Sentinel Node Mapping in Anal Canal Cancer: Systematic Review and Meta-Analysis

Shahrzad Tehranian1, Giorgio Treglia2, David N. Krag3, Vahid Reza Dabbagh Kakhki1, Seyed Rasoul Zakavi1, Ramin Sadeghi1, Mohamed Keshtgar4

INTRODUCTION

Anal carcinoma is an uncommon type of cancer which accounts for 1-2 percent of all gastrointestinal cancers [1]. It is associated with predisposing factors such as infection (especially with Human Papilloma Virus) or sexually transmitted diseases, immune suppression after transplantation or HIV infection, or smoking [2]. Squamous cell (epidermoid) carcinoma (SCC) has the highest prevalence among other histological forms of anal cancer. Tumor site, size and nodal status are considered the most important prognostic factors for treatment and survival of the patients [3, 4].

A multimodality treatment approach including surgery and preoperative chemotherapy and radiation is considered the standard of care [5]. The pathological status of the inguinal lymph nodes is an independent prognostic factor in predicting tumor recurrence and overall survival [6, 7]. Inguinal lymph node management in clinically negative (cN0) patients varies in different centers. Routine inguinal lymph node dissection can cause severe complications and due to high morbidity it is not typically recommended [8]. Close follow up of the patients without any special treatment is another approach. However, up to 20% of patients may have inguinal recurrence during follow up which can be difficult to successfully treat [8, 9]. Bilateral ilioinguinal node irradiation is another option which can result in regional disease control in the majority of patients. Irradiation also causes considerable morbidity and routine irradiation of inguinal area is considered overtreatment.

ABSTRACT

Background & Aims: The pathological condition of inguinal lymph nodes is an independent prognostic factor in predicting tumor recurrence and overall survival in anal canal cancer. Sentinel node mapping is a non-invasive method for the detection of inguinal lymph node involvement in anal cancer. In the current study, we conducted a comprehensive search of literature in this regard and then interpreted the final results in a systematic review and meta-analysis format.

Methods: Medline, SCOPUS, and ISI Web of Knowledge were searched with the following search terms: (anal OR anus) AND sentinel. Outcomes of interest were inguinal detection rate and inguinal recurrence in patients receiving inguinal sparing radiotherapy due to pathologically negative inguinal sentinel nodes (false negative cases).

Results: Overall 16 studies (323 patients) were included in the meta-analysis. Pooled inguinal detection rate was 86.2%: 73.4-93.4%: for studies using both blue dye and radiotracer it was 90.1%[78.7-95.8] and for studies using radiotracer alone it was 72.4% [46.3-88.9]. Pooled sensitivity was 90% [79-97%].

Conclusions: Sentinel node biopsy is a promising method for inguinal lymph node staging in anal cancer. Combined blue dye and radiotracer technique can maximize the inguinal detection rate. Location of the tumor is highly associated with the detection of inguinal sentinel nodes. Despite fairly high pooled sensitivity, no definite conclusion can be made regarding false negative rate of this technique due to low sample size and sub-optimal quality of the included studies. Large multicenter studies with long and consistent follow up are needed to definitely validate this technique in the future.

Key words: anal cancer – sentinel node – inguinal – systematic review – meta-analysis.
for patients without pathological inguinal lymph node involvement [6, 10, 11].

A non-invasive method for accurate detection of inguinal lymph node involvement would be invaluable to identify those patients that may benefit from more aggressive treatments and spare patients without inguinal involvement the unnecessary risks from prophylactic treatments. Sentinel lymph node (SLN) biopsy is a minimally invasive technique used for regional lymph node staging and is currently used for a variety of malignancies [12, 13]. Sentinel lymph node mapping has been applied to anal canal cancer since 2001 [14, 15] and seems to be a promising method for inguinal lymph node staging of this cancer.

In the current systematic review, we conducted a comprehensive electronic database search of literature reporting anal cancer and SLN biopsy and then interpreted the final results in a systematic review and meta-analysis format.

**METHODS**

PRISMA statement was followed for performing the current systematic review [16]. Medline, SCOPUS, and ISI web of knowledge were searched with the following search terms: (anal OR anus) AND sentinel, without any restrictions on language, publication status or publication date. The last search was done on December 2012.

The reference lists of included papers as well as citing articles (using the citation tracking tools of SCOPUS and Google scholar) were examined for additional relevant studies. Duplicate publications were excluded and only the most recent studies were included in the evaluation. The corresponding authors of the primary studies were contacted if further information was required.

The search was performed by two authors independently and all studies evaluating sentinel node mapping for inguinal lymph node staging in anal canal cancer were included in the study. Letter to editors, review articles and articles reporting accuracy of sentinel node mapping in anal melanoma were excluded.

Data extraction was independently performed by two authors to eliminate any possible inaccuracy. Any disagreement was resolved by consensus among authors or by arbitration by a third author.

Quality assessment of retrieved studies was carried out (by two authors independently) based on Oxford Center for Evidence Based Medicine Checklist of diagnostic studies [17].

The following predefined data were obtained from all including articles: authors, publication year, patients characteristics (e.g. age, gender etc), SLN mapping procedure (blue dye, radiotracer or other methods), location of SLNs, duration of follow-up, detection rate, inguinal recurrence rate during follow up.

**Statistical analysis**

A random effects model was applied for pooling detection and false negative rates across studies [18]. Forest plots were used for graphical representation of individual studies and pooled effect sizes. Cochrane Q test was used for the evaluation of heterogeneity (p value less than 0.05 was considered statistically significant). I² index was used for quantifying the heterogeneity across the studies. Funnel plots, Egger’s regression intercept [19], and Duval and Tweedie’s trim and fill method [20] were used for publication bias evaluation. Statistical analyses were done using Comprehensive Meta-analysis (version 2) and MetaDisc [21].

**RESULTS**

Figure 1 shows the PRISMA flowchart of the study. The primary search yielded 180 citations: 150 citations were excluded by title and abstract review. Full texts of the remaining 30 studies were reviewed in depth and finally 16 studies (323 patients in total) were included in the systematic review [14, 15, 22-35]. Three of the included studies were meeting abstracts [14, 30, 33]. Duplicate studies from Italy [36], France [37], Brazil [38], Germany [39], and Australia [40] were not included in the meta-analysis. Tables I and II show the characteristics of the included studies as well as their quality assessments. Fourteen studies had enough information for detection rate pooling and 11 studies had enough information for sensitivity pooling and entered the meta-analysis accordingly.

![Fig. 1. PRISMA flowchart of the study search strategy.](image-url)
Table I. Characteristics of the included studies

<table>
<thead>
<tr>
<th>First author/country and publication year</th>
<th>Patients with at least one detected inguinal sentinel node/total number of patients</th>
<th>Patients with inguinal recurrence/patients with positive sentinel nodes</th>
<th>Technique of sentinel node mapping</th>
<th>Time of radiotracer injection</th>
<th>Location of the tumor</th>
<th>T stage/mean age/female to male</th>
<th>Patients with bilateral drainage/median number of sentinel nodes per patient/patients with palpable inguinal nodes</th>
<th>Complications of sentinel node biopsy</th>
<th>Immuno histochemistry result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keshtgar/UK 2001</td>
<td>1/1</td>
<td>na/0</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>Anal verge</td>
<td>na/49/male</td>
<td>1/2/0</td>
<td>None</td>
<td>Positive</td>
</tr>
<tr>
<td>Vajda/Poland 2001</td>
<td>2/2</td>
<td>na/0</td>
<td>Radiotracer and blue dye</td>
<td>Na</td>
<td>Na/na/na</td>
<td>na/na/na</td>
<td>na/na/na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Yao et al/US 2002</td>
<td>1/1</td>
<td>na/1</td>
<td>Radiotracer and blue dye</td>
<td>Same day of surgery</td>
<td>Na/58/ female</td>
<td>Na/59.5/5 to 3</td>
<td>0/1/0</td>
<td>None</td>
<td>na</td>
</tr>
<tr>
<td>Peley/Hungary 2002</td>
<td>8/8</td>
<td>0/2</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>Na</td>
<td>na/59.5/5 to 3</td>
<td>5/2/1*</td>
<td>None</td>
<td>na</td>
</tr>
<tr>
<td>Perera/Australia 2003</td>
<td>8/12</td>
<td>na/2</td>
<td>Radiotracer and blue dye</td>
<td>On the day of surgery</td>
<td>na</td>
<td>na/59/6 to 6</td>
<td>0/na/1</td>
<td>None</td>
<td>na</td>
</tr>
<tr>
<td>Bobin/France Lion 2003</td>
<td>33/33</td>
<td>0/7</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>All anal canal/no anal verge</td>
<td>T2-T4/na/na</td>
<td>na/na/0</td>
<td>None</td>
<td>na</td>
</tr>
<tr>
<td>Ulmer/Germany Berlin 2003</td>
<td>9/11</td>
<td>0/6</td>
<td>Radiotracer</td>
<td>Day before surgery</td>
<td>Proximal part of anal canal 14, distal part 3</td>
<td>T1 1/T2 6/T3 1/T4 3/62.3/8 to 4</td>
<td>2/na/0</td>
<td>Cutaneous lymphatic fistula in 1</td>
<td>Positive in 1</td>
</tr>
<tr>
<td>Castro/Brazil Rio de Janeiro 2005</td>
<td>2/2</td>
<td>na/0</td>
<td>Radiotracer and blue dye</td>
<td>Same day of surgery</td>
<td>Anal verge</td>
<td>1 and anal canal 1</td>
<td>T2 1; the other patient not mentioned /55/2 to 0</td>
<td>None</td>
<td>na</td>
</tr>
<tr>
<td>Damin/Brazil Porto Alegre 2006</td>
<td>22/22</td>
<td>na/2</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>6 laterally, 16 in midline. All below dentate line</td>
<td>T1 3/T2/na/na</td>
<td>15**/2/0</td>
<td>Seroma in 1</td>
<td>Positive in 1</td>
</tr>
<tr>
<td>Gretschel/Germany Berlin 2008</td>
<td>20/11/40</td>
<td>1/6</td>
<td>Radiotracer</td>
<td>Day before surgery</td>
<td>Anal canal or margin</td>
<td>T1 15/T2 18; T3 5; T4 2/63.5/27 to 13</td>
<td>na/na/0</td>
<td>2 wound infections, 1 lymphatic fistula, 1 haematoma</td>
<td>Positive in 3</td>
</tr>
<tr>
<td>Mariani/France Paris 2008</td>
<td>25/25</td>
<td>2/0</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>Na</td>
<td>T1-3/57/na/na</td>
<td>na/na/0</td>
<td>3 lymphedema</td>
<td>Positive in none</td>
</tr>
<tr>
<td>de Jong/The Netherlands 2010</td>
<td>21/21</td>
<td>2/7</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>Anal canal or margin</td>
<td>T1 2/T2 15/T3 4/na/na</td>
<td>14/2/4</td>
<td>2 wound infection, 2 seroma, 1 lymphedema</td>
<td>na</td>
</tr>
<tr>
<td>Hirche/Germany Berlin 2010</td>
<td>10/12††</td>
<td>0/2</td>
<td>Fluorescent near infrared imaging</td>
<td>Day before surgery</td>
<td>Anal canal or margin</td>
<td>T1 4/T2 5/T3 2/T4 1/58/na</td>
<td>3/1/0</td>
<td>Lymphocele and lymphorrhrea each in 1</td>
<td>Positive in 1</td>
</tr>
<tr>
<td>Francois/France Nice 2010</td>
<td>16††/34</td>
<td>3†††/5</td>
<td>Radiotracer</td>
<td>Day before surgery</td>
<td>Anal canal or margin</td>
<td>T1 1/T2 19/T3 9/T4 1/63.2/6 to 8</td>
<td>na/na/2</td>
<td>None</td>
<td>Na</td>
</tr>
<tr>
<td>De Nardi/Italy Milan 2012</td>
<td>19/23***</td>
<td>0/5***</td>
<td>Radiotracer and blue dye</td>
<td>Day before surgery</td>
<td>Only anal canal not verge</td>
<td>T1 3/T2 9/T3 7/T4 4/na/na</td>
<td>2/na/0</td>
<td>Seroma 1 and lymphatic fistula 1</td>
<td>na</td>
</tr>
</tbody>
</table>

J Gastrointestin Liver Dis, September 2013 Vol. 22 No 3: 321-328
**Table I.** continued

<table>
<thead>
<tr>
<th>First author/country</th>
<th>Year</th>
<th>Radiotracer</th>
<th>Day before or the same day of surgery</th>
<th>Anal canal or margin</th>
<th>T1 7/T2 35/T3 17/T4 4/59/39 to 24</th>
<th>37/4/8</th>
<th>Positive in 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mistrangelo/ Italy Turin 2012</td>
<td>62/63</td>
<td>0/13</td>
<td>na</td>
<td>na</td>
<td>37/4/8</td>
<td>na</td>
<td>1</td>
</tr>
</tbody>
</table>

* The patient had clinically positive inguinal node. Sentinel node mapping was successful on the contralateral groin which was pathologically uninvolved.
** All were in patients with midline tumors. 15 out of 16 patients with midline tumors had bilateral drainage.
† The location of sentinel node in the remaining 4 patients was in the mesorectal area on lymphoscintigraphy imaging. Location of tumor in 3 of these patients was near dentate line.
‡ The location of tumor in the remaining 4 patients was in the mesorectal area on lymphoscintigraphy imaging. Location of tumor in 3 of these patients was near dentate line.
†† The location of tumor was higher in anal canal in patients with inguinal sentinel node detection failure.
§ One patient did not consent to undergo sentinel node mapping.
¶ One inguinal recurrence occurred in a patient who received radiotherapy due to positive sentinel node.
¶¶ One inguinal recurrence occurred in a patient who received radiotherapy due to positive sentinel node.
††† Another inguinal recurrence occurred in a patient with positive sentinel node who received radiotherapy.

---

**DISCUSSION**

In the current systematic review, we searched the available medical literature for the studies on sentinel node mapping in anal carcinoma. Overall inguinal detection rate and sensitivity were fairly high and comparable to other malignancies.

**Inguinal detection rate**

Pooled inguinal detection rate was 86.2% which is fairly high; however the heterogeneity of the included studies was...
high in this regard (I²=73.9%) and this warrants in depth evaluation of the cause of this heterogeneity. Several patient and technique related variables were associated with inguinal detection rate.

**Mapping method**

Although some groups used blue dye as a backup method in cases with radiotracer localization failure on lymphoscintigraphy images [41], this was done to avoid the risk of life threatening complications of blue dyes [42]. Our systematic review showed that studies using combined radiotracer and blue dye method had higher inguinal detection rate compared to those using radiotracer alone. This is in accordance to other malignancies such as breast and urological cancers [12, 13].

The time of radiotracer injection was the day before surgery in most of the studies. The rationale behind this is to allow sufficient time for the radiotracer to migrate into the inguinal nodes [36, 43]. However, several groups [22, 26, 27, 36] reported comparable results with a same day injection technique which is in accordance with reports on sentinel node mapping of breast cancer [43, 44].

Lymphoscintigraphy imaging was done in all studies and seems to be an indispensible part of sentinel node mapping in anal cancer. As reported by Francois et al [33], Gretschel et al [29], and De Nardi et al [34] not all patients have inguinal drainage of the radiotracer and pre-operative imaging would help to select only those patients with visible inguinal SLNs on lymphoscintigraphy for sentinel node biopsy.

Hirche et al used fluorescent dye technique and near infrared imaging and compared the results with conventional combined blue dye/radiotracer technique [32]. They reported high inguinal detection rate by both techniques. In one patient near infrared imaging showed the SLN, despite detection failure using the conventional method. This technique seems promising and needs to be validated more in larger studies.

**Location of the tumor**

The anal canal has an extremely rich lymphatic system which drains into three different lymphatic basins: inguinal, lateral pelvic and mesorectal [7, 36]. The incidence of inguinal drainage increases for anal carcinomas away from the dentate line and closer to the anal verge and the results of our systematic review also support this pattern. Perera et al reported that patients without inguinal lymph node drainage had mesorectal drainage with tumor location high in anal canal above the dentate line [26]. Mari et al and Gretschel et al both showed that the location of tumor was higher in the anal canal in patients with inguinal SLN detection failure [29, 37]. De Nardi et al showed that patients without inguinal lymph node drainage had mesorectal drainage with tumor location high in anal canal above the dentate line [34]. These results show that inguinal
Bilateral versus unilateral inguinal lymph node drainage

The lymphatic system of the anal cancers can drain unilaterally or bilaterally into the inguinal area. This is highly dependent on the location of the tumor. Damion et al showed that tumors located on either side of the anal canal without midline involvement had only unilateral inguinal drainage [28]. Bilateral drainage occurred in various numbers of patients in the included studies; however, only Damion et al reported its association with tumor location. It seems that in tumors affecting midline anal canal, unilateral inguinal lymph node drainage should raise the suspicion of possible inguinal lymph node involvement on the side without drainage [36]. This concept has been applied successfully for other midline tumors such as penile and endometrial cancers [12] and warrants further evaluation in anal cancer in future studies.

False negative rate

The accuracy of sentinel node biopsy for the prediction of inguinal node involvement in anal cancer cannot be assessed directly as none of the included studies performed inguinal lymph node dissection. The false negative cases could be identified only by the follow up of patients who were spared from inguinal radiotherapy due to pathologically negative sentinel node. Based on this definition, our systematic review showed high pooled sensitivity (low false negative rate): 90% [79-97]. However, this result should be interpreted with caution. The number of studies is not high enough and false negative rate based on inguinal recurrence during follow up cannot be highly reliable. Besides, studies conducted by De Nardi et al and Gretschel et al did not use inguinal sparing radiotherapy for all patients with negative SLNs which can underestimate the false negative cases [29, 34].

Patient selection is of importance for decreasing false negative cases as several variables can be associated with false negative results.

Clinical inguinal node involvement and previous surgical manipulation of anal canal

Palpable inguinal lymph nodes are considered as contraindications for sentinel node mapping in anal cancers. These nodes can be due to pathologically involved nodes and may be associated with false negative results [28]. However, none of the included studies substantiate this concept. Mistrangelo et al mentioned that palpable lymph nodes are generally superficial while the inguinal SLN is situated deeply. They included 8 patients with palpable inguinal nodes without any false negative results. However, Mistrangelo et al recommended diagnostic biopsy instead of sentinel node mapping in patients with massive or multiple palpable inguinal nodes [35, 41]. Although prior surgical excision of breast tumors is not considered a contraindication to sentinel node mapping [45], this is not well established for anal cancer. Previous surgical manipulation of an anal tumor can theoretically change the lymphatic drainage pattern and may be associated with false negative results. Gretschel et al reported two detection failures and one false negative result in patients with previous surgical manipulation of the anal cancer [29]. None of the other studies substantiated these results: for example, Mistrangelo et al included five patients with previous surgical manipulation of the anal mass without any problem in SLN mapping [35]. Larger studies are needed to clarify the effect of palpable inguinal nodes and prior surgical manipulation on false negative rate in SLN mapping of anal cancer.

Immunohistochemistry (IHC)

Five studies reported positive sentinel nodes by IHC despite negative H&E examinations [25, 28, 29, 31, 35]. These results show that IHC can increase the sensitivity and may be of value in the SLN mapping of anal cancers.

T stage of the tumor

Among the included studies, only Gretschel et al recommended against SLN mapping in larger anal tumors (T3 and T4). They argued that large tumors have a very high incidence of inguinal lymph node involvement and may lead to false negative sentinel node results [29]. However, published studies thus far do not corroborate this recommendation. As mentioned by Mistrangelo et al, 2 out of 3 of T3/T4 patients do not have inguinal lymph node involvement and these patients can benefit from sentinel node mapping and inguinal sparing radiotherapy [35]. Besides inguinal recurrences in sentinel node negative patients occurred in T1 or T2 patients in de Jong et al and Gretschel et al reports [29, 31]. To date, no study has reported any association between the T stage and false negative results. Further studies with a much larger sample size would be needed to clarify the effect of T stage on the accuracy of sentinel node mapping in anal canal cancer.

Complications

None of the studies reported life threatening or severe complications related to sentinel node mapping in anal cancer. Seroma, lymphatic fistula, lymphocele, hematoma, lymphporrhea, wound infection and lymphedema have all been reported. However, most of the reported complications were self limiting and resolved with conservative management.

Limitations

The major limitation of the current systematic review is the relatively small sample size of the included studies. A limit of 323 patients precludes drawing robust conclusions. Larger prospective studies with consistent design are required to substantiate the feasibility and accuracy of sentinel node mapping in anal cancer.

Quality of the included studies is another major limitation. As mentioned above, no study thus far has reported a false negative rate based on inguinal lymph node dissection results. The reported false negative rates are all based on follow up. Not all studies followed the patients for an extended time and the reported false negative rates may be underestimated.

Publication bias is a major concern in all systematic reviews. We evaluated this bias using funnel plots, Egger’s regression, and trim and fill method. These methods showed that publication bias, if present, could affect the results of our meta-analysis. This is especially true for detection rate pooling.
CONCLUSIONS

Sentinel node biopsy is a promising method for inguinal lymph node staging in anal cancer. Using this method, negative sentinel node patients may spare prophylactic inguinal lymph node irradiation. Combined technique of radiotracer and blue dye technique can maximize the inguinal detection rate. Location of the tumor is highly associated with the detection of inguinal sentinel nodes.

Despite fairly high pooled sensitivity, no definite conclusion can be drawn regarding the false negative rate of this technique in anal cancer due to the small sample size and sub-optimal quality of the included studies. Large multicenter studies with long and consistent follow up are required to definitely validate this technique in the future.


Conflicts of interest: The authors have no conflict of interest to declare.

Acknowledgements: This study is the result of a medical student thesis conducted in Nuclear Medicine Research Center and was supported financially by the Vice Chancellery of Research of Mashhad University of Medical Sciences with the approval number of 910794. The sponsor had no involvement in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

REFERENCES


J Gastrointestin Liver Dis, September 2013 Vol. 22 No 3: 321-328