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Clinical Outcomes of Perioperative Chemotherapy in Patients With Locally Advanced Penile Squamous-Cell Carcinoma: Results of a Multicenter Analysis

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Abstract

Patients with locally advanced penile squamous-cell carcinoma have a poor prognosis. No difference in survival was noted when using chemotherapy before or after surgery. Uncertainties persist regarding the optimal management of these patients, and new treatments are urgently required, particularly for patients at highest risk, with bilateral and/or pelvic lymph node involvement.

Background: The prognosis of patients with locally advanced penile squamous-cell carcinoma is primarily related to the extent of lymph node metastases. Surgery alone yields suboptimal results, and there is a paucity of data on these patients' outcomes.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2017.02.002.

Patients and Methods: This retrospective study evaluated patients who received neoadjuvant or adjuvant chemotherapy from 1990 onward at 12 centers. Cox models were used to investigate prognostic factors for relapse-free survival and overall survival (OS).

Results: Among the 201 included patients, 39 (19.4%) had disease of T3-4 and N0 clinical stage; the remaining patients had clinical lymph node involvement (cN+). Ninety-four patients received neoadjuvant chemotherapy (group 1), 78 received adjuvant chemotherapy (group 2), and 21 received both (group 3). Eight patients for whom the timing of perioperative chemotherapy administration was unavailable were included in the Cox analyses. Forty-three patients (21.4%) received chemoradiation. Multivariate analysis for OS (n = 172) revealed bilateral disease (P = .035) as a negative prognostic factor, while pelvic cN+ tended to be nonsignificantly associated with decreased OS (P = .076). One-year relapse-free survival was 35.6%, 60.6%, and 45.1% in the 3 groups, respectively. One-year OS was 61.3%, 82.2%, and 75%, respectively. No significant differences were seen on univariable analyses for OS between the groups (P = .45). Platinum type of chemotherapy and chemoradiation were not significantly associated with any outcome analyzed.

Conclusion: Benchmark survival estimates for patients receiving perioperative chemotherapy for locally advanced penile squamous-cell carcinoma have been provided, with no substantial differences observed between neoadjuvant and adjuvant administration. This analysis may result in improved patient information, although prospective studies are warranted.

Keywords

Penile cancer; Preoperative chemotherapy; Regional lymph nodes; Squamous cell carcinoma; Survival

Introduction

Penile squamous-cell carcinoma (PSCC) is a very rare tumor, and prognosis more frequently depends on locoregional spread than the development of distant metastases.[1] For patients with locally advanced disease, ie, regional lymph node involvement or unresectable bulky primary tumors, clinical guidelines and trial designs recommend induction chemotherapy, possibly before radical surgery.[2,3] Outcomes are poor for patients who experience relapse after surgery or who have extensive involvement of the locoregional lymph nodes (ie, involvement of fixed inguinal lymph nodes or pelvic lymph nodes), and new therapeutic modalities are needed for such patients.

For advanced PSCC, single therapeutic modalities like inguinal lymph node dissection, with or without the extension to pelvic lymph nodes, systemic treatments, or radiotherapy, do not significantly change the limited survival possibilities in the long term for these patients; thus, curing advanced disease often requires a multimodal approach.[4,5] Multiple neoadjuvant chemotherapies have shown moderate activity: the highest reported objective response rates (ORR) are approximately 50%, but relapses occur in the majority of cases, and long-term remission is rare.

Importantly, the optimal timing of chemotherapy and radiotherapy administration with respect to lymph node dissection is unclear, and the results of multiple small studies are

conflicting. Usually neoadjuvant therapy is the preferred treatment approach because tumor debulking can facilitate radical surgery and allow for assessment of the pathologic response to chemotherapy. Pathologic complete response (CR) is a surrogate for overall survival (OS) in these patients and is a reliable end point for phase 2 trials.[6] Although the efficacy of adjuvant chemotherapy has only been evaluated in small studies that used obsolete chemotherapy regimens, that treatment approach may benefit select high-risk patients, such as those with pathologically involved pelvic lymph nodes.[7,8] Many of the uncertainties regarding treatment for advanced PSCC described above may be clarified by the results of an ongoing prospective international study (ie, the International Penile Advanced Cancer Trial, InPACT,). That study aims to evaluate the impact of neoadjuvant chemotherapy alone or in conjunction with radiotherapy in patients with lymph node–positive disease. However, until those results are published, information can only be obtained from retrospective analyses. Therefore, the present study evaluated the outcomes of patients receiving perioperative chemotherapy to identify clinical baseline prognostic factors that can be used when determining what multimodal treatment to implement. It is expected that these objectives will provide physicians with the background information necessary to improve patient counseling and treatment.

Patients and Methods

Patient Population

Data were collected from 12 centers in Europe, the United States, and Canada. After the study was approved by the ethics committee and internal review board of each participating center, uniform anonymized data, including baseline characteristics, pathology information, treatments, and chemotherapy regimens, were collected using an Excel spreadsheet. The criteria for case collection were histologically proven PSCC (histologic variants of squamouscell carcinoma were allowed) and one of the following: clinical evidence of advanced primary tumor (eg, T3-4 N0) and/or clinically involved regional lymph nodes. We relied on the 2009 tumor, node, metastasis classification system,[9] which defines N1 stage as the presence of palpable mobile unilateral inguinal lymph node, N2 stage when mobile multiple unilateral or bilateral inguinal lymph nodes are present, and N3 stage when fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral, are found.

Administration of at least 2 cycles of any chemotherapy course in either a neoadjuvant or adjuvant setting from 1990 onward was required. Prior administration of chemotherapy (ie, vinblastine, bleomycin, and methotrexate regimens) for noninfiltrating PSCC was allowed.[10] The administration of any targeted therapy combined with chemotherapy was allowed. Concomitant or sequential delivery of radiotherapy to the regional lymph nodes was also allowed. Patients with confirmed systemic metastatic disease were not included. All statistical analyses were conducted externally by a senior statistician (G.P.).

Statistical Analyses

Patient, disease, and outcome characteristics were summarized using descriptive statistics with frequencies and percentages used for categorical variables and medians and interquartile ranges used for continuous variables.

The primary objective was to summarize the outcomes of patients who had received any neoadjuvant or adjuvant chemotherapy in addition to radical surgical resection. The secondary objective was to investigate the effect of clinical baseline (ie, presurgical) factors on the prognosis of patients who received surgery and systemic therapy as a result of the clinical evidence of lymph node metastases, irrespective of the timing of the systemic therapy (ie, before or after surgery). OS was the primary end point and was defined as the period of survival from the date of the first administration of chemotherapy.

The Kaplan-Meier method was used to estimate time-to-event outcomes. Cox proportional hazards regression was used to investigate potential prognostic factors of OS and relapse-free survival (RFS). Because clinical data were missing in many cases—the result of the retrospective nature of this analysis—multivariate models were constructed on the basis of prespecified factors that were hypothesized to be clinically important, and univariable analyses were left as exploratory only. Treatment center was used as a stratification factor throughout the analyses. Log-rank and chi-square tests were used to compare differences in OS, RFS, and ORR between patient subgroups according to the treatment received (ie, the type of chemotherapy regimen and concomitant chemoradiation). All tests were 2 sided, and differences with a *P* value of .05 or less were considered statistically significant. All analyses were performed by SAS 9.2 (SAS Institute, Cary, NC).

Results

Patient, Disease, and Treatment Characteristics and Outcomes

A total of 201 patients treated with either neoadjuvant (group 1, n = 94), adjuvant (group 2, n = 78), or neoadjuvant and adjuvant chemotherapy (group 3, n = 21) were included in this study. Eight patients for whom the timing of chemotherapy was unknown were included in the Cox analyses. Table 1 summarizes the patient and disease characteristics and the treatments administered in each group. The median age of the study cohort was 62 years (range, 35-87 years); 46 patients (22.9%) were circumcised, and 9 patients (4.5%) presented with an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2.

At clinical staging, 39 patients (19.4%) had T3-4 and N0 disease; the remaining patients had lymph node involvement. Seventy-six patients (37.8%) had bilateral (inguinal with or without pelvic) lymph node involvement, and 40 patients (19.9%) had pelvic lymph node metastases. The administered chemotherapy regimens are shown in Supplemental Table 1 in the online version; they were taxane, cisplatin, and 5-fluorouracil (TPF) chemotherapy the most frequently reported regimen. Responses and outcomes by patient subgroup are shown in Table 2. Among all patients who received neoadjuvant chemotherapy (groups 1 and 3), 20 (17.4%) had pathologic CR, and in group 1 alone, 13 patients (13.8%) had pathologic CR. An ORR of 53.2% (n = 50) was seen in group 1. Two-year OS was 35.8% (95% confidence interval [CI], 25.1%-46.6%) in group 1, 57.2% (43.9%-68.4%) in group 2, and 31.5% (11.8%-53.6%) in group 3. Two-year OS was 37.4% (95% CI, 20.5-54.4) in patients with clinically positive pelvic lymph nodes and 38.1% (95% CI, 25.9-50.1) in patients with bilateral lymph node involvement. For group 1, RFS and OS according to pathologic response are shown in Supplemental Table 2 in the online version. Figures 1 and 2 present the RFS and OS curves according to treatment group. Significant difference were found

favoring group 2 in RFS (P = .012), but no differences were seen in OS according to the timing of chemotherapy administration (P = .45).

No outcomes had statistically significant differences between the subgroups of patients who received different neoadjuvant chemotherapy regimens: taxane versus no taxane (n = 71 vs. 22, P = .75); cisplatin versus other (n = 81 vs. 12, P = .27); and TPF (n = 65) versus cisplatin and 5-fluorouracil (PF; n = 16) versus other regimens (n = 13) (P = .65). In group 2, RFS and OS were not significantly different between patients who received adjuvant chemotherapy (n = 50) and those who received adjuvant chemoradiation (n = 28) (P = .92 and P = .51, respectively; Supplemental Table 3 in the online version). Supplemental Table 4 in the online version presents the grade 3/4 adverse effects of chemotherapy according to treatment group. Thrombocytopenia and neutropenia were seen in about 2% and 10% in both group 1 and 2, while the incidence of anemia was lower in group 2 compared to group 1 (1.3% vs. 10.6%). Higher incidence of grade 3/4 hematologic and nonhematologic adverse effects was observed in group 3, probably as a result of the higher burden of chemotherapy these patients received.

Analysis of Prognostic Factors for RFS and OS

The multivariate analysis of prognostic factors for RFS and OS is presented in Table 3.

Three prespecified baseline clinical factors were included in the multivariate model: N stage, presence of bilateral lymph node metastases, and pelvic lymph node involvement. Of those, pelvic lymph node involvement was a significant negative prognostic factor for RFS (hazard ratio [HR], 2.29, 95% CI, 1.00-5.25, P = .050) but not OS (HR, 2.15, 95% CI, 0.92-5.01, P = .076). The presence of bilateral lymph node metastases was a significant negative prognostic factor for OS (HR, 1.93, 95% CI, 1.05-3.55, P = .035) but not RFS (P = .20), and clinical stage was not significantly associated with either end point (P = .57 for RFS and .74 for OS). Additional attempts were made to construct alternative prognostic models for OS that included other factors that we believed to be clinically important, such as smoking status, ECOG performance status, and age. In all cases, bilateral disease trended toward a significant negative association with OS; however, pelvic lymph node status did not (data not shown). No other variables were statistically significantly associated with OS, including the timing of perioperative chemotherapy administration (ie, group 1 vs. 2 vs. 3) in univariable analyses (Supplemental Table 5 in the online version).

Discussion

To date, the best management of patients with lymph node dissemination of PSCC is unknown. In the current study, the clinical course of patients was consistent across subgroups: despite the moderate short-term activity of chemotherapy (ie, the ORR and the rate of pathologic CR in the neoadjuvant group), disease progression occurred in the majority of cases, and the 2-year OS was poor irrespective of the treatment strategy. Significantly longer RFS was observed with adjuvant chemotherapy than with neoadjuvant chemotherapy, although the difference in OS was not statistically significant. Notably, the OS curves for the different treatment groups substantially overlapped within the first 24 months, which is when the majority of death events occurred. Therefore, a lag-time bias may

be present: the date of inclusion for this analysis was the date of first receipt of chemotherapy, and patients who received neoadjuvant chemotherapy or neoadjuvant and adjuvant chemotherapy must have lived long enough to also undergo surgery. It is possible that neoadjuvant chemotherapy followed by surgery was planned for some patients who died before surgery, resulting in their being excluded from this analysis. Of course, the retrospective nature of the study prevented us from discerning the criteria that were used to allow patients to receive chemotherapy before or after surgery, in the absence of unequivocal guidelines. Consequently, some significant differences in the distribution of baseline characteristics was found among the groups: a smaller metastatic load (fewer cN3 cases) was observed in group 2 than in group 1, but more patients in group 2 had bilateral disease (both $P < .001$).

Although our study results did not allow us to discern the best timing of perioperative chemotherapy administration, they have provided further information regarding the outcomes of lymph node–positive patients who underwent adjuvant chemotherapy after lymphadenectomy. The current clinical guidelines for the indications for adjuvant chemotherapy are based on small and outdated studies.[2] Our study showed little or no benefit of the administration of neoadjuvant and adjuvant chemotherapy after neoadjuvant chemotherapy. Reliable data on the tolerability of treatments are seldom available in retrospective studies; thus, it is difficult to draw any conclusions regarding the tolerability of chemotherapy. However, the rate of grade 3/4 toxicities substantially overlapped between groups 1 and 2, and a trend to higher incidence of adverse effects was seen in group 3. A thorough risk–benefit evaluation would have great value in this context. Notably, the median time interval between chemotherapy and lymphadenectomy was highly similar between the 3 groups, ranging from 4 to 6 weeks.

On the basis of a prospective phase 2 trial, the paclitaxel, ifosfamide, and cisplatin (TIP) regimen has the most robust evidence for neoadjuvant use in the population studied here; unfortunately, that regimen was underrepresented in this study.[11] TPF chemotherapy was the most frequently used regimen, and no significant difference in any outcome was seen between TPF and PF chemotherapy or any other regimen. In the adjuvant group, the heterogeneity of treatments was too high to allow for reasonable comparisons. On the basis of our limited data, it is difficult to determine indications for the use of particular chemotherapy regimens; however, clinicians may consider administering the PF regimen, at least in patients unfit for intense chemotherapy, as it has a lower toxicity than taxane-based triplet regimens.

In this analysis, no statistically significant difference in any outcome was observed between patients who received chemotherapy alone or in combination with chemoradiation. However, this analysis is limited by the small sample size (50 patients with chemotherapy alone vs. 28 patients with concomitant chemoradiation). Experts in the field acknowledge the presence of an ongoing debate about the use of postoperative radiotherapy in lymph node–positive patients. The data available in the literature indicate that men do not benefit from adjuvant inguinal radiotherapy in terms of decreased local recurrence or increased survival. However, some of the available data are based on outdated treatments and thus may not be applicable to contemporary practice.[12] Conversely, our study included patients who received treatment

more recently, although triple-combination chemotherapy (ie, TIP or TPF) was still used, which makes the assessment of any possible effect of additional adjuvant radiotherapy difficult. The ongoing InPACT study is also evaluating the role of adjuvant radiotherapy in patients with locally advanced PSCC, and the results of that study are highly anticipated. In this analysis, bilateral lymph node involvement was the only consistent prognostic factor for OS; pelvic regional lymph node status did not show a consistent significant association with OS. One important limitation of this study when analyzing clinical factors is the inaccuracy and heterogeneity of pelvic imaging, which may be an argument in favor of the administration of adjuvant chemotherapy after surgical staging. Our analysis included men who received chemotherapy for lymph node or soft-tissue relapses after regional lymphadenectomy, but this scenario was not shown to be an independent predictor of survival. Another important limitation of our study is the heterogeneity of surgical approaches used. The varying extent of lymphadenectomy (eg, not all patients had undergone pelvic or bilateral inguinal dissection) resulted in a disproportionate amount of missing data regarding pelvic and bilateral lymph node involvement, which may have had meaningful effects on their prognostic significance in this study.

Several articles on the role of pelvic lymph node dissection after inguinal lymphadenectomy have been published. The indication to perform pelvic lymphadenectomy is usually based on the number of observed positive inguinal lymph nodes; however, the best cutoff number is a matter of debate.[2,13,14] Data are insufficient for making any reliable risk factor–based decisions in terms of conducting bilateral or unilateral pelvic lymphadenectomy in advanced PSCC.[15] Even considering the present analysis, it remains impossible to make any recommendation on whether adjuvant chemotherapy or pelvic lymphadenectomy should be used in patients with high-risk features identified during inguinal lymphadenectomy.

Ultimately, as has always been the case in studies of penile cancer, the results of our study are limited by the relatively small sample size in each group and by limitations that are inherent to retrospective studies, including a proportion of missing or incomplete data and potential inconsistencies in reports from different centers. Attempts were made to increase the sample size of this study, including reviewing cases reported over 25 years in some databases. However, the rarity of this disease is apparent, as only 201 patients were identified from 12 treatment centers. Additionally, a control group of patients who did not receive perioperative chemotherapy or radiation would have been desirable, but such a population would likely contain substantial selection biases, including comorbidities and poor performance status.

Conclusion

Substantial uncertainties still exist regarding the indications for perioperative chemotherapy and the net benefit of administering multimodal treatment compared to surgery alone in patients with advanced PSCC and high-risk features, namely those with pelvic or bilateral lymph node involvement. Nevertheless, the present analysis may be valuable for clinicians because it provides the benchmark results that can be obtained with standard chemotherapy in the perioperative setting. This study serves as an aid for making treatment decisions in the

clinic and designing future clinical trials with new agents as neoadjuvant or adjuvant therapies in PSCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- We presented what is to our knowledge the largest retrospective effort that aimed to identify the outcomes and prognostic factors of patients who have received perioperative chemotherapy added to lymphadenectomy for locally advanced PSCC.
- The contribution of adjuvant radiotherapy to chemotherapy for operated and lymph node–positive, high-risk patients remains unclear.
- The equivocal results from efficacy comparison of different chemotherapy regimens in the neoadjuvant setting (ie, the role of cisplatin–5-fluorouracil doublet vs. triple combination regimen adding taxanes to cisplatin and 5-fluorouracil) highlight the need for additional studies as well as the need for new drugs in this disease.

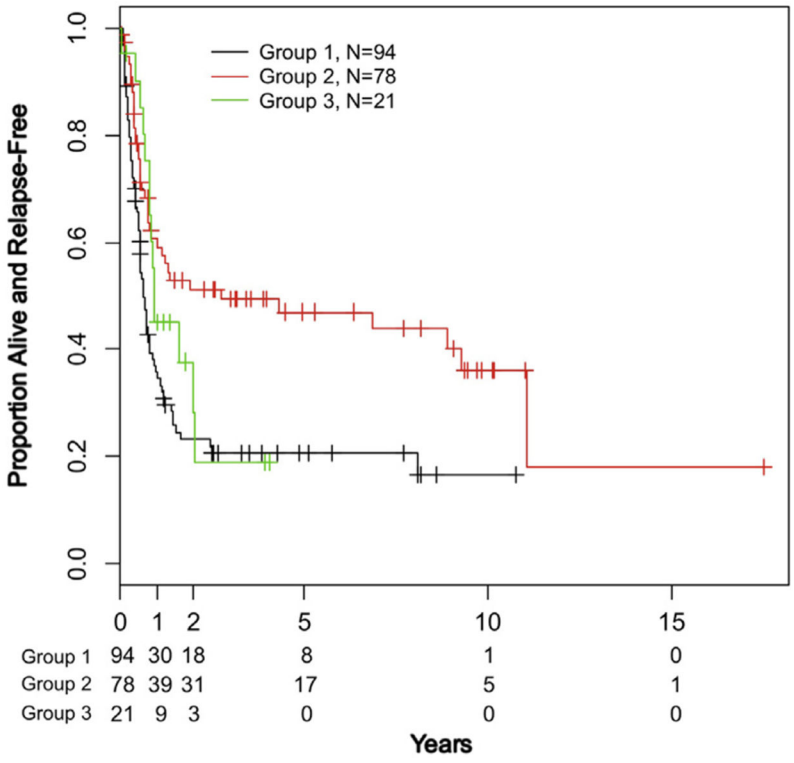

Figure 1.

Kaplan-Meier Curves of Relapse-Free Survival of Patients According to Treatment Group. Black Line, Neoadjuvant Chemotherapy Group (Group 1); Red Line, Adjuvant Chemotherapy Group (Group 2); Green Line, Neoadjuvant and Adjuvant Chemotherapy Group (Group 3)

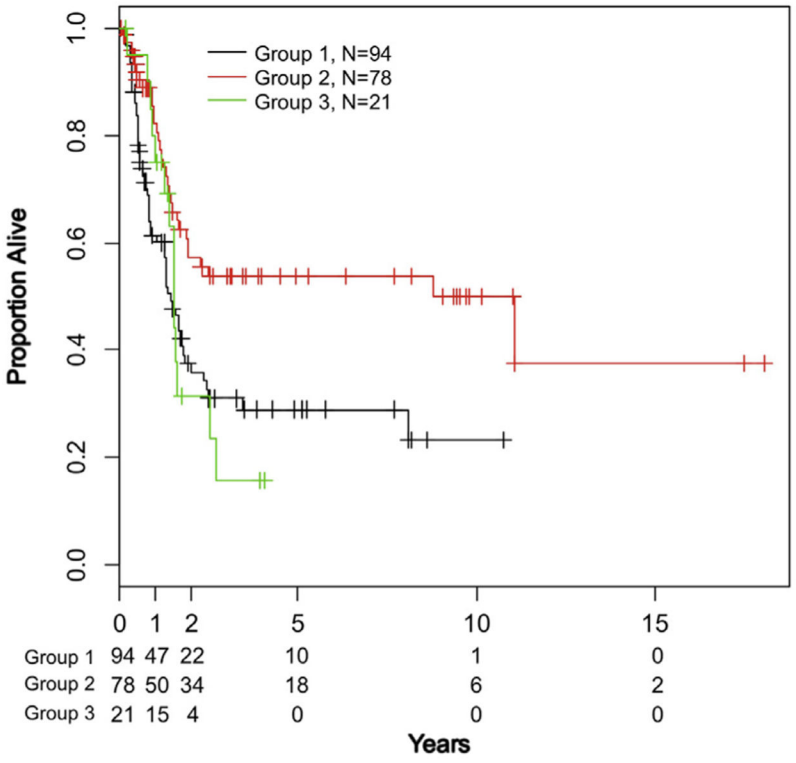

Figure 2.

Kaplan-Meier Curves of Overall Survival of Patients According to Treatment Group. Black Line, Neoadjuvant Chemotherapy Group (Group 1); Red Line, Adjuvant Chemotherapy Group (Group 2); Green Line, Neoadjuvant and Adjuvant Chemotherapy Group (Group 3)

Table 1

Patient, Disease, and Treatment Characteristics According to Treatment Group[a]

Characteristic	Statistic	Group 1 (n = 94), n (%)	Group 2 (n = 78), n (%)	Group 3 (n = 21), n (%)	*P*
Age	Mean (SD)	60.4 (10.4)	60.4 (9.3)	62 (10.0)	.58
Smoking status	Never	28 (29.8)	13 (16.7)	7 (33.3)	<.001
	Former	12 (12.8)	8 (10.3)	6 (28.6)	
	Current	15 (16.0)	16 (20.5)	8 (38.1)	
	Unknown	39 (41.5)	41 (52.6)	—	
HPV status	Negative	9 (9.6)	17 (21.8)	12 (57.1)	<.001
	Positive	1 (1.1)	3 (3.9)	4 (19.1)	
	Unknown	84 (89.4)	58 (74.4)	5 (23.8)	
Circumcision	No	63 (67.0)	63 (80.8)	18 (85.7)	.11
	Yes	30 (31.9)	13 (16.7)	3 (14.3)	
	Unknown	1 (1.1)	2 (2.6)	—	
Pathology	Papillary	4 (4.3)	11 (14.1)	1 (4.8)	<.001
	Basaloid	1 (1.1)	—	—	
	Warty	2 (2.1)	1 (1.3)	2 (9.5)	
	Verrucous	9 (9.6)	—	10 (47.6)	
	Sarcomatoid	3 (3.2)	—	5 (23.8)	
	SCC, not specified	75 (79.8)	66 (84.6)	3 (14.3)	
ECOG-PS	0	43 (45.7)	44 (56.4)	10 (47.6)	<.001
	1	21 (22.3)	34 (39.7)	11 (38.1)	
	≥2	4 (4.3)	2 (2.6)	3 (14.3)	
	Unknown	26 (27.7)	1 (1.3)	—	
Baseline Clinical Characteristics (Applicable to All Groups)					
Clinical T stage	T1	7 (7.5)	6 (7.7)	6 (28.6)	<.001
	T2	29 (30.9)	24 (30.8)	4 (19.1)	
	T3	8 (8.5)	15 (19.2)	8 (38.1)	
	T4	14 (14.9)	1 (1.3)	3 (14.3)	

Characteristic	Statistic	Group 1 (n = 94), n (%)	Group 2 (n = 78), n (%)	Group 3 (n = 21), n (%)	*P*
	Tx	36 (38.3)	32 (41.0)	—	
Clinical N stage	N0	17 (18.1)	18 (23.1)	4 (19.1)	<.001
	N1	11 (11.7)	12 (15.4)	9 (42.9)	
	N2	20 (21.3)	29 (37.2)	8 (38.1)	
	N3	45 (47.9)	19 (24.4)	—	
	Nx	1 (1.1)	—	—	
Bilateral lymph node involvement	No	32 (34.0)	50 (64.1)	12 (57.1)	<.001
	Yes	35 (37.2)	28 (35.9)	9 (42.9)	
	Unknown	27 (28.7)	—	—	
Pelvic lymph node involvement	No	46 (48.9)	61 (78.2)	20 (95.2)	<.001
	Yes	22 (23.4)	17 (21.8)	1 (4.8)	
	Unknown	26 (27.7)	—	—	
Baseline Pathologic Characteristics Before Adjuvant Chemotherapy					
Pathologic T stage	Tis	Not applicable	—	—	.045
	T0		—	—	
	T1		10 (12.8)	5 (23.8)	
	T2		37 (47.4)	4 (19.1)	
	T3		21 (26.9)	10 (47.6)	
	T4		3 (3.9)	2 (9.5)	
	Tx		7 (9.0)	—	
Pathologic N stage	N0	Not applicable	7 (9.0)	2 (9.5)	<.001
	N1		5 (6.4)	6 (28.6)	
	N2		22 (28.2)	13 (61.9)	
	N3		43 (55.1)	—	
	Nx		1 (1.3)	—	
Bilateral lymph node involvement	No	Not applicable	42 (53.9)	12 (57.1)	.75
	Yes		34 (43.6)	9 (42.9)	
	Unknown		2 (2.6)	—	
Pelvic lymph node involvement	No	Not applicable	50 (64.1)	19 (90.5)	.020

Characteristic	Statistic	Group 1 (n = 94), n (%)	Group 2 (n = 78), n (%)	Group 3 (n = 21), n (%)	*P*
	Yes		28 (35.9)	2 (9.5)	
	Unknown		—	—	
Treatment					
Margin-negative surgery	n (%) Yes	22 (68.8)	64 (94.1)	2 (12.5)	<.001
Time from end NA-CT to LAD (weeks)	Median (range)	5 (0, 71.6)	—	4 (3, 6)	.042
Time from LAD to A-CT (weeks)	Median (range)	—	6 (1, 52)	4 (3, 6)	.013
Platinum type	Cisplatin	81 (86.2)	73 (93.6)	18 (85.7)	.62
	Carboplatin	10 (10.6)	3 (3.9)	2 (9.5)	
	No platinum	2 (2.1)	2 (2.6)	1 (4.8)	
	Unknown	1 (1.1)	—	—	
Taxane-containing CT	No	22 (23.4)	53 (68.0)	8 (38.1)	<.001
	Yes	71 (75.5)	25 (32.0)	13 (61.9)	
	Unknown	1 (1.1)	—	—	
Concomitant radiotherapy	No	56 (59.6)	50 (64.1)	18 (85.7)	<.001
	Yes	12 (12.8)	28 (35.9)	3 (14.3)	
	Unknown	26 (27.7)	—	—	

Group 1 = neoadjuvant chemotherapy group; group 2 = adjuvant chemotherapy group; group 3 = neoadjuvant followed by adjuvant chemotherapy group.

Abbreviations: A = adjuvant; CT = chemotherapy; ECOG-PS = Eastern Cooperative Oncology Group performance status; HPV = human papillomavirus; LAD = lymphadenectomy; NA = neoadjuvant; SCC = squamous-cell carcinoma.

[a]Data of 8 patients with missing information about the timing of chemotherapy administration are not included here but have been included in the Cox model.

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Table 2

Response and Outcome According to Treatment Subgroup

Characteristic	Statistic	Group 1 (n = 94)	Group 2 (n = 78)	Group 3 (n = 21)
Best objective response	NR	1 (1.1)	—	—
	CR	12 (12.8)		7 (33.3)
	PR	38 (40.4)		6 (28.6)
	SD	17 (18.1)		6 (28.6)
	PD	24 (25.5)		2 (9.5)
	Unknown	2 (2.1)		—
Pathologic CR	NR	19 (20.2)	—	—
	Yes	13 (13.8)		7 (33.3)
	No	62 (66.0)		14 (66.7)
RFS, months	n (%) Events	71 (75.5)	40 (51.3)	14 (66.7)
	Median (95% CI)	7.7 (6.4, 9.8)	32.8 (9.7, 132.7)	11.1 (9.5, 24.3)
	1 y (95% CI)	35.6 (25.8, 45.5)	60.6 (48.2, 71.0)	45.1 (23.2, 64.8)
	2 y (95% CI)	23.2 (14.8, 32.6)	51.2 (38.8, 62.3)	28.2 (8.8, 51.7)
OS, months	n (%) Deaths	57 (60.6)	31 (39.7)	14 (66.7)
	Median (95% CI)	17.1 (12.5, 21.5)	105.3 (19.8, NE)	18.5 (11.8, 30.2)
	1 y (95% CI)	61.3 (50.2, 70.7)	82.2 (70.7, 89.5)	75.0 (50.0, 88.7)
	2 y (95% CI)	35.8 (25.1, 46.6)	57.2 (43.9, 68.4)	31.5 (11.8, 53.6)

Group 1 = neoadjuvant chemotherapy group; group 2 = adjuvant chemotherapy group; group 3 = neoadjuvant followed by adjuvant chemotherapy group.

Abbreviations: CI = confidence interval; CR = complete response; NE = not estimable; NR = not reported; OS = overall survival; PD = disease progression; PR = partial response; RFS = relapse-free survival; SD = stable disease.

Table 3

Results of Multivariable Cox Regression Models for Relapse-Free and Overall Survival Outcomes

Baseline Clinical Factor	RFS				OS		
	Type	n	HR (95% CI)	*P*	n	HR (95% CI)	*P*
Clinical N stage	0-1	172	1.55 (0.64, 3.75)	.57	172	0.88 (0.31, 2.47)	.74
	2		1.21 (0.53, 2.77)			1.18 (0.50, 2.83)	
	3		Ref.			Ref.	
Bilateral lymph node involvement	Yes vs. No		1.40 (0.84, 2.32)	.24		1.93 (1.05, 3.55)	.035
Pelvic lymph node involvement	Yes vs. No		2.29 (1.00, 5.25)	.050		2.15 (0.92, 5.01)	.076

Abbreviations: CI = confidence interval; CT = chemotherapy; ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LAD = lymphadenectomy; NA = neoadjuvant; OS = overall survival; RFS = relapse-free survival.