Indications for Adjuvant (Chemo) Radiotherapy in Vulvar Cancer with Groin Lymph Node Metastases

Jacobus van der Velden*, Ming Tjong
Amsterdam UMC, location University of Amsterdam, Gynecologic Oncology, Meibergdreef 9, Amsterdam, the Netherlands

Abstract

Guidelines recommend adjuvant treatment when positive lymph nodes are found after surgical treatment for squamous cell cancer of the vulva except for cases with a single occult intranodal metastasis. Recent studies questioned these recommendations and showed benefit of adjuvant radiotherapy for all patients with positive nodes irrespective of number of nodes. However, these studies did not take into account important nodal characteristics, such as clinical node status, extranodal spread or size of the metastasis. When these variables are taken into account, adjuvant radiotherapy does not seem to result in a better survival for patients with a single occult intranodal metastasis. Whether the addition of chemotherapy to the radiotherapy for patients with more than one positive node or extracapsular spread results in a better survival remains uncertain. Only a few studies have been published on this subject and come to the conclusion that adding chemotherapy results in a better survival. The conclusion is that adjuvant radiotherapy improves survival of patients with positive groin nodes, with the exception of patients with a single intranodal metastasis. The beneficial effect of chemo radiotherapy for subgroups of patients with positive nodes seems likely, although more data are needed before a definite conclusion can be made.

Aim of Review

The aim of this report is to critically review the existing literature on adjuvant therapy in patients with squamous cell cancer (SCC) of the vulva with positive groin lymph nodes after primary surgery. This is performed by a historical overview of published data on this subject. The research questions that we will try to answer are:

1. Does adjuvant radiotherapy or adjuvant concurrent chemo radiotherapy have a beneficial impact on oncological outcome in patients with vulvar cancer and positive lymph nodes?
2. Which patients/subgroups will benefit most from adjuvant therapy?

Adjuvant Radiotherapy

In 1986 the results of the first and also the only prospective randomized controlled trial (RCT) on the impact of adjuvant radiotherapy on survival in patients with SCC of the vulva and positive groin nodes was published by Homesley et al. This study, patients with positive groin nodes were randomized between adjuvant radiotherapy for the groins and pelvis versus no further radiotherapy. Disease specific survival was better in the adjuvant radiotherapy group (at 2 years 68% versus 54%; p=0.03). A detailed analysis of this study revealed that the survival gain was mainly due to a decrease in groin recurrences in the adjuvant...
radiotherapy group. Further subgroup analyses showed that no survival benefit was found for adjuvant radiotherapy in the group of patients with a single positive and clinically occult (not suspicious) node.

As shown in Table 1, the policy of abandoning adjuvant radiotherapy in patients with a single positive lymph node is recommended in most published national guidelines. All national guidelines take the number of nodes and presence of extra-capsular spread into consideration when recommending adjuvant radiotherapy. Two guidelines (DGGG and GOC) also take size of the metastasis into account. Until recently the NCCN guideline was the only one, not taking into account the variable extra-capsular spread, although now in the most updated version of the guideline adjuvant radiotherapy is not recommended anymore in patients with a single intracapsular positive node.

Despite the recommendation to abandon adjuvant radiotherapy in patients with a single intracapsular nodal metastasis in most national guidelines, several older but also more recent studies have questioned this policy, as shown in Table 2.

Surprisingly, 6 out of 11 studies show a benefit of adjuvant radiotherapy even for patients with a single positive lymph node. Five studies, including the previously discussed Homesley study, could not confirm a favorable impact of adjuvant radiotherapy in patients with a single positive node.

---

### Table 1. Indications for adjuvant (chemo)radiotherapy in patients with vulvar cancer and positive groin lymph nodes in national guidelines.

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of nodes</th>
<th>Size of metastasis</th>
<th>Extra-capsular</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGGG/DKG 2015</td>
<td>&gt;1</td>
<td>RT if any node ≥ 5 mm/fixed ulcerated node</td>
<td>If yes: RT*</td>
</tr>
<tr>
<td>ESGO 2017</td>
<td>&gt;1</td>
<td>n.m.</td>
<td>If yes: RT or CRT</td>
</tr>
<tr>
<td>JSGO 2018</td>
<td>&gt;1</td>
<td>n.m.</td>
<td>If yes: RT or CRT</td>
</tr>
<tr>
<td>GOC/SOGC 2019</td>
<td>&gt;1 (&lt;5mm)</td>
<td>RT if any node ≥5 mm</td>
<td>If yes: RT or RCT</td>
</tr>
<tr>
<td>RCOC/BGCS 2020</td>
<td>&gt;1</td>
<td>n.m.</td>
<td>If yes: RT or CRT</td>
</tr>
<tr>
<td>NCCN 2023</td>
<td>&gt;1</td>
<td>n.m.</td>
<td>If yes: RT or CRT</td>
</tr>
</tbody>
</table>

*also radiotherapy in case fixed or ulcerated lymph node

RT=radiotherapy, CRT=chemo-radiotherapy, n.m.= not mentioned

### Table 2. Collated literature data on the impact of adjuvant radiotherapy in patients with squamous cell cancer of the vulva and a single positive lymph node in the groin(s).

<table>
<thead>
<tr>
<th>Source</th>
<th>RT</th>
<th>no RT</th>
<th>Nodal characteristics</th>
<th>RT benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homesley [1]</td>
<td>Hospital 19 17</td>
<td>cN* status</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Creasman [9]</td>
<td>NCDB 212</td>
<td>no</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Parthasaraty [10]</td>
<td>SEER 106 102</td>
<td>no</td>
<td>Yes (if ≤ 12 nodes removed)</td>
<td></td>
</tr>
<tr>
<td>Fons [11]</td>
<td>Hospital 31 44</td>
<td>yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Woelber [12]</td>
<td>Hospital 14 7</td>
<td>yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mahner [13]</td>
<td>Hospital 77 86</td>
<td>no capsule</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Swanicz [14]</td>
<td>SEER 94 76</td>
<td>no capsule</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Rydzewski [15]</td>
<td>NCDB 816 620</td>
<td>no</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Xanthopoulos [16]</td>
<td>SEER 209 124</td>
<td>no</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Serre [17]</td>
<td>Hospital 28 48</td>
<td>yes capsule, no cN* status</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Van der Velden [18]</td>
<td>Hospital 96</td>
<td>yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*cN= clinical status of the groin lymph node
Serre and co-workers report on 65 patients with a single intracapsular metastasis and 11 patients with a single extracapsular metastasis. It is not clear what the indications were for adjuvant radiotherapy in 28 patients and for leaving out adjuvant radiotherapy in the other 48 patients. However, in a univariate analysis of the group of patients with a single intracapsular metastasis, adjuvant radiotherapy did not impact on recurrence free and overall survival while in a multivariate analysis adjuvant radiotherapy was an independent favorable prognostic variable for recurrence free survival but not for overall survival. Unfortunately, no comparison of the groin recurrence rate or groin recurrence free survival was available for the two groups (adjuvant radiotherapy versus no adjuvant treatment). This means that it is impossible to define specifically the impact of radiotherapy on the tumor control in the groin in this study. A variable that could theoretically have impact on the groin recurrence rate is the volume of inguino femoral lymph node dissections per surgeon or per institute. In a recently published study at least ten inguino femoral lymph node dissections per year per institute were performed, resulting in a groin recurrence rate of 2.1%, while in the series published by Serre and co-workers analyzing the data of five institutes, only one institute performed > 10 surgical procedures in vulvar cancer, while in the other four institutes only three to nine surgical procedures were performed per year. The groin recurrence rate of 9/65 (14%) patients with a single intracapsular lymph node metastasis in their series compares unfavorable with the 2.1% isolated groin recurrences in the series reported by van der Velden and co-workers.

**Studies Showing No Beneficial Impact of Adjuvant Radiotherapy for Patients with a Single Intracapsular Nodal Metastasis**

Only one (retrospective) study, analyzing the impact of adjuvant radiotherapy in patients with positive nodes, using the NCDB database came to the conclusion that there was no significant benefit of adjuvant radiotherapy for the total group of patients with positive nodes. However, the group of patients with a single positive node without extracapsular spread was not separately analyzed.

In contrast to the latter study, Mahner and co-workers came to the conclusion that patients with positive nodes benefitted from adjuvant radiotherapy. However, they did not observe a significant survival difference with or without adjuvant radiotherapy for the group of patients with a single positive node. Also this study did not take into account extracapsular spread.

In a multicenter case control study, Fons and co-workers analyzed the oncological outcome in a group of 75 patients with a single intracapsular positive node. The oncological outcome did not differ between the group who had adjuvant radiotherapy versus the group who had no further adjuvant treatment. In a recently published retrospective multicenter cohort study van der Velden and co-workers analyzed the oncological outcome of 96 patients with a single intracapsular nodal metastasis from four gynecologic oncology centers (three in the Netherlands and one in Australia), all performing a high volume of surgical procedures for vulvar cancer. In all three centers the institutional guidelines recommended to abandon adjuvant radiotherapy in patients with vulvar cancer and a single intracapsular metastasis. Three patients (3.1%) were diagnosed with a groin recurrence. Only one patient (1%) had an isolated groin recurrence, although occurring in the contralateral lymph node negative groin. The 5-year disease specific survival for the total group was 79%. On the basis of these favorable results the authors concluded that adjuvant radiotherapy can be safely omitted in patients with a single intracapsular metastasis.

**Studies on the Addition of Concurrent Chemotherapy to the Adjuvant Radiotherapy**

Only three retrospective studies reported on the oncological outcome after addition of concurrent chemotherapy to the adjuvant radiotherapy. These studies are based on NCDB data from different periods although with overlapping periods in two studies. Remarks on these studies are that extranodal spread, a known unfavorable prognostic factor, has not been taken into account or it was unclear if this was the case, overall survival was used as endpoint and there was no information on type of surgery. The overall impression was that adding chemotherapy was not beneficial. With overall survival as endpoint, the problem is that in the older age group comorbidity and resultant tendency not to add chemotherapy to the adjuvant radiotherapy for that particular group of patients may have impact on the outcome. Three other retrospective studies also reported on adjuvant chemoRT both for patients with irradical resection margins and/or positive nodes. However, from these data it was impossible to determine the value of adding chemotherapy to the adjuvant radiotherapy for patients with positive nodes because the latter group was not analyzed separately and also the numbers were very small.

**Studies on Adjuvant Chemotherapy**

Only one retrospective cohort study has been published on adjuvant chemotherapy (cisplatin) after surgery. All 14 patients had more than one positive lymph node and three of them had extranodal growth. After follow-up 2/14 were DOD. The 3 years OS was 86% in this study, which appears to be a very favorable outcome. It has to be remarked that this comprised a very small group of patients. So, more data on this topic with larger amounts of patients are necessary to draw conclusions.
Summary and Conclusions
On the basis of a randomized controlled trial, it can be concluded that adjuvant radiotherapy for patients with SCC of the vulva and positive groin lymph nodes results in a better oncological outcome compared to patients without adjuvant treatment. Although there is some controversy regarding the value of adjuvant radiotherapy for patients with a single intracapsular metastasis, studies taking into account the important prognostic variables such as extranodal spread and size of the metastasis in the node could not show a benefit of adjuvant radiotherapy for that particular group. The addition of concurrent chemotherapeutic to the adjuvant radiotherapy seems to improve the oncological outcome, although there are limited data to support this, and it is unclear which subgroup of patients might benefit. The impact of adjuvant chemotherapy without radiotherapy has only been studied in one small sized study which makes it impossible to draw firm conclusions. All these arguments result in the fact that most (inter)national guidelines recommend adjuvant radiotherapy (or adjuvant chemo radiotherapy) for patients with more than one positive lymph node or in case extranodal spread is present.

Competing Interests
none declared

References