *et al*, 2009a).

The procedure started with the radioisotope injection. We performed it in a time ranging between 3 and 24 h before surgery. The injection of the radiopharmaceutical should be carried out in the Nuclear Medicine Department in order to adhere to universal radiation-safety precautions. We used Nanocoll, which is characterised by particles with a diameter of 80 nm, which are perfect for an adequate migration.

All patients studied in our Department were injected with 37 MBq of nanocoll-Tc-99m dextran 500 in a total volume of 0.4 ml, divided in four insulin syringes with a total volume of 0.1 ml per syringe. The injection was performed at the four cardinal points around the neoplasm.

The injection could be performed directly in the case of a neoplasm located perianally or at the anal margin, while in case of neoplasms located in the anal canal, we used a disposable anoscope to achieve a correct injection of the nanocolloid around the neoplasm. For the administration of the substance, we used a 22-G needle.

The procedure did not require anaesthesia and it did not present complications. A little pain in the injection site lasting few minutes was usually reported by the patient.

Planar lymphoscintigraphic images were generally performed 2–3 h after injection. Images were obtained using a GE Millennium gamma camera (GE Healthcare, Milwaukee, WI, USA). It presents a high-resolution collimator and a rectangular detector with 59 photomultipliers and crystal thickness of 5/8 inch. Acquisition window was set at 140 KeV ($\pm 10\%$). The matrix of planar images was 256 \times 256. The images were obtained in an anterior and posterior view. Sometimes we performed a lateral scintigraphic view as well.

Lymphoscintigraphy obtained with colloid particles permits easy evaluation of the main lymphatic drainage, showing the first node in which the tracer is captured. Colloids have the advantage of delayed wash out allowing the surgical procedure the same day or the day following the injection.

Imaging analysis was performed by two readers, who participated in all phases of the procedure.

The same day of the injection or the following day patients were submitted to inguinal SLNB in the operating theatre. No difference in terms of signal detection or accuracy was noted between the two groups. The procedure started with the localisation of the sentinel node. It was carried out with the use of a manual portable gamma probe. We used a Scintiprobe MR 100, Politech, Carsoli, Italy. To read the signal, the probe was directed away from the anus in order to remove the signal originating from the site of injection. When the positive signal was found, a cutaneous mark was positioned in order to fix the point of surgical incision. Generally, the surgical procedure was done under local anaesthesia. Under signal guidance, the biopsy of sentinel lymph node/s was performed. We considered a signal to be positive only when node and background radioactivity signal ratio was equal or superior to 5 : 1. We measured the radioactivity of the resected node to confirm its positivity after removal. Then we evaluated the persistence of radioactivity in the inguinal area in order to locate further sentinel nodes. We performed the procedure bilaterally in case of lymphoscintigraphy or intraoperative signal positive for bilateral migration. Nodes were then submitted to microscopic evaluation: 5–10 microsections at representative levels of each sentinel lymph node were obtained by a step sectioning technique for nodes > 5 mm. These sections were stained with hematoxylin and eosin. If the SLN was classified free of MTS after routine hematoxylin and eosin examination, immunohistochemistry was performed by means of an anti-pancytokeratin antibody (AE1/AE3) in order to identify micrometastases or isolated tumour cells.

Then patients were stratified for T stage in order to determine the incidence of inguinal MTS for each stage.

On completion of pre-treatment assessment, patients were submitted to combined radiochemotherapy (RCT) treatment (Mistrangelo *et al*, 2009a; Mistrangelo *et al*, 2010; Mistrangelo *et al*, 2012). Inguinal radiotherapy was administered only to patients with metastatic inguinal lymph nodes at SLNB.

At 1 and 3 months after the completion of RCT, patients underwent rectal digital examination, anoscopy with biopsy and PET/CT. Then patients were submitted to a follow-up consisting of a digital rectal examination, anoscopy, clinical exam of inguinal nodes and tumour marker assay (CEA and CA 19-9, that are not specific, and only recently seric YKL-40) every 3 months for 3 years and every 6 months in the following 2 years. A CT scan of the thorax and abdomen was performed yearly for 5 years.

After the first 5 years, patients were submitted to a rectal examination, anoscopy, clinical exam of inguinal nodes and tumour marker assay every year for further 5 years. A CT scan was performed 8 and 10 years after the end of RCT.

This accurate follow-up was performed to state the results of RCT, the incidence of persistence/recurrence of the disease and the incidence of inguinal MTS.

Moreover, the follow-up was oriented to value the incidence of FN in SLNB (patients with an histological negative SLNB, but developing inguinal MTS within the first 6 months of follow up), and to compare our results with ones published in Literature after a bibliographic research on Pub Med database. All papers, including case reports, are evaluated.

Statistical analysis. Data are presented as means (\pm s.d.) or median and range and rate with percentage for continuous and categorical variables, respectively.

RESULTS

Between November 2001 and May 2011, 63 patients with anal cancer were studied at our Department. Tumour biopsy revealed 63 squamous cell carcinomas. Patient characteristics are reported in Table 1.

Migration of Nanocoll was bilateral in 37 patients (59.7%) and unilateral in 25 patients (40.3%).

Detection rate was 98.4% (62 out of 63 patients). Median number of excised lymph nodes was 4 (range 1–14).

Histological exam evidenced inguinal MTS in 13 patients (20.6%). In all, 2 (15.4% of inguinal metastatic patients) of these patients presented bilateral inguinal MTS. In 1 (7.7%) of metastatic cases, micrometastases were found. No cases of isolated tumour cells were evidenced in our series.

Regarding HIV + status, only 1 patient presented MTS (6.7% of HIV + patients). This patient had a CD 4 + count = 163. Considering this aspect, only three patients had a CD 4 + count < 200 (20%).

Incidence of inguinal MTS in HIV – patients was 25% (12 out of 48).

Patients with inguinal metastatic disease were stratified for T stage (Table 2).

In 53 patients, PET-CT was performed and compared with SLNB in 41 patients (Mistrangelo *et al*, 2012). PET/CT was

positive for inguinal MTS in 12 of 53 patients (22.6%) and negative in 41 of 53 patients (77.4%). Inguinal node staging was compared with the results of SLNB, which was performed in 41 patients. Comparison between SLNB and PET/CT findings showed that SLNB confirmed the presence of inguinal MTS in only 8 cases, with 4 of 41 patients (9.7%) false positive and 2 of 41 patients (4.9%) FN.

Median follow-up was 35 months (range 3–86 months). In the first 6 months of follow up, none FN inguinal MTS occurred in our series. During follow-up, none of the patients negative for inguinal MTS at SLNB developed metachronous MTS.

DISCUSSION

Anal cancer remains a rare disease but its incidence is increasing (Siegel *et al*, 2011), mainly in association with human papilloma-viruses infection.

Since 1974, multimodality treatment as proposed by Nigro *et al* (1974), which combines radiation and chemotherapy, has become the standard of care, with surgery reserved for salvage treatment following local failure.

The overall 5-year survival rate reaches 70% in the absence of inguinal MTS (Gerard *et al*, 2001), which are an independent prognostic factor for local failure and overall mortality according to a multivariate analysis in a phase 3 EORTC trial (Bartelink *et al*, 1997). The average incidence rate of synchronous inguinal MTS is 13% (range 3–23%), but if metachronous inguinal MTS are taken into account, the overall rate of inguinal involvement is 24% (16–36%) (Gerard *et al*, 2001). Inguinal involvement is usually unilateral, with < 5% bilateral either synchronous or metachronous extension (Gerard *et al*, 2001). Gerard *et al* (2001) reported a severe prognosis for patients with clinically large inguinal lymph nodes (37% 5-year overall survival rate for patients with lymph nodes > 2 cm in greatest dimension), for patients with anal margin involvement (22.7%), and for patients with T3-T4 lesions (39%). Otherwise, the presence of concomitant perirectal lymph nodes did not significantly affect the prognosis.

Considering these aspects, the detection of inguinal lymph nodes is mandatory in the treatment of these patients and for their prognosis.

An array of tools for assessing inguinal metastasis have been proposed: clinical examination, endosonography, CT and magnetic resonance imaging; however, they are unable to detect nodal involvement in all the cases. Furthermore, only histological study can confirm MTS in an enlarged node or a micrometastasis in a normal-sized node. Wade *et al* (1989) at the Roswell Park Cancer Institute using a 'clearing technique' found that 44% of perianal, perirectal and pericolic lymph node MTS were < 5 mm in diameter, and therefore undetectable by usual diagnostic tools.

Recently, the use of FDG PET has also gained an important place in this setting, even if its role has yet to be defined (Mistrangelo *et al*, 2010; Mistrangelo *et al*, 2012). To better diagnose inguinal MTS, in recent years, SLNB has proven to be a safe and an effective technique (Spratt, 2000; Keshtgar *et al*, 2001; Vajda *et al*, 2001; Mistrangelo *et al*, 2002; Peley *et al*, 2002; Rabbit *et al*, 2002; Bobin *et al*, 2003; Damin *et al*, 2003; Ulmer *et al*, 2003; Castro *et al*, 2005; Damin *et al*, 2006; Gretschesel *et al*, 2008; Mariani *et al*, 2008; Mistrangelo *et al*, 2009a; De Jong *et al*, 2010; Hirche *et al*, 2010; De Nardi *et al*, 2011).

The present study confirms that SLNB is a simple and feasible technique with a high detection rate (98.4%), as reported in Literature (47–100%). Inguinal MTS are found in 20.6% of cases (13 patients), comparable with Literature (range 9.1–33% in major published series).

Table 1. Patient characteristics

Patient Characteristics	No. of patients (%)
Sex	63
Male	24 (38.1)
Female	39 (61.9)
Race	
White	63 (100)
Age (years)	
Median	59
Range	32–82
HIV-seropositive	15 (23.8)
Localisation	
Anal canal	43 (68.2)
Anal margin	20 (31.7)
T	
T1	7 (11.1)
T2	35 (55.5)
T3	17 (26.9)
T4	4 (6.3)

Table 2. Inguinal metastases stratified for T stage. Our experience and review of the Literature

Author (year)	Patients	MTS	T1	T2	T3	T4
Vajda <i>et al</i> (2001)	2	0	n.v.	n.v.	n.v.	n.v.
Peley <i>et al</i> (2002)	8	2	n.v.	n.v.	n.v.	n.v.
Perera <i>et al</i> (2003)	12	2	0/2 (0%)	2/10 (20%)	0/0	0/0
Bobin <i>et al</i> (2003)	33	7	0/3 (0%)	3/19 (15.8%)	4/8 (50%)	0/2 (0%)
Damin <i>et al</i> (2006)	22	2	n.v.	n.v.	n.v.	n.v.
Gretschel <i>et al</i> (2008)	40	6/20	4/7 (57%)	0/10 (0%)	2/3 (66.6%)	0/0 (0%)
Mariani <i>et al</i> (2008)	25	0	n.v.	n.v.	n.v.	n.v.
De Nardi <i>et al</i> (2011)	11	3	0/2 (0%)	1/4 (25%)	2/5 (40%)	0/0 (0%)
Hirche <i>et al</i> (2010)	12	2	1/4 (25%)	0/5 (0%)	0/2 (0%)	1/1 (100%)
De Jong <i>et al</i> (2010)	21	7	0/2 (0%)	6/15 (40%)	1/4 (25%)	0/0 (0%)
Francois <i>et al</i> (2010)	34	5	n.v.	n.v.	n.v.	n.v.
Mistrangelo <i>et al</i> (this paper)	63	13	1/7 (14.3%)	5/35 (14.3%)	6/17 (35.3%)	1/4 (25%)
Total valuables	192	45/172 (26.2%)	6/27 (22.2%)	17/98 (17.3%)	15/39 (38.5%)	2/7 (28.6%)

MTS = metastases; n.v. = not valuated.

Table 3. Review of the Literature of SLNB with the count of false negative (FN)

Author (year)	Patients	Localisation	Palpable nodes	Detection rate	Technique	MTS	FU (mo)	FN
Vajda <i>et al</i> (2001)	2	Not specified	Not specified	100%	Combined	0%	Not specified	Not specified
Keshtgar <i>et al</i> (2001)	1	Anal margin	No	100%	Combined	0%	Not specified	Not specified
Peley <i>et al</i> (2002)	8	Not specified	Not specified	100%	Combined	25%	5–35	0/6 0%
Perera <i>et al</i> (2003)	12	Anal canal or margin	Not specified	67%	Combined	29%	Not specified	Not specified
Bobin <i>et al</i> (2003)	33	Not specified	No	100%	Combined	21%	18	0/26 0%
Castro <i>et al</i> (2005)	2	Anal canal or margin	No	100%	Combined	0%	Not specified	Not specified
Damin <i>et al</i> (2006)	22	Not specified	No	100%	Combined	9.1%	Not specified	Not specified
Gretschel <i>et al</i> (2008)	40	Anal canal or margin	Not specified	90% (inguinal 56%)	Nanocoll	30% on 20 patients inguinal SLNB	27	1/14 7.1%
Mariani <i>et al</i> (2008)	25	Not specified	Not specified	100%	Combined	0%	20	2/25 8%
De Nardi <i>et al</i> (2011)	11	Anal canal	No	100%	Combined	27.2%	16	0/8 0%
Hirche <i>et al</i> (2010)	12	Anal canal or margin	No	83.3%	Combined and ICG	20%	44	0/8 0%
De Jong <i>et al</i> (2010)	21	Anal canal or margin	No	100%	Combined	33%	31	2/14 14%
Francois <i>et al</i> (2010)	34	Anal canal or margin	Not specified	47%	Nanocis	31.2%	50	1/11 9%
Mistrangelo <i>et al</i> (this paper)	63	Anal canal or margin	14	98.4%	Nanocoll	20.6%	44.1	0/50 0%

Abbreviations: FU = follow up; ICG = indocyanine green; MTS = metastases; SLNB = sentinel lymph node biopsy.

In their paper, Gretschel *et al* (2008) concluded that the SLNB can be used to select patients for inguinal irradiation appropriately, especially in T1 and T2 tumours. These patients receive either additional treatment or are spared from unnecessary radiation. In their opinion, SLNB technique is not recommendable for larger T3-T4 tumours and in

patients with previous surgical manipulation in the anal or inguinal region.

Published data up to date do not justify these conclusions. In fact, cumulative data evidenced that almost 2 out of 3 of T3 and T4 patients are disease free from inguinal MTS at SLNB. Moreover, systematic irradiation of the groins has proved to demand a larger

volume of radiotherapy, which increases toxicity especially when associated with chemotherapy: acute toxicity-related deaths occurred in 2–2.7% of cases (Bartelink *et al*, 1997) and late toxicity related to primary treatment, such a small bowel injury, soft tissue injury and neurogenic bladder, was reported to be as high as 33%, with 15% of patients requiring major medical or surgical intervention (Myerson *et al*, 2001). Otherwise in a study on 223 patients treated with chemoradiation sparing inguinal fields, Papillon and Montbarbon (1987) found metachronous inguinal MTS in only 7.4% of cases over a follow-up period of >3 years; and in a more recent study on 270 patients treated without elective inguinal irradiation, late inguinal MTS were diagnosed in 7.8% of patients (Gerard *et al*, 2001). In light of these results, authors concluded that the vast majority of patients (92%) submitted to routine inguinal irradiation are actually being overtreated (Gerard *et al*, 2001). Following on these considerations, Sapienza *et al* (1992) suggested that the low incidence of metachronous MTS and the high morbidity after inguinal lymphadenectomy and radiotherapy do not advocate the choice of preventive treatment.

When we stratify patients for T stage, inguinal MTS are observed in 14.3% of T1 and T2 patients, 35.3% of T3 and 25% of T4 ones. Considering overall data published in Literature on SLNB, inguinal MTS are found in 26.2% of all patients (45 out of 172): 22.2% of T1; 17.3% of T2; 38.5% of T3; and 28.6% of T4 patients.

Our series suggest that inguinal SLNB is indicated for all patients affected by anal cancer (obviously in the absence of large palpable inguinal lymph nodes, which must be directly biopsied) in order to select patients to submit to inguinal radiotherapy and avoid unnecessary treatment and associated morbidity. Also patients previously submitted to surgical manipulation in the anal or inguinal region could be submitted to SLNB, even if the migration of the tracer could be altered by previous anal surgery and the detection of inguinal nodes could be difficult. In case of absence of inguinal migration of the tracer, patient must be treated following the personal standard inguinal approach. In our series, five patients were previously submitted to surgery for an anal mass that revealed a squamous cancer with margins involved. Inguinal SLNB was performed without problems.

The second aim of the study was to value the incidence of FN lymph nodes after SLNB. De Jong *et al* (2010) suggested that inguinal SLNB has a limited value considering the incidence of FN after the procedure. Our series were compared with the published ones in order to value the global incidence of FN. The result of the review, including our experience, evidenced that 6 out of 163 (3.7%) lymph nodes negative at immunochemistry after SLNB developed inguinal MTS after a medium follow up of 27.3 months (range 5–50 months). FN lymph nodes developed in three T1N0 cancers, one T2N0 and one T3N0 (in the case of Mariani *et al* (2008), the stage was not specified). Data of the review are reported in Table 3.

Considering these data, a FN rate of 3.7% should be considered as acceptable for patients affected by anal cancer.

Moreover, 4 out of 5 (80%) of FN were T1-T2 patients (in one case, T stage was not specified) confirming that SLNB is indicated in all T stage and not only in T1-T2 as suggested by Gretschesl *et al* (2008), considering that long follow-up confirm that almost 2 out of 3 of T3-T4 patients are N0 or N1.

CONCLUSIONS

Up-to-date SLNB technique in the detection of inguinal MTS in patients affected by anal cancer should be considered as a standard of care. It is indicated for all T stages in order to select patients

to be submitted to inguinal radiotherapy, avoiding morbidity associated to this treatment in patients negative for inguinal MTS.

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