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EDITORIAL

New approach to anal cancer: Individualized therapy based on sentinel lymph node biopsy

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Abstract

Oncological treatment is currently directed toward a tailored therapy concept. Squamous cell carcinoma of the anal canal could be considered a suitable platform to test new therapeutic strategies to minimize treatment morbidity. Standard of care for patients with anal canal cancer consists of a combination of radiotherapy and chemotherapy. This treatment has led to a high rate of local control and a 60% cure rate with preservation of the anal sphincter, thus replacing surgical abdomino-perineal resection. Lymph node metastases represent a critical independent prognostic factor for local recurrence and survival. Mesorectal and iliac lymph nodes are usually included in the radiation field, whereas the inclusion of inguinal regions still remains controversial because of the subsequent adverse side effects. Sentinel lymph node biopsies could clearly identify inguinal node-positive patients eligible for therapeutic groin irradiation. A sentinel lymph node navigation procedure is reported here to be a feasible and effective method for establishing the true inguinal node status in patients suffering from anal canal cancer. Based on the results of sentinel node biopsies, a selective approach could be proposed where node-positive patients could be selected for inguinal node irradiation while node-negative patients could take advantage of inguinal sparing irradiation, thus avoiding toxic side effects.

Key words: Anal carcinomal; Lymphnode metastasis; Sentinel lymphnode; Tumor staging

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INTRODUCTION

In the past two decades, tangible efforts have been made to understand the natural course and behavior of anal canal carcinoma, and, especially, to improve the efficacy of multimodality chemo-radiation treatment. Currently, the main issues in the treatment of this neoplasm are the recognition of a reliable staging system and strategies to obtain long-term survival while reducing radiation related side effects.

Anal canal squamous cell carcinoma represents 1% to 2% of all gastrointestinal malignancies[1-3] and is associated with human papilloma virus infection[4]. Diagnostic procedures include clinical and rectal examination, endorectal ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) scan, and positron emission tomography (PET) scan[1]. Clinical and pathological classification is based on tumor-node-metastasis

staging developed by the American Joint Committee on Cancer[5].

The two most significant prognostic factors are tumor size and nodal status[6,7]. Inguinal lymph node involvement is considered a major independent prognostic factor for local recurrence and overall survival[2] with survival rates dropping from 70% in node-negative to 40% in node-positive patients. Syncronous inguinal metastases are strictly related to the tumor size and occur in 10% to 25% of patients[8,9]. Metachronous metastases are found, usually during follow-up, in 5% to 25% of patients who were groin lymph node-negative at the time of diagnosis[9].

Identification of the anal canal lymphatic drainage pattern is essential to predict secondary nodal involvement. Lymphatic drainage of anal canal cancer mostly depends on the tumor location. Based on anatomic and physiopathological studies, tumors located under the dentate line are more likely to drain to groin chains while tumors located above the dentate line are prone to drain to the internal iliac lymph node system, although the two drain systems are not separated from each other (Figure 1)[10-12]. A tumor located laterally in the anal canal is more likely to drain to the homolateral side. Moreover, tumors located in the midline have the tendency to drain bilaterally in the inguinal regions[12].

TREATMENT OPTIONS AND PROGNOSIS

Local excision with neoplasm-free margins is recommended for T1 well-differentiated tumors[13]. Abdominoperineal resection and permanent colostomy has been traditionally performed for anal canal cancer achieving 40% to 70% survival rate at five years[2,14]. Chemo-radiation treatment has replaced surgical resection since Nigro *et al*[15] introduced his protocol in 1974 and has raised survival and eradication of tumors from 70% to 90% in selected patients[16-19]. Predictably, prognosis is worsened by 50% with nodal involvement and tumor size larger than 5 cm[2]. Local recurrence shown by pathology or incomplete pathological response after multimodality chemo-radiotherapy treatment is an indication of subsequent abdominoperineal resection[13,20,21]. However, dose-related radiation side effects, such as anal ulcers, stenosis, and necrosis, can necessitate a subsequent colostomy in 6% to 12% of patients[18,22-25]. Irradiation fields involving the groin lymph nodes chain can cause inguinal fibrosis, external genitalia edema, epidermolysis with superinfection of skin, necrosis of the femoral head, femoral head fracture, and stenosis of iliac artery[18,22,24,26-30]. Death from radiation toxicity is reported in 2.0% to 2.7% of patients[9]. Moreover, risk of radiation side effects do not decrease over time and might pose a lifelong risk of developing late complications[24,29]. For these reasons, strategies to reduce the radiation field are advisable.

Metastatic involvement of inguinal nodes is a crucial point in the correct assessment of these patients.

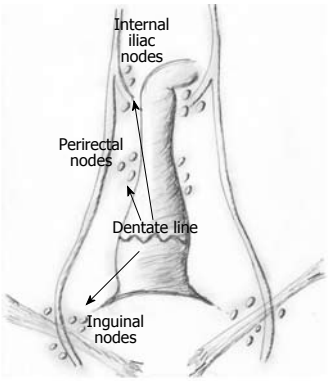

Figure 1 Anal canal lymphatic drainage pattern.

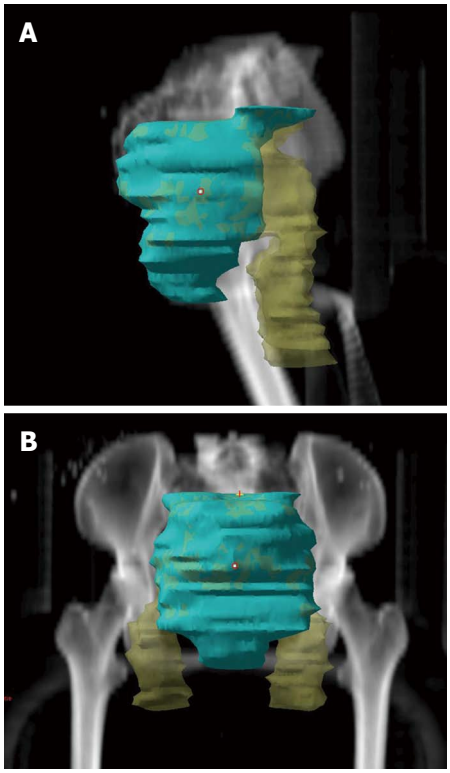

Figure 2 Radiation field of anal carcinoma with exclusion (green field) or inclusion of inguinal regions. A: Lateral view; B: Anterior view.

In fact, involvement of mesorectal nodes does not affect the therapeutic approach because they are generally included in the radiation fields, while routine inclusion of groin lymph node stations remains controversial. Inguinal lymph node involvement is difficult to establish. The diagnostic accuracy of clinical evaluation and imaging tools remains low. In the case of clinically palpable nodes, a biopsy could be performed. However, as in the majority of cases, a clinically negative groin does not imply absence of metastatic disease. A "wait and see" position is recommended by some institutions[31], while prophylactic groin irradiation is ordinarily practiced by other groups[32]. Less frequently, the decision to irradiate the inguinal region is based on primary anal tumor size[33]

(Figure 2).

Prophylactic groin irradiation has been proposed by several authors with a reduction of inguinal metastatic recurrence as low as 2.5% to 3%[22,34-40]. Otherwise, Papillon *et al*[41] and Gerard *et al*[9] examined a large series of clinically node-negative patients after groin sparing irradiation and observed inguinal metachronous recurrence in 7.4% and 7.8% of patients, respectively.

Given this premise, it is clear that the majority of patients are over treated because effective nodal staging is not achieved. On the other hand, early T stage neoplasms with underrated nodal status may not receive the proper treatment by inguinal sparing.

RATIONALE AND IMPLICATIONS OF SENTINEL LYMPH NODE MAPPING

Because the standard treatment does not provide any specimens for pathological evaluation, the effective node status of these patients is not determined. Moreover, the wide lymphatic drainage pattern that characterizes the inguinal and the pelvic lymph node basin makes it difficult to predict synchronous and metachronous metastatic involvement[42]. Furthermore, it has been observed that the size of the nodes is not a predictable parameter for nodal involvement because 44% of positive inguinal lymph nodes at pathological examination are smaller than 5 mm[27]. Conversely, 50% of larger nodes appear to be inflammatory[14]. Of note, in our previous case series, smaller lymph nodes (4-7 mm) were more likely to harbor metastases than larger ones[43].

For these reasons, even more advanced imaging techniques, such as MRI, are not accurate in the detection of metastatic lymph nodes[44]. PET has been used as an aid to achieve better staging and it has been demonstrated to detect up to 20% of metastases not diagnosed by clinical or radiological examination[44]. Bannas *et al*[45] has demonstrated that PET/CT is superior to PET or CT alone for staging anal cancer, particularly in identifying local regional lymph node metastases. Recently, Mistrangelo *et al*[46] demonstrated that sentinel lymph node biopsy (SLNB) was superior to PET-CT for the staging of inguinal lymph nodes. In our experience, PET has a sensitivity of 33% and a specificity of 84%. Even though sensitivity of SLNB of the anal canal has not been yet addressed, the sensitivity of sentinel node biopsy detection in melanoma is reported to be up to 99%[47-49].

These findings advocate the need to find a more reliable technique to identify positive nodes. Currently, histological evaluation is the gold standard to assess the presence of metastases in lymph nodes. Standard surgical node dissection for suspicious inguinal nodes has been proposed[50,51]. However, this approach is also fraught with side effects[52,53]. In addition, elective inguinal dissection for clinically suspicious nodal involvement revealed metastasis only in 50% of cases at histology[14].

In this scenario, SLNB could help to accurately identify patients with inguinal metastatic spread and to avoid irradiation morbidity in node-negative subjects or, conversely, to enroll node-positive patients for inguinal irradiation. SLNB should not be performed in patients with clear evidence of clinically positive or suspicious inguinal nodes. Some reports have also suggested the exclusion of patients with locally advanced T4 cancer. Metastatic or even reactive nodes may alter the lymphatic drainage pattern, thus making the SLNB unreliable. For the same reason, patients who underwent prior surgical manipulation in the anal region should be excluded from the procedure[12,54,55].

PATIENT SELECTION AND FEATURES

Patients with histologically confirmed squamous cell carcinoma of the anal canal were eligible for the SLNB procedure. Previous reports have also included tumors of the anal margin, which should be considered separately due to different clinical behavior. For the reasons explained above, patients with clear or suspicious inguinal nodes were generally not enrolled[54].

From 2007 to 2012, 23 patients with proven squamous cell carcinoma of the anal canal and clinically negative inguinal nodes were enrolled in the prospective study. Pre-operative work-up included endoscopy and biopsy, pelvic RMI, endoanal ultrasound, and abdominal and lung CT scans. Tumor stage was classified as follows: T1, 3 pts; T2, 9 pts; T3, 7 pts; and T4, 4 pts.

In 2009, an inguinal sparing irradiation protocol was started. Fifteen patients were observed and three patients were excluded from the SLNB study for positive inguinal lymph nodes confirmed by cytology. Twelve patients with clinically negative inguinal regions were enrolled. After the SLNB procedure, patients with histologically positive inguinal nodes were treated with combined chemotherapy using 5-fluorouracil/mitomycin-C, and the standard radiotherapy field, including inguinal basins. Patients with tumor-free nodes did not undergo inguinal irradiation. Patients were then regularly followed-up every three months.

DESCRIPTION OF TECHNIQUES

Many authors have reported a standardized technique to isolate and retrieve sentinel lymph nodes for metastatic assessment[12,28,54-64]. The first procedural step was a lymphoscintigraphy to evaluate the main lymphatic drainage and the first node in which the tracer is captured. The radiotracer (0.2 mL 99mTC nanocolloid) injection was performed submucosally, directly around the anal lesion in the four cardinal points with the aid of an anoscope. As the injection can be painful, a needle-free injection system[56] could also be utilized to minimize patient discomfort. After injection, planar anterior and posterior images were taken with a Philips gamma camera, as previously described[43], to localize the sentinel lymph

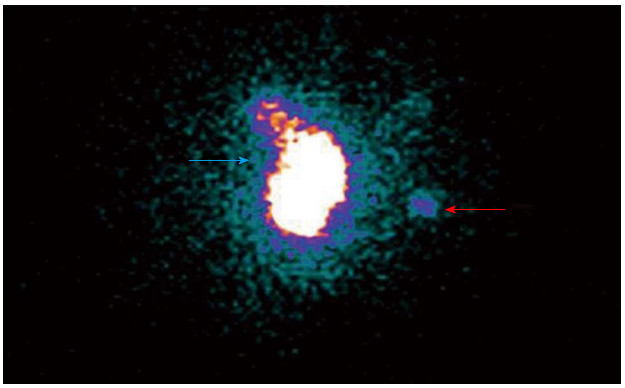

Figure 3 Lymphoscintigraphy of a sentinel lymph node in anal carcinoma. Anterior view showing injection site (blue arrow) and sentinel lymph node (red arrow).

node. Typical drainage patterns displayed radiotracer accumulation in the inguinal area or in the iliac internal lymph node system (Figure 3). If the accumulation was observed in the perirectal or external iliac lymph nodes, then patients did not undergo the sentinel lymph node procedure. Only patients showing radio accumulation in the inguinal area were enrolled for sentinel node surgical retrieval, and the overlying skin was marked by a waterproof pen. Marking the skin assisted in the intraoperative identification of the nodes and minimized surgical incision.

There was no consensus about the time gap between injection, lymphoscintigraphy acquisition, and surgery. Clearance of radioactive colloids by lymphatic drainage is related to the particle size; small particles are cleared first and large particles later[65]. Moreover, tracers with small particle size are washed out from true sentinel nodes and move to other nodes[66]. Therefore, a shorter period between injection and surgery is recommended with smaller particles. In our experience, 99mTC-nanocolloid with particles between 80 and 150 nm were employed. By virtue of their delayed wash-out, surgery could be performed even the day after injection. A delay of 12 to 16 h between injection and surgery allowed good intraoperative radio-localization with minimal interference by primary tumor radioactivity.

During surgery a second vital tracer, blue patent, was injected around the site of the anal tumor. In other reports, nearly all groups have used blue dye as a second vital tracer. The addition of intraoperative dye aids in the intraoperative search[67] and tends to result in higher rates of lymph node detection. There are no data regarding the usefulness of dye with SLNB in anal cancer; however, the importance of dual mapping to reduce false negative results has recently been demonstrated in breast cancer[68]. When accumulation was shown at lymphoscintigraphy on both groin regions, inguinal dissection was made bilaterally.

Local anesthesia was routinely employed in our institute, although the procedure can be performed under general or local regional anesthesia. During surgery, a hand-held gamma detection probe was used to identify the radioactive lymph node (NEOPROBE Neo2000 Gamma Detection System). A small incision was made under radio probe guidance and over the marked skin. The sentinel lymph node was retrieved by visualization through the blue dye and radio detection by the hand-held gamma probe. During radio-navigation the gamma probe was directed away from the anus to avoid signal detection from the primary site of injection[28]. Significant radio-colloid capture, compared to lymphatic basin, should be in a ratio of 5:1. After nodal excision, the surgical site was explored by the gamma probe to identify accessory nodes.

The isolated lymph node was sent for pathological examination and metastatic assessment. Hematoxylin and eosin (HE) staining was used to assess the presence of malignancy. Other reports have suggested using immunohistochemistry with pan-cytokeratin antibody markers for cases of negative HE[28,54,56]. In our study, the specimen was examined using a particularly accurate technique. Briefly, sentinel lymph nodes were step-sectioned into 50-micron slices and serial sections of three microns thick were cut at each level. This number of sections provided good accuracy without having to resort to the more costly immunohistochemical analysis. Among the other related reports, only Gretschel *et al*[54] have found micro-metastases or isolated tumor cells in lymph nodes examined after a negative HE.

Common complications related to lymph node mapping include wound infection, hematoma, and lymphorrea from lymphatic fistula with subsequent seroma in the surgical site. Post-procedural side effects are easily managed and rarely require reintervention.

RESULTS OF SENTINEL LYMPH NODE ASSESSMENT

Since the first report published by Keshtgar *et al*[56] in 2000, several reports have demonstrated the feasibility and effectiveness of the SLNB procedure in anal cancer[43,54,57-63,69,70]. The technical aspects and results of the published studies are shown in Table 1. In these studies, patients with T1-T4 anal tumors with clinical or imaging negative inguinal nodes were enrolled. Lymphoscintigraphy accuracy was generally high, rating 90% to 100% in examined reports, and inguinal capture, as explained above, depended on the localization of the primary tumor. Surgical gamma probe detection was nearly 100%[43,54,57-63,65,69,70]. Almost all groups suggested the double tracer technique to better visualize the sentinel lymph node intraoperatively. Metastatic node rate, among the sentinel nodes, varied between 0% and 33%; however, the case series were very heterogeneous and included advanced tumors (T stage ranging from T1 to T4) even though the majority of patients were clinically node-negative.

Table 1 Technical aspects and results of the published case series

Ref.	Year	T stage	Groin clinical	Tot N cases	Inguinal detection rate (%)	Double tracer	N positive (%)	Complication	Bilateral detection	Surgical retrieval rate
Keshtgar *et al*[56]	2000	NA	Negative	1	1/1	Yes	1/1	NA	0/1	1/1
Perera *et al*[58]	2002	T1-T2	1/12	12	8/12 (66)	Yes	2/18 (11)	NA	0/8	8/8
Péley *et al*[57]	2002	NA	1/8	8	8/8 (100)	Yes	2/8 (25)	No complication	5/8	8/8
Rabbit *et al*[69]	2002	NA	Negative	4	3/4 (75)	Yes	0/3 (0)	NA	2/3	3/3
Bobin *et al*[62]	2003	NA	Negative	33	33/33 (100)	Yes	7/33 (21.2)	NA	NA	33/33
Ulmer *et al*[60]	2004	T2-T4	Negative	17	13/17 (76)	Yes	5/12 (41.6)	Lymphatic fistula (1 pt)	4/13	12/12
Gretschel *et al*[54]	2008	T1-T4	Negative	40	20/40 (50)	Yes	6/20 (30)	Wound infection (2 pts), lymphatic fistula (1 pt), hematoma (1 pt)	NA	20/20
Mistrangelo *et al*[64]	2009	T1-T4	NA	35	35/35 (100)	No	7/35 (20)	Lymphatic fistula (18 pts), lower limb lymphedema (1 pt)	22/35	34/35
Damin *et al*[55]	2010	T1-T3	Negative	15	15/15 (100)	Yes	4/15 (26.6)	Lymphatic fistula (1 pt)	13/15	15/15
de Jong *et al*[70]	2010	T1-T3	4/21	21	21/21 (100)	Yes	7/21 (33)	NA	14/21	21/21
De Nardi *et al*[43]	2011	T1-T3	Negative	11	9/11 (81)	Yes	3/9 (33)	Lymphatic fistula (1 pt)	2/11	9/9

NA: Not applicable.

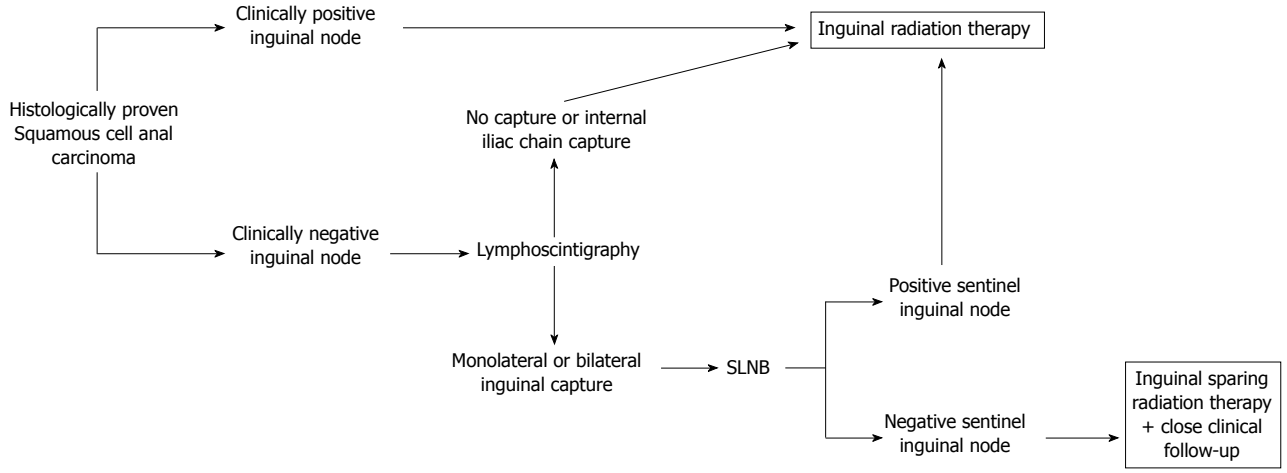

Figure 4 Diagnostic-therapeutic algorithm for squamous cell anal carcinoma. SLNB: Sentinel lymph node biopsy.

Among 23 patients, 19 with inguinal capture at lymphoscintigraphy underwent the SLNB procedure. Inguinal dissection was made bilaterally in two patients where accumulation was shown at lymphoscintigraphy on both groin regions. Sentinel lymph node retrieval by gamma probe was possible in all patients. Histological examination of nodes showed the presence of metastases in five patients (26%).

Among the 12 patients enrolled in the inguinal sparing radiation protocol with a clinically negative inguinal region, 10 patients had negative pathological SLN and received an inguinal sparing irradiation. At a median follow-up of 20 mo, none of these patients had developed inguinal metastases.

Gretschel *et al*[54] reported that inguinal lymph node assessment was able to change the treatment plan recommended by national guidelines in 50% of patients. In the group of patients with inguinal sparing irradiation, inguinal recurrence was found in two out of 20 patients: one patient suffering from a T4 tumor, associated with disseminated disease, and one patient with T1 tumor that was previously treated by local excision. Mistrangelo *et al*[28] did not observe isolated inguinal recurrence in 28 node-negative patients at a median follow-up of 22 mo.

De Jong *et al*[70] reported that SNLB provided alteration of treatment in at least 11 of 21 patients. However, inguinal recurrence within 12 to 24 mo was observed in two out of 14 node-negative patients undergoing node-sparing irradiation. Figure 4 demonstrates a simple diagnostic-therapeutic algorithm to identify patients eligible for the SLNB procedure to individualize irradiation treatment based on inguinal node status.

CONCLUSION

In spite of the low incidence of anal canal carcinoma, noticeable advances have been achieved in the past 30 years in understanding its etiology, biological behavior and therapy, with the current therapeutic approach be-

ing primary radio-chemotherapy. The identification of lymph nodes metastases, especially in the inguinal area, is still the main issue that needs to be addressed.

The low incidence of metachronous metastases and the considerable side effects after inguinal node dissection and radiotherapy do not justify a prophylactic treatment[71]. A refined staging system with precise identification of disease extent could allow individualized therapy, ensuring the accurate coverage of disease while sparing disease-free organs.

In this context, SLNB, as a minimally invasive procedure, may improve disease staging and may be useful to select patients for inguinal radiation. Feasibility and efficacy of SLNB has been addressed by several reports and the clinical utility of this procedure in changing the therapeutic plan has also been outlined. However, further larger prospective studies are needed to confirm the clinical impact of this procedure. Continuous and stringent long-term follow-up is necessary to estimate the outcome in node-negative patients who did not undergo groin irradiation.

REFERENCES

1 **Fuchshuber PR**, Rodriguez-Bigas M, Weber T, Petrelli NJ. Anal canal and perianal epidermoid cancers. *J Am Coll Surg* 1997; **185**: 494-505
2 **Ryan DP**, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med* 2000; **342**: 792-800
3 **Jemal A**, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007; **57**: 43-66
4 **Critchlow CW**, Surawicz CM, Holmes KK, Kuypers J, Daling JR, Hawes SE, Goldbaum GM, Sayer J, Hurt C, Dunphy C. Prospective study of high grade anal squamous intraepithelial neoplasia in a cohort of homosexual men: influence of HIV infection, immunosuppression and human papillomavirus infection. *AIDS* 1995; **9**: 1255-1262
5 **Edge SB**, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17**: 1471-1474
6 **Clark J**, Petrelli N, Herrera L, Mittelman A. Epidermoid carcinoma of the anal canal. *Cancer* 1986; **57**: 400-406
7 **Shepherd NA**, Scholefield JH, Love SB, England J, Northover JM. Prognostic factors in anal squamous carcinoma: a multivariate analysis of clinical, pathological and flow cytometric parameters in 235 cases. *Histopathology* 1990; **16**: 545-555
8 **Mistrangelo M**, Mobiglia A, Bellò M, Beltramo G, Cassoni P, Mussa A. [The technique of sentinel lymph nodes in patients with anus neoplasm]. *Suppl Tumori* 2005; **4**: S32-S33
9 **Gerard JP**, Chapet O, Samiei F, Morignat E, Isaac S, Paulin C, Romestaing P, Favrel V, Mornex F, Bobin JY. Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. *Cancer* 2001; **92**: 77-84
10 **Cummings BJ**. Current management of anal canal cancer. *Semin Oncol* 2005; **32**: S123-S128
11 **Cohen AM**, Wong WD. Anal squamous cell cancer nodal metastases: prognostic significance and therapeutic considerations. *Surg Oncol Clin N Am* 1996; **5**: 203-210
12 **Damin DC**, Rosito MA, Schwartsmann G. Sentinel lymph node in carcinoma of the anal canal: a review. *Eur J Surg Oncol* 2006; **32**: 247-252
13 **Engstrom PF**, Arnoletti JP, Benson AB, Berlin JD, Berry JM, Chen YJ, Choti MA, Cooper HS, Dilawari RA, Early DS, Enzinger PC, Fakih MG, Fleshman J, Fuchs C, Grem JL, Knol JA, Leong LA, Lin E, Mulcahy MF, Rohren E, Ryan DP, Saltz L, Shibata D, Skibber JM, Small W, Sofocleous C, Thomas J, Venook AP, Willett C. NCCN clinical practice guidelines in oncology. Anal carcinoma. *J Natl Compr Canc Netw* 2010; **8**: 106-120
14 **Pintor MP**, Northover JM, Nicholls RJ. Squamous cell carcinoma of the anus at one hospital from 1948 to 1984. *Br J Surg* 1989; **76**: 806-810
15 **Nigro ND**, Vaitkevicius VK, Considine B. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum* 1974; **17**: 354-356
16 **Bilimoria KY**, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, Halverson AL. Squamous cell carcinoma of the anal canal: utilization and outcomes of recommended treatment in the United States. *Ann Surg Oncol* 2008; **15**: 1948-1958
17 **Cummings BJ**, Rider WD, Harwood AR, Keane TJ, Thomas GM, Erlichman C, Fine S. Combined radical radiation therapy and chemotherapy for primary squamous cell carcinoma of the anal canal. *Cancer Treat Rep* 1982; **66**: 489-492
18 **Gabriele AM**, Rovea P, Sola B, Trotti AB, Comandone A. Radiation therapy and chemotherapy in the conservative treatment of carcinoma of the anal canal: survival and late morbidity in a series of 25 patients. *Anticancer Res* 1997; **17**: 653-656
19 **Tomaszewski JM**, Link E, Leong T, Heriot A, Vazquez M, Chander S, Chu J, Foo M, Lee MT, Lynch CA, Mackay J, Michael M, Tran P, Ngan SY. Twenty-five-year experience with radical chemoradiation for anal cancer. *Int J Radiat Oncol Biol Phys* 2012; **83**: 552-558
20 **Eeson G**, Foo M, Harrow S, McGregor G, Hay J. Outcomes of salvage surgery for epidermoid carcinoma of the anus following failed combined modality treatment. *Am J Surg* 2011; **201**: 628-633
21 **Causey MW**, Steele SR, Maykel J, Champagne B, Johnson EK. Surgical therapy for epidermoid carcinoma of the anal canal: an NSQIP assessment of short-term outcomes. *J Surg Res* 2012; **177**: 235-240
22 **Cummings BJ**, Thomas GM, Keane TJ, Harwood AR, Rider WD. Primary radiation therapy in the treatment of anal canal carcinoma. *Dis Colon Rectum* 1982; **25**: 778-782
23 **Saarilahti K**, Arponen P, Vaalavirta L, Tenhunen M. The effect of intensity-modulated radiotherapy and high dose rate brachytherapy on acute and late radiotherapy-related adverse events following chemoradiotherapy of anal cancer. *Radiother Oncol* 2008; **87**: 383-390
24 **Putta S**, Andreyev HJ. Faecal incontinence: A late side-effect of pelvic radiotherapy. *Clin Oncol* (*R Coll Radiol*) 2005; **17**: 469-477
25 **de Bree E**, van Ruth S, Dewit LG, Zoetmulder FA. High risk of colostomy with primary radiotherapy for anal cancer. *Ann Surg Oncol* 2007; **14**: 100-108
26 **Cummings BJ**. Radiation therapy and chemotherapy in the treatment of primary anal canal carcinoma. *Compr Ther* 1983; **9**: 59-65
27 **Wade DS**, Herrera L, Castillo NB, Petrelli NJ. Metastases to the lymph nodes in epidermoid carcinoma of the anal canal studied by a clearing technique. *Surg Gynecol Obstet* 1989; **169**: 238-242
28 **Mistrangelo M**, Bellò M, Mobiglia A, Beltramo G, Cassoni P, Milanesi E, Cornaglia S, Pelosi E, Giunta F, Sandrucci S, Mussa A. Feasibility of the sentinel node biopsy in anal cancer. *Q J Nucl Med Mol Imaging* 2009; **53**: 3-8
29 **Jung H**, Beck-Bornholdt HP, Svoboda V, Alberti W, Herrmann T. Quantification of late complications after radiation therapy. *Radiother Oncol* 2001; **61**: 233-246

30 **Lim F**, Glynne-Jones R. Chemotherapy/chemoradiation in anal cancer: a systematic review. *Cancer Treat Rev* 2011; **37**: 520-532
31 **Matthews JH**, Burmeister BH, Borg M, Capp AL, Joseph D, Thompson KM, Thompson PI, Harvey JA, Spry NA. T1-2 anal carcinoma requires elective inguinal radiation treatment--the results of Trans Tasman Radiation Oncology Group study TROG 99.02. *Radiother Oncol* 2011; **98**: 93-98
32 **Ortholan C**, Resbeut M, Hannoun-Levi JM, Teissier E, Gerard JP, Ronchin P, Zaccariotto A, Minsat M, Benezery K, François E, Salem N, Ellis S, Azria D, Champetier C, Gross E, Cowen D. Anal canal cancer: management of inguinal nodes and benefit of prophylactic inguinal irradiation (CORS-03 Study). *Int J Radiat Oncol Biol Phys* 2012; **82**: 1988-1995
33 **Wright JL**, Patil SM, Temple LK, Minsky BD, Saltz LB, Goodman KA. Squamous cell carcinoma of the anal canal: patterns and predictors of failure and implications for intensity-modulated radiation treatment planning. *Int J Radiat Oncol Biol Phys* 2010; **78**: 1064-1072
34 **Salmon RJ**, Fenton J, Asselain B, Mathieu G, Girodet J, Durand JC, Decroix Y, Pilleron JP, Rousseau J. Treatment of epidermoid anal canal cancer. *Am J Surg* 1984; **147**: 43-48
35 **Stewart D**, Yan Y, Kodner IJ, Birnbaum E, Fleshman J, Myerson R, Dietz D. Salvage surgery after failed chemoradiation for anal canal cancer: should the paradigm be changed for high-risk tumors? *J Gastrointest Surg* 2007; **11**: 1744-1751
36 **Mitchell SE**, Mendenhall WM, Zlotecki RA, Carroll RR. Squamous cell carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2001; **49**: 1007-1013
37 **Roelofsen F**, Bartelink H. Combined Modality Treatment of Anal Carcinoma. *Oncologist* 1998; **3**: 413-418
38 **Flam M**, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, Quivey J, Rotman M, Kerman H, Coia L, Murray K. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol* 1996; **14**: 2527-2539
39 **Tanum G**, Tveit KM, Karlsen KO. Chemoradiotherapy of anal carcinoma: tumour response and acute toxicity. *Oncology* 1993; **50**: 14-17
40 **Myerson RJ**, Kong F, Birnbaum EH, Fleshman JW, Kodner IJ, Picus J, Ratkin GA, Read TE, Walz BJ. Radiation therapy for epidermoid carcinoma of the anal canal, clinical and treatment factors associated with outcome. *Radiother Oncol* 2001; **61**: 15-22
41 **Papillon J**, Montbarbon JF. Epidermoid carcinoma of the anal canal. A series of 276 cases. *Dis Colon Rectum* 1987; **30**: 324-333
42 **Godlewski G**, Prudhomme M. Embryology and anatomy of the anorectum. Basis of surgery. *Surg Clin North Am* 2000; **80**: 319-343
43 **De Nardi P**, Carvello M, Canevari C, Passoni P, Staudacher C. Sentinel node biopsy in squamous-cell carcinoma of the anal canal. *Ann Surg Oncol* 2011; **18**: 365-370
44 **Trautmann TG**, Zuger JH. Positron Emission Tomography for pretreatment staging and posttreatment evaluation in cancer of the anal canal. *Mol Imaging Biol* 2005; **7**: 309-313
45 **Bannas P**, Weber C, Adam G, Frenzel T, Derlin T, Mester J, Klutmann S. Contrast-enhanced [(18)F]fluorodeoxyglucose-positron emission tomography/computed tomography for staging and radiotherapy planning in patients with anal cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**: 445-451
46 **Mistrangelo M**, Pelosi E, Bellò M, Castellano I, Cassoni P, Ricardi U, Munoz F, Racca P, Contu V, Beltramo G, Morino M, Mussa A. Comparison of positron emission tomography scanning and sentinel node biopsy in the detection of inguinal node metastases in patients with anal cancer. *Int J Radiat Oncol Biol Phys* 2010; **77**: 73-78
47 **Morton DL**, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**: 392-399
48 **Kapteijn BA**, Nieweg OE, Liem I, Mooi WJ, Balm AJ, Muller SH, Peterse JL, Valdés Olmos RA, Hoefnagel CA, Kroon BB. Localizing the sentinel node in cutaneous melanoma: gamma probe detection versus blue dye. *Ann Surg Oncol* 1997; **4**: 156-160
49 **Balch CM**, Ross MI. Sentinel lymphadenectomy for melanoma--is it a substitute for elective lymphadenectomy? *Ann Surg Oncol* 1999; **6**: 416-417
50 **Cortese AF**. Surgical approach for treatment of epidermoid anal carcinoma. *Cancer* 1975; **36**: 1869-1875
51 **Golden GT**, Horsley JS. Surgical management of epidermoid carcinoma of the anus. *Am J Surg* 1976; **131**: 275-280
52 Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet* 1996; **348**: 1049-1054
53 **Northover J**, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, Jitlal M, Ledermann J. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *Br J Cancer* 2010; **102**: 1123-1128
54 **Gretschel S**, Warnick P, Bembenek A, Dresel S, Koswig S, String A, Hünerbein M, Schlag PM. Lymphatic mapping and sentinel lymph node biopsy in epidermoid carcinoma of the anal canal. *Eur J Surg Oncol* 2008; **34**: 890-894
55 **Damin DC**, Tolfo GC, Rosito MA, Spiro BL, Kliemann LM. Sentinel lymph node in patients with rectal cancer invading the anal canal. *Tech Coloproctol* 2010; **14**: 133-139
56 **Keshtgar MR**, Amin A, Taylor I, Ell PJ. The sentinel node in anal carcinoma. *Eur J Surg Oncol* 2001; **27**: 113-114
57 **Péley G**, Farkas E, Sinkovics I, Kovács T, Keresztes S, Orosz Z, Köves I. Inguinal sentinel lymph node biopsy for staging anal cancer. *Scand J Surg* 2002; **91**: 336-338
58 **Perera D**, Pathma-Nathan N, Rabbitt P, Hewett P, Rieger N. Sentinel node biopsy for squamous-cell carcinoma of the anus and anal margin. *Dis Colon Rectum* 2003; **46**: 1027-1029; discussion 1027-1029
59 **Ulmer C**, Bembenek A, Gretschel S, Markwardt J, Koswig S, Slisow W, Schneider U, Schlag PM. Sentinel node biopsy in anal cancer - a promising strategy to individualize therapy. *Onkologie* 2003; **26**: 456-460
60 **Ulmer C**, Bembenek A, Gretschel S, Markwardt J, Koswig S, Schneider U, Schlag PM. Refined staging by sentinel lymph node biopsy to individualize therapy in anal cancer. *Ann Surg Oncol* 2004; **11**: 259S-262S
61 **Damin DC**, Rosito MA, Gus P, Spiro BL, Amaral BB, Meurer L, Cartel A, Schwartsmann G. Sentinel lymph node procedure in patients with epidermoid carcinoma of the anal canal: early experience. *Dis Colon Rectum* 2003; **46**: 1032-1037
62 **Bobin JY**, Gérard JP, Chapet O, Romestaing P, Isaac S. [Lymphatic mapping and inguinal sentinel lymph node biopsy in anal canal cancers to avoid prophylactic inguinal irradiation]. *Cancer Radiother* 2003; **7** Suppl 1: 85s-90s
63 **Mistrangelo M**, Mobiglia A, Mussa B, Bellò M, Pelosi E, Goss M, Bosso MC, Moro F, Sandrucci S. The sentinel node in anal carcinoma. *Tumori* 2002; **88**: S51-S52
64 **Mistrangelo M**, Morino M. Sentinel lymph node biopsy in anal cancer: a review. *Gastroenterol Clin Biol* 2009; **33**: 446-450
65 **Mariani G**, Erba P, Manca G, Villa G, Gipponi M, Boni G, Buffoni F, Suriano S, Castagnola F, Bartolomei M, Strauss HW. Radioguided sentinel lymph node biopsy in patients with malignant cutaneous melanoma: the nuclear medicine

contribution. *J Surg Oncol* 2004; **85**: 141-151
66 **Ali J**, Alireza R, Mostafa M, Naser FM, Bahram M, Ramin S. Comparison between one day and two days protocols for sentinel node mapping of breast cancer patients. *Hell J Nucl Med* 2011; **14**: 313-315
67 **Tsopelas C**, Sutton R. Why certain dyes are useful for localizing the sentinel lymph node. *J Nucl Med* 2002; **43**: 1377-1382
68 **Hindié E**, Groheux D, Brenot-Rossi I, Rubello D, Moretti JL, Espié M. The sentinel node procedure in breast cancer: nuclear medicine as the starting point. *J Nucl Med* 2011; **52**: 405-414
69 **Rabbitt P**, Pathma-Nathan N, Collinson T, Hewett P, Rieger N. Sentinel lymph node biopsy for squamous cell carcinoma of the anal canal. *ANZ J Surg* 2002; **72**: 651-654
70 **de Jong JS**, Beukema JC, van Dam GM, Slart R, Lemstra C, Wiggers T. Limited value of staging squamous cell carcinoma of the anal margin and canal using the sentinel lymph node procedure: a prospective study with long-term follow-up. *Ann Surg Oncol* 2010; **17**: 2656-2662
71 **Sapienza P**, Mingoli A, Nicolanti V, Maldini G, Picchio M, Stipa F. [Massive metachronous inguinal metastases of carcinoma of the anal margin. A clinical case report]. *Minerva Chir* 1992; **47**: 1207-1210

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