Advances in Radiation Oncology (2020) **5**, 412-418

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Patterns of Care and Outcomes for Small Cell Carcinoma of the Cervix: A National Retrospective Analysis of 542 Cases

David Wharton, MD, MBA,[a] Ellen Kim, MD, MPH,[b] Jonathan Pagan, MD, MS,[c] William Small Jr, MD,[d] Jerry Jaboin, MD, PhD,[e] and Diandra Ayala-Peacock, MD[b,*]

[b]Department of Radiation Oncology, [a]Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee; [c]Radiation Oncology Associates Carson City, Carson City, Nevada; [d]Department of Radiation Oncology, Loyola University Medical Center, Chicago, Illinois; and [e]Department of Radiation Medicine, Oregon Health and Science University, Portland, Oregon

Received 20 February 2019; revised 23 July 2019; accepted 26 August 2019

Abstract

Purpose: Small cell carcinoma of the cervix (SCCC) represents 1% to 5% of cervical cancers, with limited data on management and outcomes. We evaluated patterns of care and outcomes for SCCC using the National Cancer Database.

Methods and Materials: This retrospective cohort study of SCCC (2004-2011) included 542 cases. Patient demographic, diagnosis, treatment information, and overall survival (OS) were compared with descriptive statistics, logistic regression, Kaplan-Meier, and Cox models. Clinical reasoning was used to select variables for multivariable models to avoid overfitting.

Results: SCCC had more comorbidities, higher grade, and advanced stage than other histologies. SCCC received neoadjuvant chemotherapy (36%) more often than squamous cell carcinoma (23%) and adenocarcinoma (13%, $P < .001$). SCCC had worse OS across all stages ($P < .001$). Looking at SCCC alone, patients who received chemoradiation (CRT) (with external beam and brachytherapy) and those who received chemotherapy and surgery (without RT) had similar OS (median OS 44 vs 47 months; $P = .7$) on Kaplan-Meier. Patients receiving CRT were more likely to have stage II or III and N+ disease ($P < .001$). When evaluating chemoradiation, the addition of brachytherapy resulted in improved median OS (35 vs 19 months; $P = .001$) regardless of surgical resection status and controlling for age and stage. Even after controlling for stage, age, and comorbidities, the addition of brachytherapy was associated with a 40% improvement in OS (hazard ratio 1.4, 95% confidence interval 1.0-2.0).

Conclusions: SCCC patients benefit from chemotherapy with aggressive local treatment. Patients who receive CRT that included brachytherapy did as well as patients who received chemotherapy followed by surgery. Brachytherapy remains an essential component in the treatment of SCCC with CRT.

Introduction

Small cell carcinoma of the cervix (SCCC) is a rare neuroendocrine subtype of cervical cancer comprising 1% to 5% of all cervical cancer cases.[1] SCCC is more

Sources of support: This work had no specific funding.

Disclosures: Dr Small reports personal fees from Carl Zeiss; other disclosures of Varian, NRG Oncology, Merck.

* Corresponding author: Diandra Ayala-Peacock, MD; E-mail: diandra.n.ayala.peacock@vumc.org

https://doi.org/10.1016/j.adro.2019.08.008

aggressive than squamous cell carcinoma (SqCC) and adenocarcinoma (ACA), with higher rates of nodal and distant metastatic spread seen even with earlier stage disease; SCCC is also more likely to present at a later stage.[2,3] The more common histologies of cervical cancer have well-established management strategies: surgical excision for early stage disease, combination chemoradiation for locally advanced cancers, and systemic therapy for distant metastatic disease.

In contrast, no definitive treatment guidelines exist for SCCC, with providers most commonly extrapolating from small cell lung cancer management and incorporating various combinations of surgery, chemotherapy, and radiation. Owing to the low incidence of SCCC, few prospectively gathered data sets have been published to date.[4] In addition, previous retrospective studies attempting to determine best treatment modalities for the various stages are often limited by small sample size, with the largest series still totaling <200 patients.[2,5,6] To our knowledge, this 542-patient series comprises one of the largest retrospective study evaluating the various treatment algorithms. The aim of this study was to determine whether any trends for improved overall survival (OS) could be identified among the different treatment modalities.

Materials and Methods

We performed a retrospective cohort study using the National Cancer Database (NCDB) to study patients with SCCC. The NCDB is a hospital-based cancer registry sponsored jointly by the American College of Surgeons and the American Cancer Society. Comprised of <1400 facilities accredited by the American College of Surgeons' Commission on Cancer, the NCDB contains de-identified data on >70% of all newly diagnosed cancers in the United States.[7]

We initially queried the NCDB for patients with cervical cancer. After excluding patients with any other cancer diagnoses, no microscopic confirmation of cancer diagnosis, stage 0 or unknown stage, or insufficient treatment information, we found a total of 52,761 cases of cervical cancer with histologies including SCCC (542, 1.0%), SqCC (43,415, 82.3%), and ACA (8804, 16.7%). Selection criteria did not require a minimum duration of follow-up.

Demographic information included sex, age, race, type of insurance, regional average income, regional education level, regional population size, type of treatment facility, and geographic region. Regional income, education, and population size were provided as estimates from the NCDB based on the patient's zip code or city and state of residence at the time of diagnosis. Clinical information included an adapted Charlson comorbidity index,[8,9] cancer grade, lymph node status, lymphovascular invasion status, American Joint Committee on Cancer stage (6th or 7th editions), treatments received (surgery, radiation, chemotherapy), and surgical margin status.

Missing values were considered as their own "unknown" subgroup within each category. Some categories were combined to accommodate statistical analysis of very small categories. When small categories were combined, it was performed logically to keep the largest categories distinct (eg, white, black, and other race), or to create loosely similar group sizes (eg, higher and lower income). Specifically, higher income was defined as a regional income greater than $47,900. Higher education was defined as a <13% adults living in the region without a high school degree or equivalent. Higher population was defined as living in a county in a metropolitan area with a population of at least 1 million.

We compared the demographics and clinical characteristics of patients by histology using the χ^2 test (Table 1). Significant *P*-values were defined as <.05. We also performed a multivariable regression to identify characteristics of patients with SCCC compared with those with SqCC or ACA.

Overall survival (OS) for a single variable used the Kaplan-Meier survival method and the log-rank test for significance. Patients were censored after last known vital status. Multivariable survival analysis used the Cox proportional hazards model using variables with clinical or statistical significant in single variable analysis. We compared OS by histology for each stage.

Subsequent analyses focused on patients with small cell histology alone (SCCC), selected based on *International Classification of Diseases* codes. Initial query found 663 patients who received a diagnosis of cervical cancer and small cell histology between 2004 and 2011. Patients were excluded if they had any other cancer diagnoses, insufficient treatment information, no microscopic confirmation of diagnosis, or stage 0 or unknown stage. The final analysis included 542 cases of SCCC. We performed Cox proportional hazards analysis of SCCC. We also looked more closely at combinations of treatment modalities by stage and compared their OS. The final cohort included patients with SCCC who received both chemotherapy and external beam radiation therapy, and some patients also received brachytherapy radiation and some patients also received surgery. Patient selection is shown in Fig 1.

Results

For all histologies, follow-up ranged from 0 to 132 months with median 43 months. For SCCC, SqCC, and ACA, respectively, follow-up ranged 0 to 121 (median 19), 0 to 132 (median 42), and 0 to 130 (median

Table 1 Demographic and clinical characteristics of patients with cervical cancer diagnosed 2004 to 2011 by histology, compared by variable with χ^2 tests

	Adenocarcinoma N = 8804	Small cell N = 542	Squamous N = 43,415	*P* values
Age <48 y	5071 (58)	268 (50)	21,084 (49)	<.0001
Age 48 + y	3733 (42)	274 (51)	22,331 (51)	
Race black	761 (9)	86 (16)	7947 (18)	<.0001
Race other	590 (7)	36 (7)	3076 (7)	
Race white	7453 (85)	420 (77)	32,392 (75)	
Insurance Medicaid	1169 (13)	91 (17)	10,312 (24)	<.0001
Insurance Medicare	1152 (13)	98 (18)	7184 (17)	
Insurance other	980 (11)	64 (12)	6654 (15)	
Insurance private	5503 (63)	289 (53)	19,265 (44)	
Income lower	3780 (43)	274 (51)	23,924 (55)	<.0001
Income higher	5024 (57)	268 (49)	19,491 (45)	
Education lower	4211 (48)	287 (53)	26,106 (60)	<.0001
Education higher	4593 (52)	255 (47)	17,309 (40)	
Population lower	4026 (46)	242 (45)	20,518 (47)	.02
Population higher	4778 (54)	300 (55)	22,897 (53)	
Charlson 0	7862 (89)	461 (85)	37,716 (87)	<.0001
Charlson 1	785 (9)	69 (13)	4555 (10)	
Charlson 2	157 (2)	12 (2)	1144 (3)	
Facility CCC	2460 (28)	140 (26)	12,298 (28)	<.0001
Facility academic/research	2666 (30)	163 (30)	14,990 (35)	
Facility other	3678 (42)	239 (44)	16,127 (37)	
Region central	2335 (27)	147 (27)	13,488 (31)	<.0001
Region east/Atlantic	2317 (26)	144 (27)	12,981 (30)	
Region unknown	2862 (33)	178 (33)	11,331 (26)	
Region west	1290 (15)	73 (13)	5615 (13)	
stage I	5815 (66)	143 (26)	19,022 (44)	<.0001
stage II	993 (11)	51 (9)	8241 (19)	
stage III	1150 (13)	171 (32)	10,929 (25)	
stage IV	846 (10)	177 (33)	5223 (12)	
grade 1-2	4821 (55)	12 (2)	17,508 (40)	<.0001
grade 3	1711 (19)	193 (36)	13,472 (31)	
grade 4	77 (1)	113 (21)	388 (1)	
Grade unknown	2195 (25)	224 (41)	12,047 (28)	
Node negative	4183 (48)	89 (16)	11,067 (25)	<.0001
Node positive	4621 (52)	453 (84)	32,348 (75)	
Lymphovascular space invasion (LVSI) negative	1186 (13)	31 (6)	3507 (8)	<.0001
LVSI positive	262 (3)	25 (5)	1807 (4)	
LVSI unknown	7356 (84)	486 (90)	38,101 (88)	
No treatment	268 (0.5)	41 (0.1)	1658 (3)	<.0001
Chemotherapy	145 (0.3)	62 (0.1)	675 (1)	
Chemotherapy and radiation	1662 (3)	209 (0.4)	16,258 (31)	
Radiation	431 (0.8)	26 (0.1)	3346 (6)	
Surgery	4476 (8)	26 (0.1)	13,199 (25)	
Surgery and radiation	585 (1)	5 (0.01)	2280 (4)	
Surgery, chemotherapy, and radiation	1125 (2)	114 (0.2)	5658 (11)	
Surgery and chemotherapy	112 (0.2)	59 (0.1)	341 (0.7)	
Surgical margin negative	5413 (61)	140 (26)	17,057 (39)	<.0001
Surgical margin positive	651 (7)	49 (9)	3606 (8)	
Surgical margin unknown	2740 (31)	353 (65)	22,752 (52)	

49) months. Regarding patient demographics, patients with SCCC were more similar to those with SqCC than ACA. Compared with patients with SqCC, patients with SCCC were more likely to have private insurance, higher income, higher education, live in larger cities, receive treatment at a nonacademic facility, have higher grade (grade 3-4) disease, have positive lymph nodes, have more advanced stage, receive RT, not receive

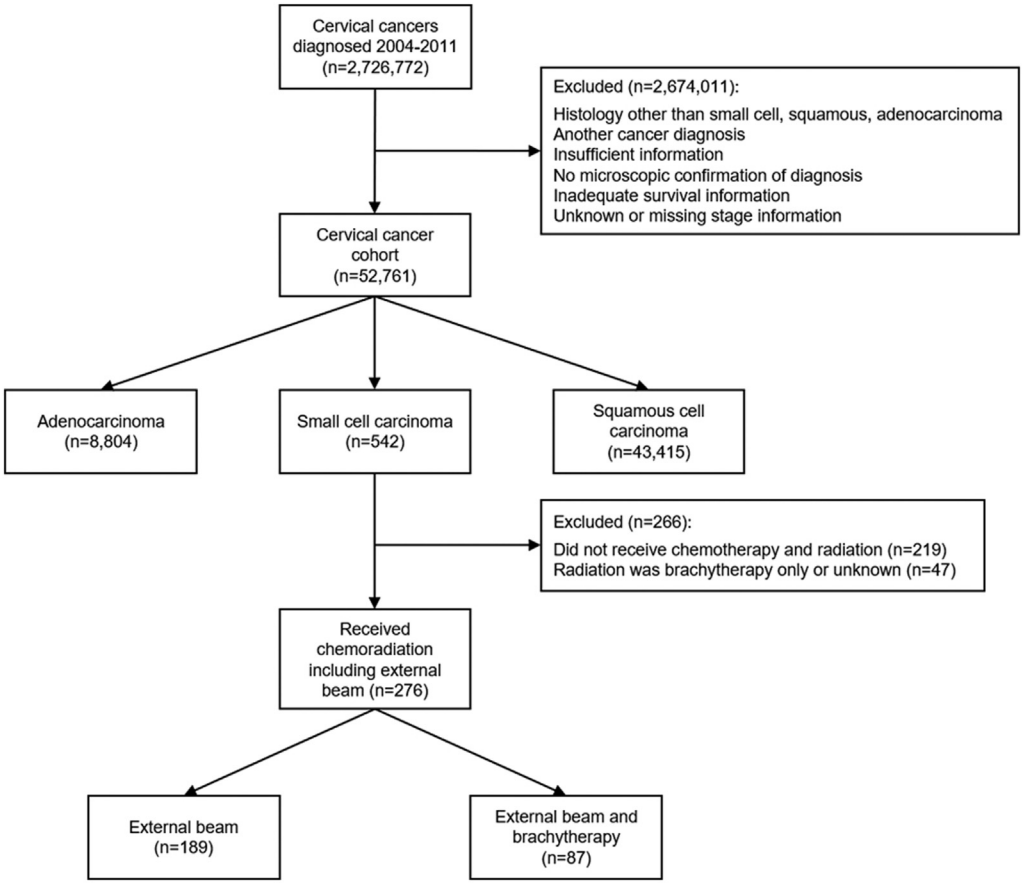

Figure 1 Flow diagram of case selection.

surgery, and were also much more likely to receive chemotherapy.

Table E1 shows the results of the multivariable analysis to characterize patients with SCCC compared with other histologies while controlling for other variables. Patients with SCCC were less likely to have Medicaid for insurance (odds ratio [OR] 0.5; 95% confidence interval [CI] 0.4-0.7), higher education (OR 1.3; 95% CI 1.0-1.6), moderate comorbidities (Charlson score of 1; OR 1.4; 95% CI 1.0-1.8), higher grade (grade 3 OR 17.2, 95% CI 9.6-30.9; grade 4 OR 333.2, 95% CI 180.3-615.9; unknown grade OR 28.9, 95% CI 16.1-51.9), and more advanced stage (stage II OR 0.5, 95% CI 0.3-0.7; stage IV OR 1.6, 95% CI 1.2-2.2), and were less likely to live in an unspecified region of the United States (OR 1.9; 95% CI 1.2-3.0). SCCC were also more likely to start treatment with chemotherapy rather than RT (OR 0.5; 95% CI 0.4-0.7) or surgery (OR 0.4; 95% CI 0.3-0.6), to receive chemotherapy with surgery (OR 7.9; 95% CI 3.5-18.0) or without surgery (OR 3.0; 95% CI 1.9-4.5), and less likely to receive radiation therapy or surgery without chemotherapy. SCCC patients had worse overall survival compared with other histologies across all stages ($P < .001$; Fig E1).

On review of SCCC patients alone, KM survival analysis revealed that patients who received chemoradiation (CRT) (including external beam and brachytherapy) and patients who received chemotherapy and surgery (without RT) had similar OS (median OS 44 vs 47 months; $P = .7$; Fig E2). SCCC patients receiving CRT were more likely to have stage II or III and N + disease ($P < .001$).

When evaluating chemo-EBRT and brachytherapy versus chemo-EBRT alone in univariable Kaplan-Meier analysis, the addition of brachytherapy resulted in improved median OS (35 vs 19 months; $P = .001$; Table 2, Fig. E2. No difference in survival was appreciated between patients who received definitive chemoradiation with EBRT and brachytherapy versus patients who received

Table 2 Overall survival of SCCC patients treated with chemo and radiation therapy (RT) by type of RT

OS	Brachytherapy + beam N = 86	Beam N = 189
1 y	88% (<100 at risk)	64%
2 y	63%	43% (<100 at risk)
3 y	49%	32%
4 y	43%	30%
5 y	38% (<20 at risk)	27%
Median	35 mo	19 mo

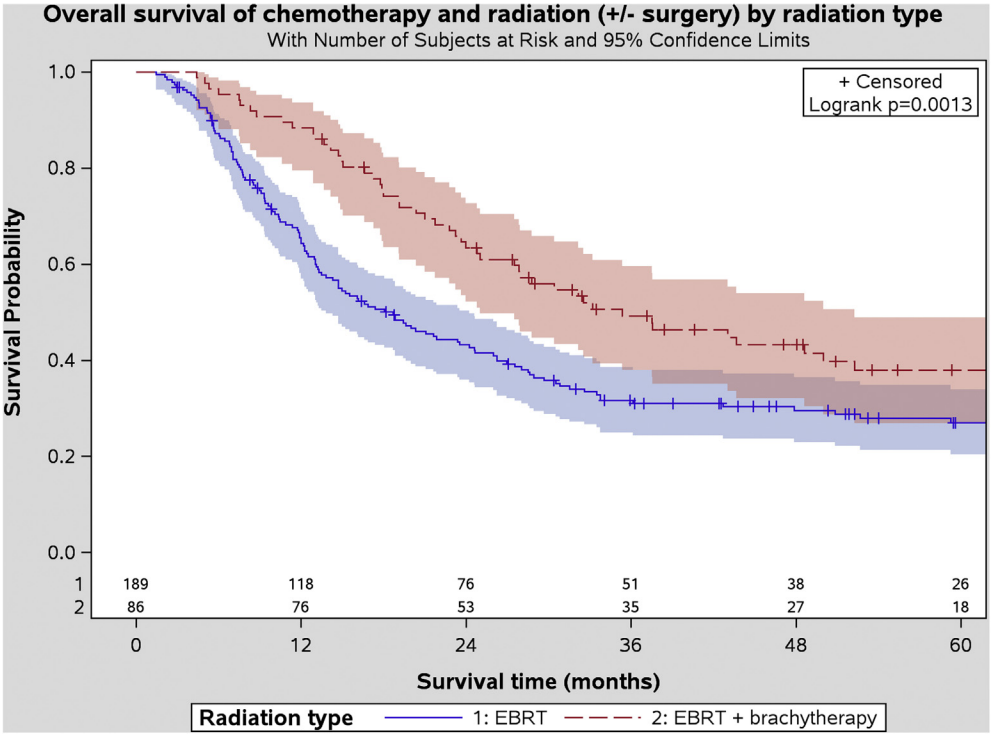

Figure 2 Overall survival of small cell carcinoma of the cervix patients treated with chemotherapy and radiation therapy (with or without surgery) by mode of radiation therapy.

chemotherapy with surgery.) regardless of surgical resection status and when controlling for age and stage (Fig 2). Even after controlling for stage, age, and comorbidities in the multivariable analysis, the addition of brachytherapy was still associated with a 40% improvement in OS (hazard ratio 1.4; 95% CI, 1.0-2.0).

Discussion

SCCC has been shown to have worse clinical outcomes compared with SqCC or ACA owing to the increased likelihood for lymphovascular infiltration, nodal metastases, and other high-risk features that can be present even when diagnosed at an earlier stage.[2] Owing to its low incidence, however, there is limited and sometimes conflicting information regarding the optimal management of SCCC.[10]

Several studies support the use of chemotherapy and aggressive local treatment for early stage SCCC, whether in combination with surgery for very early stages IA to IB1 or radiation for stages IB2 to IIB.[4,11-14] Across studies, chemotherapy has been shown to be a critical component of treatment of even early stage (1A1-1B2) SCCC. Lee et al identified a significantly inferior time to progression and OS in early stage SCCC patients (FIGO 1B2 or below) who did not receive chemotherapy compared with both early and late stage SCCC who did.[15]

To our knowledge, this is one of the largest retrospective analysis of SCC of the cervix to date with a total of 542 histologically confirmed cases. In keeping with previously published data, we demonstrate that patients with SCCC are more likely to receive chemotherapy (36%) compared with SqCC (23%) and ACA (13%, $P < .001$).

Among SCCC patients who received chemotherapy, there was no significant difference in survival for patients who had subsequent surgery (median survival 47 months) versus concurrent external beam followed by brachytherapy (median survival 44 months; $P = .7$). In addition, the chemoRT and chemo plus surgery groups exhibited nearly identical rates of survival at all time points, including 1 year (86% vs 88%), 2 years (71% vs 71%), and 3 years (55% vs 58%). This is noteworthy as the chemoRT patients were also more likely to have stage II or III disease ($P < .001$) and positive nodes ($P < .001$) compared with the chemo plus surgery group. Although there were not enough patients to stratify these results by stage, this suggests that chemoRT (EBRT plus brachytherapy) has comparable OS to chemo plus surgery.

Hypotheses for this finding include the possibility that surgical excision of early stage lesions that are deemed node negative after LN dissection are not identifying sites of microscopic spread, whereas chemoRT (EBRT plus brachytherapy) results in more comprehensive coverage of subclinical sites. Alternatively, it is possible that the synergistic effect of chemotherapy concurrent with radiation is more effective in this disease.

For those patients who received chemoRT (with or without surgery), we found a significant survival benefit for patients undergoing a combination of EBRT and brachytherapy (median survival 35 months) compared with patients who received EBRT alone (median survival 19 months; $P = .001$). Chen et al previously suggested that for stage I to II SCCC, patients who received primary radiation therapy (majority EBRT plus brachytherapy) with at least 5 cycles of platinum-based chemotherapy may have superior outcomes compared with primary surgery plus neoadjuvant chemotherapy.[16] Our results show that among patients who receive chemoRT, those who receive brachytherapy in addition to EBRT have longer OS than those who receive EBRT alone. Although patients receiving chemoRT (EBRT plus brachytherapy) were more likely to be stage I and II and younger age compared with chemoRT (EBRT alone; $P = .002$), even after controlling for stage, age, and comorbidity score, there was an OS benefit with the addition of brachytherapy (HR 1.4; 95% CI 1.0-2.0). The benefit of brachytherapy in traditional cervical cancer (SqCC and ADA) is well known. Our data suggest that a similar approach for early stage SCCC is warranted.

Overall, our results validate previous findings that SCCC has worse prognosis compared with SqCC and ACA histologic types, which is reflected by increased likelihood for chemotherapy treatment. In addition, for definitive treatment, combined EBRT and brachytherapy can provide survival comparable to surgical resection, thereby eliminating the potential morbidity associated with an oncologic resection and providing an alternative for patients who are nonoperable candidates. Finally, our findings reinforce the importance of a brachytherapy boost for SCCC, as for other histologies. We recommend that clinicians strongly consider including brachytherapy for stages I and IV SCCC. Ultimately, all patients with SCCC will require complex care that needs to be discussed in a multidisciplinary setting to ensure that proper treatments are pursued with brachytherapy as part of that conversation.

There are several limitations to this study. Only overall survival, was available for evaluation; cause specific survival, disease free survival, and other outcomes were not available. However, because SCCC is an aggressive disease, it is assumed that the majority of deaths occurred as a direct result of the cancer which mitigates some of this potential bias. Another limitation is that this study is a retrospective analysis that cannot control for several important clinical factors such as treatment selection bias and patient goals of care. The chemoRT patients who received a combination of EBRT and brachytherapy had improved survival, but were statistically more likely to be younger and early stage (I or II) compared with chemoRT with EBRT alone. This makes intuitive sense because earlier stage lesions would be more likely to be offered brachytherapy for definitive local control (if surgery was not pursued). Our data showing that the survival benefit to chemoRT with EBRT and brachytherapy is maintained when both stage and age are controlled for, helps to reduce this limitation. Other confounding factors include differences among the populations' goals of treatment, difference in access to a brachytherapy-equipped center or variation in the number of doctors that are willing or have the expertise to perform brachytherapy procedures. Although a strength of this relatively large study is the information on use of chemotherapy, we unfortunately did not have information on specific chemotherapy regimens that were used.

Conclusions

SCCC is a rare and aggressive subtype of cervical cancer with limited data on optimal management schemas. This large NCDB study identifies chemotherapy as an integral part of treatment for all stages of disease, which when combined with EBRT and brachytherapy has similar outcomes as chemotherapy with surgery. Brachytherapy portends a survival advantage with this histologic subtype and should be considered for definitive management as it is in other cervical cancer histologies.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2019.08.008.

References

1. Satoh T, Takei Y, Treilleux I, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for small cell carcinoma of the cervix. *Int J Gynecol Cancer*. 2014;24(9 Suppl 3):S102-108.
2. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: Treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol*. 2010;203:347.e1-347.e6.
3. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. *Obstet Gynecol*. 2008;111:1394-1402.
4. Hoskins PJ, Swenerton KD, Pike JA, et al. Small cell carcinoma of the cervix: Fourteen years of experience at a single institution using a combined-modality regimen of involved-field irradiation and platinum-based combination chemotherapy. *J Clin Oncol*. 2003;21:3495-3501.
5. Wang K-L, Chang T-C, Jung S-M, et al. Primary treatment and prognostic factors of small cell neuroendocrine carcinoma of the uterine cervix: A Taiwanese Gynecologic Oncology Group study. *Eur J Cancer*. 2012;48:1484-1494.
6. Bajaj A, Frumovitz M, Martin B, et al. Small cell carcinoma of the cervix: Definitive chemoradiation for locally advanced disease. *Gynecol Oncol*. 2018;102:S85-S86.
7. National Cancer Database. American College of Surgeons. Available at: https://www.facs.org/quality-programs/cancer/ncdb. Accessed November 20, 2018.

8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40:373-383.
9. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613-619.
10. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: A Society of Gynecologic Oncology (SGO) clinical document. *Gynecol Oncol*. 2011;122:190-198.
11. Tempfer CB, Tischoff I, Dogan A, et al. Neuroendocrine carcinoma of the cervix: A systematic review of the literature. *BMC Cancer*. 2018;18:530.
12. Li X, Yang R, Jia Y, Zhou J, Ma D, Li S. Prognostic risk factors for small cell carcinoma of the cervix and impact of platinum-based neoadjuvant chemotherapy. *Int J Gynaecol Obstet*. 2015;130:31-35.
13. Zhang Q, Xiong Y, Ye J, Zhang L, Li L. Influence of clinicopathologic characteristics and comprehensive treatment models on the prognosis of small cell carcinoma of the cervix: A systematic review and meta-analysis. *PLoS One*. 2018;13:e0192784.
14. Zivanovic O, Leitao MM, Park KJ, et al. Small cell neuroendocrine carcinoma of the cervix: Analysis of outcome, recurrence pattern and the impact of platinum-based combination chemotherapy. *Gynecol Oncol*. 2009;112:590-593.
15. Lee S-W, Lim K-T, Bae DS, et al. A multicenter study of the importance of systemic chemotherapy for patients with small cell neuroendocrine carcinoma of the uterine cervix. *Gynecol Obstet Invest*. 2015;79:172-178.
16. Chen T-C, Huang H-J, Wang T-Y, et al. Primary surgery versus primary radiation therapy for FIGO stages I-II small cell carcinoma of the uterine cervix: A retrospective Taiwanese Gynecologic Oncology Group study. *Gynecol Oncol*. 2015;137:468-473.