



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

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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^{1,2}. In this study, patients with positive groin nodes were randomized between adjuvant radiotherapy for the groins and pelvis versus adjuvant pelvic node dissection and 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 guidelines³⁻⁸. 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^{3,6}. 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 node⁸.

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**^{1,9-18}.

Surprisingly, 6 out of 11 studies^{10,12,14-17} 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^{1,9,11,13}.

Studies in Favor of Adjuvant Radiotherapy for Patients with a Single Intracapsular Nodal Metastasis

The main flaw in the majority of the studies is the fact that nodal characteristics are not always taken into account in their analyses. Clinically suspicious nodes, large diameter of the nodal metastasis and especially extra nodal tumor growth are well known poor prognostic variables¹⁹⁻²¹. Analyzing the impact of no further treatment in patients with a single positive node is only reliable and scientifically valid when the frequencies of these poor nodal characteristics are reported. Moreover, when comparing the outcome of no further treatment with adjuvant radiotherapy, the groups must be well balanced regarding these important nodal characteristics. Four studies, expressing a preference for adjuvant radiotherapy for all patients, including patients with a single positive node, do not mention these nodal characteristics^{10,14-16}. Consequently, these studies cannot be used in analyzing the impact of adjuvant (chemo) radiotherapy in patients with a single intracapsular metastasis.

Two studies took into account extracapsular spread and or size of the metastasis in their analyses^{12,17}. One of the latter studies¹², however, did not provide specific information on extra capsular spread and/or recurrence pattern in the seven reported patients with a single positive lymph node who did not get adjuvant radiotherapy. The other study by

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

	Number of nodes	Size of metastasis	Extra-capsular
DGGG/DKG 2015 ^[3]	>1	RT if any node ≥ 5 mm/fixed ulcerated node	If yes: RT*
ESGO 2017 ^[4]	>1	n.m.	If yes: RT or CRT
JSGO 2018 ^[5]	>1	n.m.	If yes: RT or CRT
GOC/SOGC 2019 ^[6]	>1 (< 5mm)	RT if any node ≥5 mm	If yes: RT or RCT
RCOG/BGCS 2020 ^[7]	>1	n.m.	If yes: RT or CRT
NCCN 2023 ^[8]	>1	n.m.	If yes: RT or CRT

*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).

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

*cN= clinical status of the groin lymph node

Serre and co-workers¹⁷ 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 study¹⁸ 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-workers¹⁷ 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 database⁹ 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 radiotherapy¹³. 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 treatment¹¹. 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 cancer¹⁸. 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^{15,22,23}. These studies are based on NCDB data from different periods although with overlapping periods in two studies^{15,22}. 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 for that particular group of patients may have impact on the outcome. Three other retrospective studies²⁴⁻²⁶ 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 surgery²⁷. 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 chemotherapy 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

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