Controversies in the Management of Metastatic Melanoma to Regional Lymphatic Basins

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The primary management of lymph nodes involved with metastatic melanoma is regional lymphadenectomy. Many controversies of regional lymph node dissection exist including extent and nature of the lymphadenectomy, treatment of lymphatic metastases in unusual locations and the role of adjuvant radiotherapy. Although radical neck dissection has been the gold standard for cervical disease, modified dissections do not seem to compromise regional control in appropriately selected patients. In the axilla, a Level I, II, and III dissection is most commonly performed. Combined superficial and deep groin dissection is justified for clinically palpable disease although management of patients with histologically positive yet clinically non-palpable disease is more controversial. Burden of disease, imaging, patient comorbidity, and Cloquet nodal status must be considered. Many technical variations exist in an attempt to improve morbidity rates secondary to lymphadenectomy. Unfortunately, complication rates are difficult to compare secondary to variable study designs, definitions, and patient populations. Adjuvant radiation therapy appears warranted in patients with high risk of regional recurrence including bulky disease, extracapsular extension or cervical location.


KEY WORDS: melanoma; nodal metastases; lymphadenectomy; radiation therapy

INTRODUCTION

Despite the decline of elective node dissection for melanoma and the rise of the sentinel node biopsy procedure, the surgical treatment of metastatic disease in regional nodes has changed relatively little [1]. For now at least, any patient with a positive lymph node, microscopic or macroscopic, is treated with a regional node dissection. However, surgical technique, morbidity, and outcomes vary widely in the surgical literature. Many controversies surrounding regional node dissection remain, including extent and nature of the dissection, treatment of lymphatic metastases in unusual locations, and the role of regional radiotherapy. The following review will concentrate on these management controversies of metastatic melanoma to regional lymphatic basins.

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NECK DISSECTION

Role

Approximately 10–25% of cutaneous melanomas arise within the head and neck region [2]. Metastatic melanoma to regional cervical nodes is diagnosed by clinical presentation, sentinel lymph node biopsy, or historically, elective lymphadenectomy [2–4]. Neck dissection is the best method available to control regional disease in this situation. However, the extent of
lymphadenectomy is controversial and evolving. A radical neck dissection (RND) including removal of Level I–IV lymph nodes as well as the sternomastoid muscle, internal jugular vein, and spinal accessory nerve has classically been considered the gold standard for treating neck regional disease [4–6]. A large experience by O’Brien et al. includes 397 neck dissections for malignant melanoma [4]. One hundred fifty-two dissections were considered therapeutic for clinically palpable lymph nodes, 234 were elective dissections prior to implementation of sentinel node biopsy, and 11 were for unknown indication (therapeutic vs. elective). One hundred eighty-eight patients had RND (47%) and the rest had a modified radical neck dissection (MRND) or an even more selective procedure. Thirty-nine percent of dissections had positive lymph nodes although only 7% were positive after elective lymphadenectomy. Overall, 94 of 397 (24%) patients developed regional recurrence. This rose to 28% if lymph nodes contained metastatic disease. Recurrence correlated with the extent of disease. Of those patients with palpable disease, 34% recurred in the neck. Of those whose nodal metastases were undetected until removed by elective resection, only 9% recurred in the neck. The authors noted changes in approach over time with increased preservation of the spinal accessory nerve even when clinically palpable nodes are present, more use of MRND or selective neck dissection in elective lymphadenectomy, and increased use of adjuvant radiation [7].

In a series of 70 patients from the Netherlands, Jonk et al. reported 64 patients undergoing RND for therapeutic intent had a regional recurrence rate of 23% [9]. These authors reinforce that there is no current consensus on the appropriate extent of cervical lymph node surgery. Unfortunately, many patients will still develop regional recurrence or distant metastases despite RND (Table I) [4,8,9]. Furthermore, a RND can be associated with significant morbidity. MRND or functional neck dissection includes preservation of any or all of the sternomastoid muscle, internal jugular vein, and spinal accessory nerve [10,11]. This procedure has been advocated even in the setting of clinically palpable disease [9]. In a study of 58 patients, Turkula and Woods describe their patients’ experience after RND (34), MRND (7), and selective neck dissection (17) [9]. All patients had node positive disease and regional recurrence rates were 32%, 0%, and 29% in the three groups, respectively. Survival was also similar among groups. Although this was a small study without multivariate analysis, the authors suggest there is no appreciable difference in the risk of regional recurrence or death based on type or extent of lymphadenectomy. Similar results have been reported by others [12].

### TABLE I. Regional Recurrence Rate Following Cervical Lymphadenectomy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of patients</th>
<th>Regional recurrence rate (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkula and Woods [9]</td>
<td>1984</td>
<td>Total = 58</td>
<td>28</td>
<td>No difference in survival between neck dissections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RND = 34</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRND = 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SND = 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byers [14]</td>
<td>1986</td>
<td>181</td>
<td>16</td>
<td>MRND used uniformly</td>
</tr>
<tr>
<td>O’Brien et al. [4]</td>
<td>1992</td>
<td>Total = 397</td>
<td>24</td>
<td>188 had RND; remainder had MRND or more selective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Therapeutic = 152</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elective = 234</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van de Vrie et al. [12]</td>
<td>1993</td>
<td>23</td>
<td>43</td>
<td>RT employed in 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonk et al. [8]</td>
<td>1998</td>
<td>70</td>
<td>23</td>
<td>64 patients treated by RND</td>
</tr>
<tr>
<td>Shen et al. [75]</td>
<td>2000</td>
<td>217</td>
<td>14</td>
<td>Higher recurrence rate with ENE</td>
</tr>
<tr>
<td>Neck dissection plus adjuvant radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang et al. [16]</td>
<td>1994</td>
<td>95</td>
<td>3</td>
<td>Compared to 18.7% in 107 non-irradiated necks</td>
</tr>
<tr>
<td>O’Brien et al. [74]</td>
<td>1997</td>
<td>45</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Ballo et al. [77]</td>
<td>2003</td>
<td>160</td>
<td>6</td>
<td>93% had palpable disease</td>
</tr>
</tbody>
</table>

MRND, modified radical neck dissection; RND, radical neck dissection; SND, selective neck dissection; ENE, extranodal extension.
Byers suggests that a MRND is an appropriate surgical option since lymph nodes containing melanoma uncommonly invade contiguous structures [13,14]. One hundred eighty-one patients were treated by MRND with a 16% overall regional failure rate in this series.

An even more selective approach has been described [15]. O’Brien et al. summarized selective nodal dissections when a patient presents with clinically palpable disease: Level I–IV dissection for clinical disease at Level I and primary of the face and Level II–V dissection for clinical disease at Level IV or V and primary of the posterior scalp or lower neck. Furthermore, more selective operations are described in the elective situation. In their most recent review of 182 neck dissections, 75 were for clinically palpable disease or with therapeutic intent. Thirty-two underwent RND, 15 underwent MRND, and 28 underwent selective procedures. Recurrence rates of 14%, 0%, and 23% were reported for the three operations at a minimum of 2-year follow-up. More patients in the RND group had adjuvant radiation therapy because of high-risk features. Clinical metastatic melanoma was well controlled in selected patients by MRND, although selective dissection may not have been as effective. Reasonable local control rates are also described following “limited” neck dissections plus adjuvant radiation therapy [16]. The role of adjuvant radiation therapy for dissected lymphatic basins is discussed later in this review.

In summary, evidence suggests that: (1) recurrence rates for palpable disease are high even with radical surgery, (2) for microscopic disease, modified neck dissection preserving sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve may be adequate.

Role of Parotidectomy

Patients with clinically palpable metastatic melanoma of the parotid area have a high risk of occult involvement in the neck ranging from 28% to 58% [17–19]. Most authors include a neck dissection whenever parotid disease is present. However, the need to treat the parotid for clinical disease of the neck is more controversial. Shah et al. described 111 patients undergoing RND with 57 undergoing RND plus superficial parotidectomy [5]. Thirty-three of 57 patients had melanoma involving the preauricular nodes, intraparotid nodes, or parotid parenchyma. Patients at high risk of parotid involvement included those with primary melanomas of the ear, face, and anterior scalp. Interestingly, 25% of head and neck sentinel lymph node biopsies were in the periparotid area in the Sunbelt Melanoma Trial [3]. A series of 107 parotidectomies (25 therapeutic, 82 elective) noted 27 with positive histology. Although all 25 patients with clinically palpable disease had positive histology, only 2 of 82 elective procedures were positive on final pathology. A European series of 46 parotidectomies combined with therapeutic neck dissection found 5 of 16 (31%) clinically uninvolved parotid glands had occult disease [20]. The authors found patients with primary melanoma of the zygomatic, temporal, or frontal areas at higher risk of parotid involvement.

In summary, superficial parotidectomy is performed for clinically palpable disease in this region and should be combined with a neck dissection (MRND or selective I–IV) due to the relatively high risk of occult cervical metastases. However, in patients with involved cervical nodes without clinical disease of the parotid, many authors selectively perform superficial parotidectomy. For primaries of the ear, face, and anterior scalp, the regional nodal basins include parotid and neck. Palpable disease in either area necessitates complete dissection of both. In patients with primaries on the posterior scalp or neck, parotidectomy may be omitted although evidence is sparse.

AXILLARY DISSECTION

Extent of Dissection

The surgical removal of axillary lymph nodes for patients with malignant melanoma is for cure, local control, and to a lesser extent, staging [21]. Most authors concur that the extent of dissection should include Level I, II, and III lymph nodes, although some include Level III only when suspicious nodes are present [22–24]. With this approach, local recurrence is reported in 3–17% of patients (Table II) [21,25–27]. Furthermore, Chan et al., in an analysis of a large database of melanoma patients, demonstrated that overall 5-year survival is improved when comparing patients with the highest quartile of number of nodes excised at surgery to the lowest quartile (a measure of completeness of surgical node removal) [28]. Some authors recommend an even more extensive dissection including removal of the supra-axillary fat pad having found that approximately 14% of patients will have involved nodes in this area [21,26]. However, the supra-axillary fat pad lies directly over the brachial plexus with the potential for increased complications without careful dissection. Also, completely skeletonizing the axillary vein above and below should theoretically increase the rate of lymphedema. In practice, no increase in complications was noted by Karakousis et al. with this approach although there was no concurrent comparison group [26]. Preservation of the long thoracic and thoracodorsal nerve is considered routine although the intercostobrachial nerves are often resected in a therapeutic nodal dissection [22,23].
There is no consensus of the optimal surgical technique for axillary dissection for melanoma patients. Two incisions are most commonly used: a transverse incision extending from the edge of pectoralis major to the border of latissimus dorsi or an extended incision following the contour of the pectoralis major into the axillary apex and then down the medial arm [25–27,29]. Optimal exposure may or may not require transection of pectoralis minor although some authors suggest routine en bloc resection of the pectoralis minor with therapeutic axillary dissection [23,26,30,31]. Most surgeons selectively transect the pectoralis minor for improved exposure or when the muscle is involved with tumor [25,26].

Lawton et al. advocated preservation of pectoralis, interpectoral, and latissimus dorsi fascia during axillary dissection in an attempt to decrease lymphedema rates [27]. A review of 116 fascia-preserving axillary dissections (elective and therapeutic) performed by a single surgeon revealed an 8% transient lymphedema rate and 5% long-term lymphedema rate. Lymphedema, recorded prospectively, was defined as an increase of more than 2 cm in diameter in the affected extremity compared to the unaffected extremity. The group experienced only two local recurrences (3%); none related to the muscular fascia and all outside the dissection borders. The authors suggest that preservation of overlying muscular fascia results in less operative-field fibrosis, preservation of fascial lymphatics, and improved lymphedema rates without compromise of local control. As noted by Lawton et al., comparison of results among studies is often difficult. Surgical techniques, patient characteristics, length of follow-up, and definitions of lymphedema are highly variable among studies. Nonetheless, a long-term lymphedema rate of 5% is comparable to a range of 1–12% noted by other publications [23,26,29,32–35].

Regardless of the technical nuances of axillary dissection chosen by the operator, Kretschmer and Preusser show quite definitively that the introduction of a standardized axillary lymphadenectomy will improve local control [25]. Two groups of patients were analyzed at their institution: 57 before (1983–1988) and 63 after (1989–1994) the introduction of a standardized axillary dissection. All consecutive procedures were performed by experienced surgeons and patients in the two groups appear balanced for other prognostic features. The standard technique included the extended skin incision, dissection of all three levels of the axilla, removal of fascia of the pectoral muscles, interpectoral space and lateral chest wall, routine removal of the supra-axillary fat pad, and selective division of pectoralis minor if involved by tumor. Axillary recurrence rates improved from 36.8% prior to and 9.5% after the introduction of the standardized technique. No patient had adjuvant irradiation. Overall survival was no different between groups and differences in complications other than local recurrence were not commented on in this study.

### Technical Variables

**TABLE II. Regional Recurrence Rate Following Lymphadenectomy**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of patients</th>
<th>Regional recurrence rate (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series combining all lymphatic basins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calbro et al. [69]</td>
<td>1989</td>
<td>1,001</td>
<td>16</td>
<td>One node positive—9% recurrence</td>
</tr>
<tr>
<td>Gadd and Coit [70]</td>
<td>1992</td>
<td>403</td>
<td>18</td>
<td>Axillary and groin lymphadenectomies</td>
</tr>
<tr>
<td>Lee et al. [72]</td>
<td>2000</td>
<td>338</td>
<td>30</td>
<td>ENE had 63% risk of recurrence</td>
</tr>
<tr>
<td>Pidhorecky et al. [71]</td>
<td>2001</td>
<td>Total = 338</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elective = 85</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Therapeutic = 253</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Axillary dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karakousis et al. [26]</td>
<td>1990</td>
<td>66</td>
<td>17</td>
<td>Among those with histologically involved nodes</td>
</tr>
<tr>
<td>Kretschmer and Preusser [25]</td>
<td>2001</td>
<td>63</td>
<td>9.5</td>
<td>Compared to 37% recurrence prior to standardized axillary dissection</td>
</tr>
<tr>
<td>Lawton et al. [27]</td>
<td>2002</td>
<td>119</td>
<td>3</td>
<td>Includes 65% node negative dissections</td>
</tr>
<tr>
<td>Groin dissection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singletary and Shallenberger [41]</td>
<td>1992</td>
<td>264</td>
<td>15</td>
<td>23% recurrence with superficial dissection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9% recurrence with combined dissection</td>
</tr>
<tr>
<td>Hughes et al. [37]</td>
<td>2000</td>
<td>132</td>
<td>5</td>
<td>All patients had clinically palpable nodal disease</td>
</tr>
<tr>
<td>Kretschmer et al. [38]</td>
<td>2001</td>
<td>104</td>
<td>34</td>
<td>All patients had clinically palpable nodal disease</td>
</tr>
<tr>
<td>Lawton et al. [27]</td>
<td>2002</td>
<td>93</td>
<td>2</td>
<td>Includes 59% node negative dissections</td>
</tr>
</tbody>
</table>

ENE, extranodal extension.
An area of considerable uncertainty is the appropriate operative management of patients with metastatic melanoma involving the groin. The most controversial area is the choice between a superficial inguinal lymphadenectomy alone or the routine addition of deep iliac and obturator lymphadenectomy [23,24,36–39]. The arguments for either option involve potential differences in overall survival, local control rates, and significant morbidity. Clearly, the presentation of positive superficial groin lymph nodes may influence this decision. Clinically palpable disease, histologically positive disease that is non-palpable, and exclusively micrometastatic disease have different risks of pelvic nodal involvement.

Few studies deal exclusively with patients presenting with clinically palpable disease [24,37,38]. A retrospective review by Hughes et al. describes 132 patients presenting in this fashion [37]. The extent of lymphadenectomy was determined by clinical suspicion of involved pelvic nodes, patient morbidity and performance status, preoperative CT scan, and Cloquet node. Seventy-two patients had both a superficial and deep dissection and 60 had only a superficial dissection. Forty percent of patients undergoing combined superficial and deep dissection had positive deep pelvic nodes. There was no significant difference in early morbidity or postoperative mortality rates between the two groups, although there was a trend towards increased lymphedema rates after deep dissection (24%) when compared to superficial dissection alone (13%). An excellent review notes similar non-statistical differences in lymphedema rates, although sample sizes may be insufficient to detect a difference in many series [37,40]. There was no overall survival rate difference between groups in the study by Hughes et al.; similar to other reports [41]. However, 7 of 60 patients treated with superficial lymphadenectomy recurred compared to only 1 of 72 patients following combined superficial and deep pelvic lymphadenectomy. The authors concluded that superficial and deep groin lymphadenectomy provided additional prognostic information and improved regional recurrence rates without increased morbidity. However, there was no overall impact on survival.

Another retrospective review by Kretschmer et al. [38] describes 104 consecutive patients presenting with clinically palpable metastatic groin nodes. Sixty-nine underwent combined superficial and deep groin dissection and the remaining thirty-five underwent only superficial dissection. Superficial groin lymphadenectomy alone was reserved for elderly patients with cardiopulmonary risk factors and without evidence of deep nodal involvement. Twenty-four patients (34.8%) undergoing deep groin dissection had positive pelvic nodes; similar to other reports [24,37,39]. Not surprisingly, there was a survival difference comparing those with only positive superficial groin nodes (30-month median survival) compared to those with positive superficial and deep nodes (12-month median survival). Three- and 5-year survival of those with positive deep lymph nodes was 25% and 6.2% respectively. Despite this finding, extent of lymph node dissection did not have an effect on overall survival in multivariate analysis. Although 34% of patients had a local recurrence, there was no statistically significant difference between the two operations. Comparison of relative morbidity for the two operations was not reported. The authors recommend deep dissection for adequate staging and because a proportion of those with positive deep nodes will have reasonable 3- and 5-year survival. However, no disadvantage of an exclusive superficial groin nodal dissection was demonstrated in selected patients with higher general morbidity.

What is the prognosis of patients with positive deep pelvic lymph nodes? In a heterogeneous population of elective and therapeutic lymph node dissections, many centers report 5-year survival rates up to 20–35% after surgical dissection of positive deep pelvic nodes [39,40,42–45]. In contrast, some series have no long-term survivors [41,46]. Clearly, increasing burden of disease or number of involved nodes predicts a worse outcome [33,44].

In summary, although there is no definitive statistical difference in overall survival and a possible yet unproven difference in overall morbidity, a combined deep and superficial lymphadenectomy appears prudent considering approximately 30–40% of patients with clinically involved groins will have positive deep pelvic nodes [24,37,38,40]. Such patients do have the potential for long-term survival [39,40,42–45]. Furthermore, a policy of non-treatment of pelvic nodes may be associated with a higher overall recurrence rate [37] (Table II).

Unfortunately, neither randomized controlled trials nor prospective cohort trials exist on the topic of superficial against combined lymphadenectomy. Most studies combine patients with elective, therapeutic, and palliative dissections. Although deep nodal dissection is justified for those with palpable lymphatic disease, patients with non-palpable disease are a separate group. A review by Hughes and Thomas attempts to provide assistance in selecting patients most likely to benefit from the addition of deep pelvic lymphadenectomy in this situation [40]. Patients with positive superficial lymph nodes at time of elective lymphadenectomy have a 9–31% risk of harboring deep nodal metastases (mean 16%) [40,47,48]. Increasing number of positive superficial nodes may further predict the pelvic lymph node status [37,39,40,48].
noted a 32% risk of metastatic pelvic lymph nodes when one to three superficial nodes were involved against a 67% risk if more than three superficial nodes were positive [39]. Similarly, a study of 72 patients with combined superficial and deep dissections noted a 17% and 51% risk of positive deep nodes when one superficial node or greater than one superficial node was involved respectively [37].

Preoperative CT scanning is routinely performed in many centers to assess possible involvement of deep pelvic nodes. Among ninety-four asymptomatic patients with superficial groin adenopathy, pelvic CT scans were positive for deep or para-aortic nodes in seven [49]. Unfortunately, true positive scans are infrequent and often exceeded by false negative results [49,50]. Although CT scans may detect extensive pelvic nodal involvement, the current sensitivity appears poor with a substantial risk of understaging. Positron emission tomography (PET) scanning did change management in 15% of 95 clinically Stage III melanoma patients in one series [51]. Seven patients had increased PET activity in iliac lymph nodes although only three of these had histopathologically confirmed metastatic melanoma following deep dissection.

The value of Cloquet node in predicting pelvic nodal status is debatable. Cloquet node is defined as the highest deep inguinal node in the femoral canal [52]. In a study where 68 patients had Cloquet node evaluated, Shen et al. described a 67% risk of pelvic node involvement when Cloquet node was positive [52]. Pelvic nodes were negative in 77% if Cloquet node was similarly negative. Immunohistochemical analysis with S-100 and HMB45 increased the sensitivity of Cloquet node in predicting pelvic node involvement to 82% in a small subset of patients. A larger study of 194 patients from the Netherlands Cancer Institute found an overall 54% sensitivity, 90% specificity, 69% positive predictive value, and 82% negative predictive value for Cloquet node. Immunohistochemical analysis for HMB45 and S-100 was employed in approximately 25% of the group. Overall, the value of Cloquet node is quite variable in the literature with sensitivities ranging from 44% to 90% [48,52,53]. In summary, surgeons should use all predictive information available when assessing patients with histologically positive yet non-palpable disease—number of involved superficial nodes, preoperative imaging, and Cloquet node—as well as patient comorbidity when considering selective dissection of pelvic nodes.

In the current era of sentinel node procedures, approximately 15–25% of those who are sentinel node positive will have further positive lymph nodes [54,55]. The proportion of patients with positive deep pelvic nodes after only one positive sentinel node will be small. More information regarding the usefulness of therapeutic lymphadenectomy in these situations will be determined from the Sunbelt Melanoma Trial, discussed in another chapter of this issue [56].

### Technical Variables

Not surprisingly, technical issues are also debated in groin lymphadenectomy. The options for skin incision include: an oblique or sigmoid shaped incision from just medial to the anterior superior iliac spine to the inferior margin of the femoral triangle, paired oblique incisions (above and below the inguinal crease), or a oblique/transverse incision above the crease with a longitudinal incision below and a skin bridge between [22,27,57]. Proponents of the oblique/sigmoid incision cite optimal exposure and less subcutaneous lymphatic disruption as advantages of this incision [22]. In contrast, oblique/transverse or a combination of incisions are primarily employed to avoid an incision in the inguinal crease with the goal of decreasing wound complications [27]. A transverse incision will disrupt more subcutaneous lymphatics although whether this leads to an increase in clinically relevant lymphedema rates is unknown [27].

The most commonly described technical details of a radical groin lymphadenectomy include thin (2–3 mm) skin flaps, removal of the saphenous vein, incontinuity dissection with division of the inguinal ligament for combined superficial and deep lymphadenectomy, a sartorius transposition flap for coverage of the femoral artery, and trimming of skin edges at time of closure [22]. Morbidity is significant: 5–15% wound infection rates, 2–8% risk of skin edge necrosis, and 21–40% risk of lymphedema [33,36,47,58].

When performing a combined procedure (superficial and deep lymphadenectomy), options include an incontinuity dissection by dividing the inguinal ligament or an abdominal wall incision above and parallel to the inguinal ligament to expose the retroperitoneum [27,36,42]. Proposed advantages of dividing the ligament include optimal exposure and the avoidance of splitting the nodal specimen which theoretically could lead to wound contamination and local recurrence [36]. The main disadvantage is possible long-term weakness of the abdominal wall, although this has been reported infrequently.

Pearlman et al. discussed the modified groin lymphadenectomy and its possible utility in improving lymphedema rates [57]. The technique was modified from an initially described procedure for penile cancer [59]. Saphenous vein is preserved and the sartorius flap for coverage of the femoral artery, and trimming of skin edges at time of closure [22]. Morbidity is significant: 5–15% wound infection rates, 2–8% risk of skin edge necrosis, and 21–40% risk of lymphedema [33,36,47,58].

When performing a combined procedure (superficial and deep lymphadenectomy), options include an incontinuity dissection by dividing the inguinal ligament or an abdominal wall incision above and parallel to the inguinal ligament to expose the retroperitoneum [27,36,42]. Proposed advantages of dividing the ligament include optimal exposure and the avoidance of splitting the nodal specimen which theoretically could lead to wound contamination and local recurrence [36]. The main disadvantage is possible long-term weakness of the abdominal wall, although this has been reported infrequently.

Pearlman et al. discussed the modified groin lymphadenectomy and its possible utility in improving lymphedema rates [57]. The technique was modified from an initially described procedure for penile cancer [59]. Saphenous vein is preserved and the sartorius flap for vessel coverage is avoided in this procedure designed to reduce lymphedema rates [57]. In a small series of 19 patients, none developed postoperative lymphedema as defined by a difference in circumference of 2 cm or more when comparing the operated and non-operated leg.
In addition, a thicker skin flap raised at the level of Scarpa’s fascia was employed in this series. The advantage of thicker flaps is the minimal risk of metastatic melanoma in lymphatics superficial to Scarpa’s fascia and that thicker flaps may improve rates of necrosis or slough [27,57]. It is especially advocated when the sartorius flap is not used for vessel coverage [27,57]. Despite thicker flaps, 26% of patients in the series by Pealman et al. had partial wound necrosis or infection [57]. They did not comment on whether the femoral artery was exposed in any case. Lawton et al. noted a 30% wound infection rate and 4% necrosis rate in their experience with thicker skin flaps avoiding the inguinal crease [27].

Finally, Lawton et al. advocated fascia preserving groin lymphadenectomy, similar to their experience with axillary dissection [27]. In 93 consecutive ilioinguino-femoral lymphadenectomies, transient and permanent lymphedema rates were 48% and 14%. Lymphedema was defined by limb circumference differences of greater than 2 cm. There was no compromise in local control with a 2% local recurrence rate.

Despite numerous technical options, each with strong advocates, it is difficult to compare different procedures because of different study designs, variable definitions for complications, and a heterogeneous patient population. It is doubtful whether a standardized groin lymphadenectomy will be accepted until a multi-center, prospective trial with well-defined measures of complications is performed.

UNUSUAL SITES OF METASTASES

Lymph node metastases may occur outside usual lymphatic basins. Lymphoscintigraphy identifies sentinel nodes in unusual locations in 3.3–7.2% [30,60,61]. Furthermore, these aberrant or interval lymph nodes have a similar rate of microscopic disease as nodes from usual lymphatic basins and may be the only site of metastases. Interval nodes lie along the course of lymphatic drainage between a primary melanoma and a recognized nodal basin [30]. Potential sites of interval nodes or unusual nodal basins include occipital, supraclavicular, epitrochlear, triangular intermuscular space, popliteal, subcutaneous, intramuscular, internal mammary, mediastinal, or retroperitoneal locations [30,60–65]. Most authors retrieve sentinel nodes in unusual sites if significant morbidity can be avoided. Furthermore, therapeutic lymphadenectomies have been described to treat metastases in many less common nodal sites [22,62,66]. What is the appropriate therapy of the usual regional lymphatic basin when positive interval nodes are found in unusual sites? For example, should a groin lymphadenectomy be performed for positive disease in the popliteal space?

Data are scarce in the literature concerning this topic. Some authors suggest treating the regional nodal basin only if there is a positive sentinel node in that basin [61,62]. A possible exception to consider is when clinically palpable disease presents in the unusual basin. Hunt et al. described 10 patients who had therapeutic epitrochlear lymphadenectomy for clinically evident disease [63]. Six patients underwent simultaneous axillary lymphadenectomy and three of these had occult metastatic melanoma. Interestingly, lymphatic mapping and sentinel node biopsy have recently been applied quite accurately after local or in-transit skin recurrence [67,68]. In a series of 30 such patients, 47% had positive sentinel nodes in a predictable regional basin [67]. Only patients with positive sentinel lymph nodes were considered for therapeutic lymphadenectomy. It seems likely that the rate of metastatic disease in the more proximal nodal basin is related to the tumor burden in the interval nodal basin—alogous to either parotid and neck nodes or superficial and deep inguinal nodes.

ROLE OF ADJUVANT RADIOTHERAPY

A considerable proportion of patients will recur within the nodal dissection field after surgical management [69,70]. In a large study of 1,001 Stage III patients from M. D. Anderson Cancer Center, an overall risk of nodal recurrence following surgery was 16% [69]. Similarly, an 18% recurrence rate was determined among 403 patients after axillary or inguinal lymphadenectomy in another large series [70]. Furthermore, many studies have identified high-risk features resulting in regional recurrence rates of 15–60% [7,69,71–75] (Tables I and II). Regional recurrence is significantly associated with an increasing number of positive lymph nodes and extracapsular extension of melanoma [69,71,72]. Calabro et al. noted a 9% risk of recurrence following lymphadenectomy with one positive lymph node against a 15–33% risk correlated to increasing number of positive nodes [69]. Lee et al. found extracapsular extension to be a significant predictor of nodal recurrence on multivariate analysis; similar to other series [71,72]. Furthermore, Lee et al. found metastatic lymph node size larger than 6 cm, 3–6 cm, and <3 cm was associated with a 80%, 42%, and 24% risk of recurrence, respectively [72]. Not surprisingly, recurrence rates are higher after therapeutic compared to elective dissections [71,72]. The neck appears to be at more risk of recurrence compared to other nodal basins in most retrospective or prospective series [7,69,72,76]. A large experience of 397 neck dissections for primary melanoma of the head and neck included 39% with involved cervical nodes [7]. Overall, 24% of patients had a nodal bed recurrence; 34% versus 9% for therapeutic and elective lymphadenectomy,
respectively. Finally, most authors consider patients who recur regionally after lymphadenectomy to be at significant risk for further recurrence [77,78].

Due to unacceptable recurrence rates in some high-risk groups, adjuvant radiotherapy has been explored in an effort to improve locoregional control. Only one randomized trial has been published on the topic of adjuvant radiation therapy after lymphadenectomy [79]. Fifty-six patients underwent lymphadenectomy alone [28] or regional radiation therapy following lymphadenectomy [26]. No significant overall or disease-free survival difference was determined. Recurrence within the lymph node basin was not specifically examined.

Despite an early reputation of being relatively radioresistant, melanoma does have significant response rates to radiation therapy [78,80–82]. Adjuvant radiation therapy post-lymphadenectomy has been employed in several series, either in large doses per fraction (hypofractionation) or in more traditional radiation schedules [16,74,77,78,83–86]. Reports of adjuvant radiation after neck dissection from M. D. Anderson Cancer Center are quite promising [16,77]. A prospective study utilizing adjuvant radiation therapy with five fractions of 6 Gy each included 95 high-risk patients after limited neck lymphadenectomy. After a median follow-up of 35 months, only three patients had nodal recurrence. This was an improved local control rate compared to historical controls and acute tolerance to radiation therapy was felt to be excellent. A further trial of 160 high-risk patients achieved a 91% locoregional control rate with adjuvant radiation therapy following either radical, comprehensive, or selective neck lymphadenectomy [77]. Studies from Australia are also encouraging [74]. A large non-randomized trial of 152 neck lymphadenectomies compared surgery alone (107 patients) to surgery plus adjuvant radiation therapy (45) [74]. Despite higher risk features in the irradiated group, the locoregional recurrence rate was 6.5% in the irradiated group compared to 18.7% in the surgery alone group. Shen et al. advocated a selective approach to adjuvant radiation therapy. Regional recurrence after neck dissection alone was 14% in their series of 217 patients [75]. However, patients with extranodal extension had a much higher recurrence rate of 31%.

Adjuvant radiation therapy has also been applied to axillary and inguinal lymphatic basins [82,84–87] (Table II). A recent trial reported 89 consecutive patients who had adjuvant radiation therapy following axillary dissection [84]. All patients except two had high-risk features for recurrence. At median follow-up of 63 months, 5-year actuarial axillary control was 87%. However, a high lymphedema rate of 29% was reported—although nearly half were transient or asymptomatic. A smaller series of 42 patients (21 neck, 12 axilla, 9 groin) noted a 22% nodal recurrence rate using traditional radiation schedules (median 50 Gy, 2 Gy per fraction) [82]. Eighty-six percent of patients had high-risk features including multiple positive nodes, extracapsular extension, or recurrent nodal disease. Finally, a trial of adjuvant radiation following lymphadenectomy in 139 patients (55% neck, 34% axilla, 8% groin) had an 11% local recurrence rate [87]. In summary, 5-year locoregional control rates appear to range from 78% to 93% with adjuvant radiation therapy; all series include a majority of high-risk patients [16,73,74,77,78,82,84,86–88].

A recent report suggests elective regional radiotherapy after wide local excision of a head and neck primary melanoma maintains regional control without cervical lymphadenectomy [89]. One hundred fifty-seven Stage I or II head and neck melanoma patients (median 2.4-mm thick) without evidence of clinically involved nodes were treated with adjuvant regional radiotherapy alone. It was estimated that 33–40 patients should have nodal disease based on Breslow thickness of the primary tumor but only 15 of the group (11%) had a regional recurrence. At a median follow-up time of 68 months (range 7–185), the regional control rate was 89%. As noted, no patient had a lymphadenectomy performed or a sentinel node biopsy. Radiotherapy with a median dose of 30 Gy was delivered to the ipsilateral neck and supraclavicular fossa. Approximately 6% of patients developed symptomatic Grade 2 or 3 treatment-related complications. The authors of this study suggest therapeutic irradiation may be an alternative to completion lymphadenectomy in patients with a positive sentinel node biopsy. This may be particularly relevant in patients with comorbidity that precludes dissection, patients who refuse surgery, and patients with only positive sentinel node where further disease within the regional basin is likely microscopic. The authors conclude that a randomized trial comparing regional radiation against completion lymphadenectomy is justified.

Despite apparently improved locoregional control among high-risk patients, adjuvant radiation following lymphadenectomy is still controversial [78,90]. First, only a proportion of high-risk patients will benefit since many will develop distant metastases and have an overall poor prognosis [91]. Second, most published series have a paucity of data regarding long-term toxicity—especially rates of lymphedema. As noted, Ballo et al. described a 29% risk of lymphedema following adjuvant axillary radiation although approximately half of the cases were transient or asymptomatic [84]. Similarly, Stevens et al. noted a 58% risk of lymphedema following adjuvant axillary radiation [87]. Two of three long-term survivors developed significant lymphedema after inguinal irradiation. Adjuvant inguinal irradiation has been recommended less often because of this concern [78,87].
In fairness, lymphedema has been difficult to estimate even in surgical trials because of different study designs, various definitions of lymphedema, and different measurement methods. Perhaps most importantly, adjuvant radiation to lymphatic basins is still controversial because of a lack of phase III trial data [90].

**SUMMARY**

The appropriate extent of lymphadenectomy is controversial in all lymphatic basins that harbor metastatic malignant melanoma. Although radical neck dissection has been the gold standard for cervical disease, modified radical node dissection or a more selective nodal dissection is becoming more common. With careful patient selection, regional control does not appear to be compromised. In the axilla, Level I, II, and III dissection is most commonly performed although some advocate less extensive procedures. Combined superficial and deep groin lymphadenectomy is justified for clinically palpable involvement. Management of patients with histologically positive yet clinical non-palpable disease is more controversial. Extent of nodal involvement, imaging, patient co-morbidity, and possibly Cloquet node status should be considered before performing superficial dissection without deep dissection. Numerous technical variations exist in an attempt to improve morbidity rates following lymphadenectomy. It is difficult to compare significant complications between studies because of different study designs, variable definitions for complications, and a heterogeneous patient population. It is doubtful whether a standardized technique of lymphadenectomy will be accepted until a multi-center, prospective trial with well-defined end-points is performed.

A small subset of patients will have metastatic melanoma in interval nodes or unusual lymphatic basins. Dissection of concurrent regional lymphatic basins should be performed selectively based on tumor burden and location.

Finally, adjuvant radiation therapy does seem warranted in patients with high risk for recurrence. Ideally, a sufficiently powered randomized controlled trial will help confirm or discount its utility.

**REFERENCES**

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