Gynecologic Oncology Reports 27 (2019) 54–59

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Small cell carcinoma of cervix: A population-based study evaluating standardized provincial treatment protocols

Soumyajit Roy[a,b], Jenny J. Ko[a,c], Gaurav Bahl[a,b,*]

[a] University of British Columbia, British Columbia, Canada
[b] Department of Radiation Oncology, British Columbia Cancer Agency, Abbotsford Cancer Center, Abbotsford, BC V2S 0C2, Canada
[c] Department of Medical Oncology, British Columbia Cancer Agency, Abbotsford Cancer Center, Abbotsford, BC V2S 0C2, Canada

ARTICLE INFO

Keywords:
Small cell carcinoma of cervix
Chemo-radiotherapy
Platinum-based chemotherapy and external beam radiotherapy
Distant failure
Stage
Nodal involvement

ABSTRACT

Objectives: To describe the patient characteristics, patterns of treatment, and outcome of patients with small cell carcinoma of Cervix (SmCC) treated with radical radiotherapy from a provincial cancer registry database.
Methods: Overall 25 patients with SmCC were treated with radical radiotherapy (with or without chemotherapy) from January 1, 1994 to December 31, 2013. Nineteen patients had pure SmCC while 6 had additional neuroendocrine component. Patients were treated with combined chemo-radiotherapy using multi-agent chemotherapy with pelvic or combined pelvic and para-aortic radiotherapy. All patients received brachytherapy. Use of prophylactic cranial irradiation was dependent on physician discretion. Survival was estimated using Kaplan-Meier method and compared using log-rank test.
Results: We report a median overall survival of 53.8 months for our cohort. After a median follow-up of 54 months for surviving patients, the overall survival (OS) and progression free survival (PFS) at 5-years were 48% and 46.4% respectively. Patients with stage I-IIA disease had superior 5-year PFS (67.3% vs. 11.1%; $p = .004$) and 5-year OS (62.5% vs. 22.2%; $p = .006$). Patients with node-negative disease had a trend towards better 5-year PFS (55.7% vs. 19%; $p = .07$) and OS (61.1% vs. 14.3% at 5-years; $p = .06$) Distant metastasis was the predominant site of disease progression ($n = 12$; 48%).
Conclusion: Distant metastasis is the predominant pattern of failure for patients with SmCC treated with radical chemo-radiotherapy. With modern chemo-radiotherapy protocols we can expect a 5 year survival of around 50%. Early stage and node-negative status appear to be favorable prognostic factors with survival rates at 5-year over 60%.

1. Introduction

Small cell carcinoma of cervix (SmCC) is a relatively rare subtype in the spectrum of cervical malignancies (Tavassoli and Devilee, 2003). It accounts for approximately 2–5% of all cervical malignancies (Miller et al., 1991; Albores-Saavedra et al., 1976; Scully et al., 1984). SmCC, however, is far more aggressive compared to the more common variants such as squamous cell carcinoma, and these patients are more likely to develop lymph-node and distant metastasis (Sevin et al., 1996a; Boruta II et al., 2001). Several case series have reported relatively poor outcomes despite aggressive combined modality treatment (Chan et al., 2003; Sevin et al., 1996b; Zivanovic et al., 2009). Cohen et al., in their literature review of 188 patients, reported 5-year disease-specific survival of 36.8%, 9.8%, and 0%, in stage I-IIA, IIB-IVA, and IVB respectively (Cohen et al., 2010). Furthermore, due to rarity of this entity, management recommendations are based on retrospective institutional studies and often guided by the treatment protocols in small-cell lung cancer. The generalizability of those recommendations is debateable, and there remains a need for further studies to establish clinical parameters, prognosis, and outcomes in a wider population of patients. We report the results of a population-based study form a cancer registry database, to describe demographics, patterns of care and survival of patients of SmCC treated with radical intent chemo-radiotherapy on standardized provincial treatment protocols.

2. Materials and methods

Approval was obtained from the University Research Ethics Board to review our provincial cancer registry for all patients of cervical cancer treated with radical radiotherapy including brachytherapy (with or

* Corresponding author at: Department of Radiation Oncology, BC Cancer, Abbotsford Regional Hospital and Cancer Center, 32900 Marshall Road, Abbotsford, BC V2S 0C2, Canada.
E-mail address: Gaurav.bahl@bccancer.bc.ca (G. Bahl).

https://doi.org/10.1016/j.gore.2019.01.003
Received 15 October 2018; Received in revised form 31 December 2018; Accepted 8 January 2019
Available online 09 January 2019

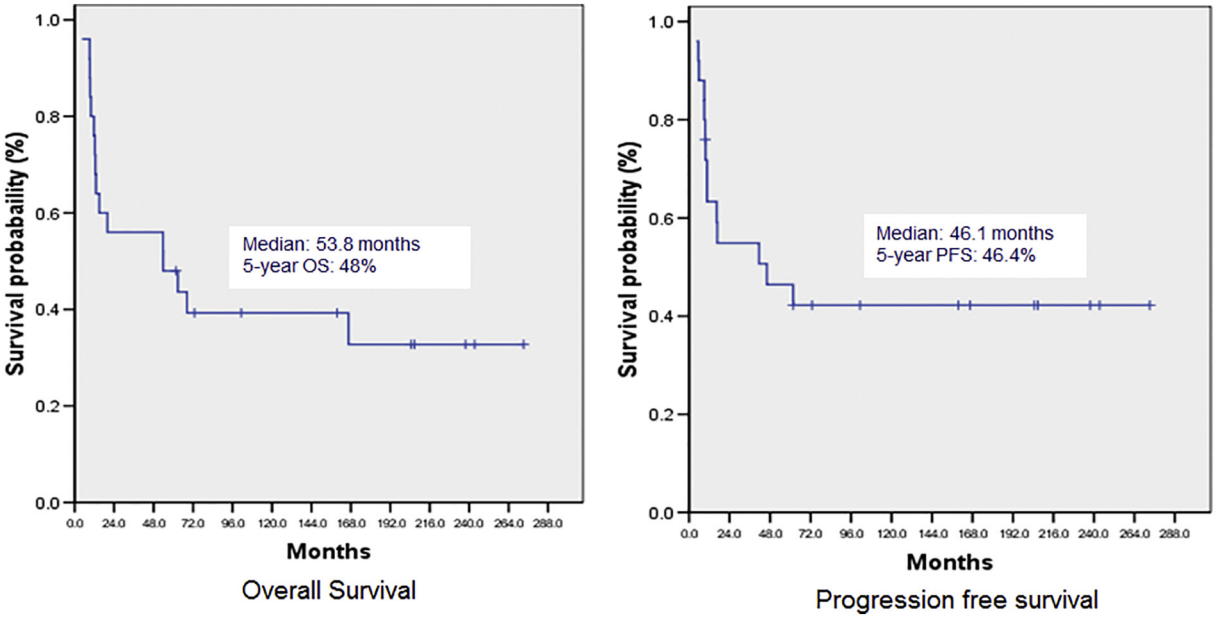

Fig. 1. Overall survival and progression free survival.

without chemotherapy) from January 1, 1994 to December 31, 2013. These patients were treated in the six regional cancer centers of the province operated by British Columbia Cancer (BC Cancer). Uniform provincial management guidelines set by experts from all six cancer centers were followed. The histopathologic diagnosis of SmCC was primarily based on light microscopic findings and immunohistochemical markers like synaptophysin, chromogranin or CD56. Electron microscopy was not used. These patients were primarily seen by a Gynecological Oncologist and after discussion in a multidisciplinary tumor board they were subsequently referred to Medical and Radiation Oncologists. We included all patients with a small cell neuroendocrine component in the histopathology report and treated with primary radiotherapy (with or without concomitant chemotherapy) for this review. Patients who were treated primarily with hysterectomy were not included in this study. A total of 25 consecutive patients of SmCC treated with primary radiotherapy were identified and included in our analysis. Patient, tumor and treatment details, as well as outcomes were verified from computerized medical records or paper charts.

Patients were staged using Federation Internationale Gynecologica Obstetrica (FIGO) staging system. Staging evaluation included contrast enhanced computed tomography (CECT) of head, chest, abdomen and pelvis. Further investigations like magnetic resonance imaging of brain, examination under anesthesia or ultrasonography of abdomen was carried out based on individual physician discretion.

Standard chemotherapy protocol ($n = 20$; 80%) consisted of intravenous (IV) Paclitaxel (175 mg/m^2) on day 1 and 98; IV Cisplatin 60 mg/m^2 on day 1,2,21,22; IV Etoposide 75 mg/m^2 on day 21,22; etoposide 100 mg orally on day 23–25 and day 126–130; IV Cisplatin 40 mg/m^2 on day 42, 49, 56, 63, 70; IV Carboplatin (area under curve 5/6) on day 98 and 126. There were no planned dose reductions, but instead, treatment on days 21, 98, and 126 were delayed, if required, until the absolute neutrophil count was > 1000/cubic millimetre (cmm) and the platelet count was > 100,000/cmm. External beam radiation treatment (EBRT) typically began on day 42 concurrently with third cycle of chemotherapy. PCI, when used, was delivered after the completion of EBRT and brachytherapy (day 130–144). The dose-fraction schedule for PCI was 25 Gy in 10 fractions over two weeks. Use of PCI was at the discretion of the treating Radiation Oncologist.

Patients diagnosed before 1996 were treated with an alternate chemotherapy regimen, which included IV injection of etoposide (40 mg/m^2/day) and cisplatin (25 mg/m^2/day) for 5 consecutive days starting on days 1, 15, 29, and 43. EBRT started on day 15. PCI, if used, started on day 46. This was used in 5 patients.

EBRT target volume consisted of whole pelvis (consisting primary tumor and pelvic lymph node stations i.e. obturator, internal, external and common iliac, and upper pre-sacral nodes) ($n = 9$; 36%) or whole pelvis with para-aortic nodal basin starting from the lower border of 12th thoracic vertebra to the junction of L5/S1 ($n = 16$; 64%). Total dose ranged from 40 to 45 Gy in 20–25 fractions delivered over 4–5 weeks. For majority of patients, virtual simulation was used to design anterior and posterior beams, avoiding the kidneys with MLC shielding. However, patients in recent years have received conformal radiation using intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Brachytherapy was delivered using two sessions of remote after-loading low-dose rate (LDR) technique using Cesium-137 prior to 2008. The dose prescription was 13.5 Gy to point A in each session. Since 2008, patients have received 5 fractions of high-dose rate (HDR) technique using Iridium-192, 6 Gy delivered in each fraction. The fractions of brachytherapy were often interdigitated with EBRT schedule. Overall, 20 (80%) patients received LDR brachytherapy while HDR brachytherapy was used in 5 (20%) patients.

Descriptive statistics were used to calculate the incidence, prevalence and other demographic characteristics of the study population. Comparison of categorical variables was carried out using chi-square test. Progression free survival (PFS) was defined as the period from the date of diagnosis to the date of progression or last follow-up. Overall survival (OS) was defined as the period from the date of diagnosis to death or last follow-up. PFS and OS estimation was done using the Kaplan-Meier method and association of prognostic factors with survival was estimated using the log-rank test. All reported *p*-values were two sided. A p-value of < 0.05 was considered significant. The SPSS® v. 14.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for all statistical analyses.

3. Results

3.1. Patients

A total of 25 patients was included in the study. Of note, over 1200 patients with cervical malignancies were treated with radical radiotherapy in the province over the study period. The median age of

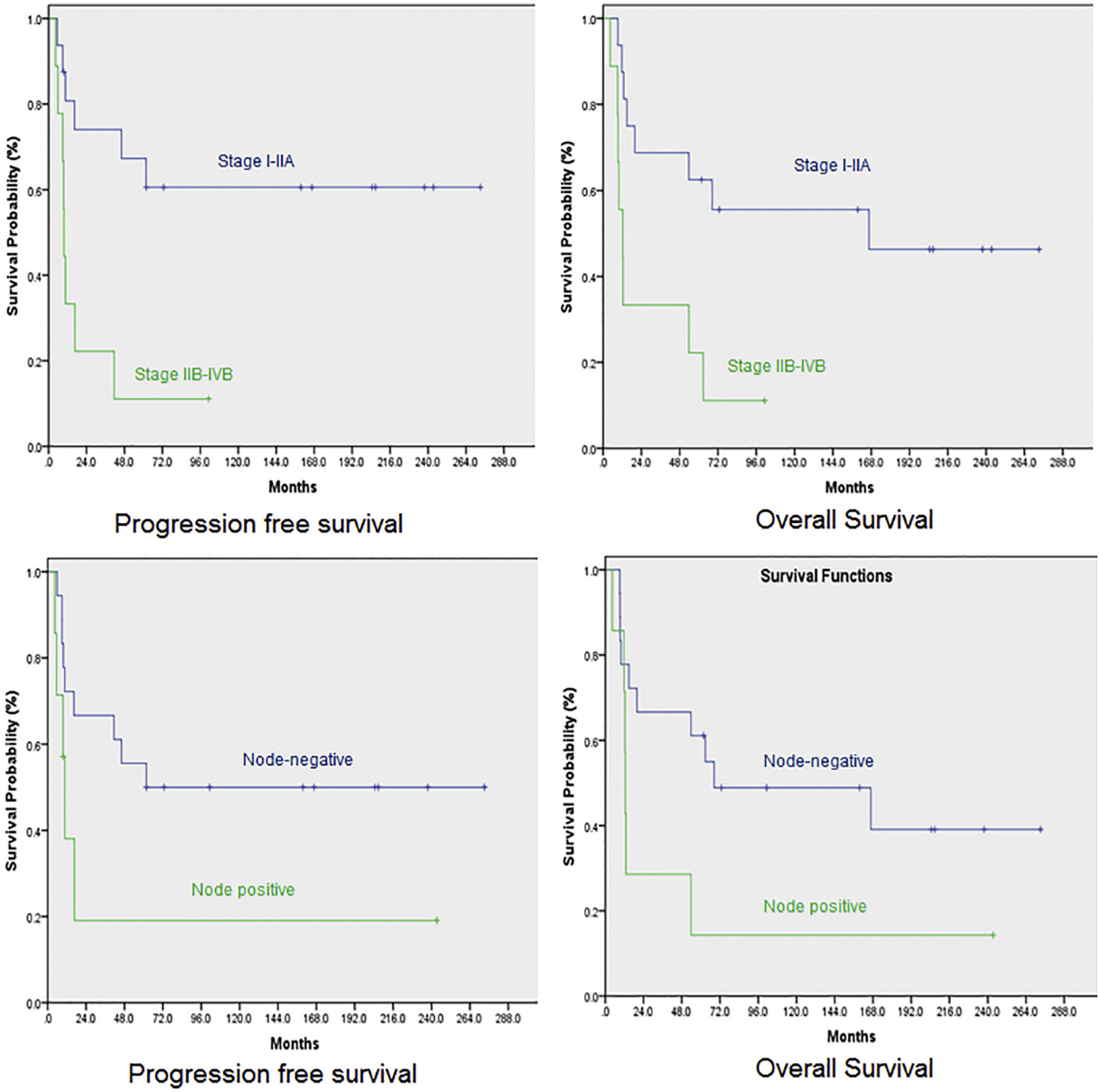

Fig. 2. Impact of stage and nodal involvement on overall and progression free survival.

patient was 41 (range: 23–80). Pure small cell carcinoma was noted in 17 (68%) patients while 6 (24%) patients had additional neuroendocrine component. Mixed adenocarcinoma with SmCC was noted in 2 (8%) patients. Majority of patients (n = 20; 80%) had high grade cancer, rest (n = 5, 20%) had intermediate grade. Most (n = 16; 64%) of the patients had early stage (stage I-IIA) disease: stage IB (n = 12; 48%) and IIA (n = 4; 16%). Stage IIB, IIIB and IVB disease were identified in 5 (20%), 3 (12%) and 1 (4%) patients respectively. Overall 7 (28%) patients had radiographically node-positive (N+) disease while 18 (72%) had node-negative (N-) disease. Five out of 7 (71%) (N+) patients had combined pelvic and para-aortic EBRT and 2 had pelvic EBRT (29%). A total of 11 out of 18 (61%) (N-) patients underwent pelvic and para-aortic EBRT while 7 (39%) had pelvic EBRT. Total 24 (96%) patients completed the full course of EBRT and brachytherapy; one patient did not receive full course EBRT due to interim disease progression. PCI was used in 6 (24%) patients after completion of loco-regional EBRT. A total of five (20%) patients had salvage surgery after completion of chemo-radiotherapy.

3.2. Pattern of failure

After a median follow-up duration of 54 months (range: 4.5–270.9 months), 15 (60%) patients had disease progression; 12 (48%) patients had distant metastasis. Isolated distant metastasis was seen in 6 (24%) patients, combined distant and nodal metastasis was noted in 5 (20%) patients, and combined local, nodal and distant failure was noted in 1 (4%) patient. One (4%) patient had disease progression locally and in pelvic nodes. Isolated local and isolated nodal metastasis were identified in 1 (4%) patient each. The frequent sites of distant metastasis were liver (n = 4), brain (n = 3), bone (n = 2), lung/pleural metastasis (n = 2), bone marrow (n = 1).

There was no difference in local failure rate between patients treated with pelvic EBRT (n = 1; 11%) and combined pelvic & para-aortic EBRT (n = 2; 12.5%). Nodal failure rate was also comparable between the combined pelvic & para-aortic (n = 6; 37.5%) and pelvic EBRT group (n = 3; 33%). Among 6 patients with nodal failures in the combined pelvic & para-aortic EBRT group, 3 (50%) had (N+) disease on the pre-treatment staging while among 3 patients with nodal failure in the pelvic EBRT group, 1 (33%) had (N+) disease. The sites of nodal

Table 1
Result of univariate analysis (log-rank test).

Factors	5-yr PFS	'p' value	5-year OS	'p' value
Age				
≤ 40	82%	0.461	85%	0.474
> 40	64%		69%	
RT target volume				
Pelvic + Para-aortic	50%	0.699	56.3%	0.444
Pelvic alone	40%		33.3%	
Delay in start of Rx:				
≤ 1 month	44.2%	0.588	56%	0.444
> 1 month	50%		33%	
Stage:				
I-IIA	55.7%	0.004	62.5%	0.006
IIB	0%		22.2%	
Node involvement				
No (N-)	55.7%	0.07	61.1%	0.06
Yes (N+)	19%		14.3%	
Prophylactic cranial RT				
Used	66.7%	0.142	66.7%	0.09
Not-used	36.4%		38.9%	
Presence of NEC				
No	47.4%	0.254	52.6%	0.210
Yes	50%		33%	

PFS: progression free survival; OS: overall survival; RT: radiotherapy; NEC: neuro-endocrine carcinoma component.

failure in patients treated with pelvic EBRT included retroperitoneal chain ($n = 1$) and supraclavicular fossa (n = 1) respectively. For those who had combined pelvic and para-aortic EBRT, 3 had failure in retroperitoneal chain, 2 in both retroperitoneal and pelvic nodal areas and 1 in supraclavicular fossa.

Overall incidence of distant failure ($n = 1$; 16.67% vs. $n = 11$; 57.9%) and intra-cranial failure (0% vs. $n = 3$; 15.8%) were less in patients who had PCI compared to those treated without PCI.

3.3. Survival analysis

At the time of analysis, 16 (64%) patients had died. 13 (81.3%) had deaths related to their primary cancer, remaining 3 (18.7%) died from second malignancies (colon cancer, ovarian carcinoma and leukemia, respectively). The 5-year OS and PFS were 48% and 46.4%, respectively (Fig. 1). On univariate analysis we found that patients with stage I-IIA disease had superior 5-year PFS (67.3% vs. 11.1%; $p = .004$) and 5-year OS (62.5% vs. 22.2%; $p = .006$). Patients with radiographic (N-) disease had a trend towards better 5-year PFS (55.7% vs. 19%; $p = .07$) and OS (61.1% vs. 14.3% at 5-years; $p = .06$) (Fig. 2). Patients treated with pelvic & paraaortic EBRT had 5-year OS and PFS of 56.3% and 50% compared to 40% and 33.3% in patients treated with pelvic EBRT. Patients with ≤ 40 years of age had 5-year OS and PFS of 85% and 82% compared to 69% and 64% in patients older than 40 years. There were no significant differences among the groups on log-rank test. Patients treated with PCI had numerically superior OS (67% vs. 39%, $p = .09$) and PFS (67% and 36%, $p = .142$). The results of log-rank tests have been summarized in Table 1.

A comparative description of outcome in available literature on SmCC (Boruta II et al., 2001; Zivanovic et al., 2009; Cohen et al., 2010; Kuji et al., 2013; Lee et al., 2015; Chen et al., 2008; Viswanathan et al., 2004; Wang et al., 2012a; Huang et al., 2014; Li et al., 2015a; Lee et al., 2008; Stecklein et al., 2016; Peng et al., 2012; Lan-Fang et al., 2012; Yuan et al., 2015; Nagao et al., 2015; McCann et al., 2013; Lee et al., 2016) have been summarized in Table 2.

4. Discussion

The current study describes the outcomes of a cohort of SmCC treated with radical chemo-radiation in our province. The findings of our study consolidate the results of the study by Hoskins et al. (Hoskins et al., 2003). Patients in our study were treated radically using uniform chemo-radiotherapy protocol across the province. The follow-up duration in our study is relatively longer compared to other reports and the survival figures and overall failure rates are in agreement with available literature (Zivanovic et al., 2009; Viswanathan et al., 2004; Wang et al., 2012a). We found distant metastasis to be the predominant pattern of disease progression while stage and nodal involvement were noted to have association with survival. These findings are also in accordance with existing studies (Cohen et al., 2010; Kuji et al., 2013; Chen et al., 2008; Wang et al., 2012a; Huang et al., 2014; Li et al., 2015a; Lee et al., 2008).

Radiation therapy plays a pivotal role in the management of SmCC. The survival outcome in our series which primarily includes a cohort of patients treated with chemo-radiation, is compatible with that from other surgical series (Kuji et al., 2013; Lee et al., 2008; Lee et al., 2016). This highlights the efficacy of EBRT as a loco-regional treatment modality. Other studies including a large Taiwanese Gynecologic Oncology Group (TGOG) (Wang et al., 2012a) study have established the efficacy of concurrent chemo-radiation in the treatment of SmCC. Chen et al. reported a lower locoregional failure rate in patients who received primary radiotherapy than those who had primary surgery in stage I-II SCCC (6% vs. 27%, $P = .009$) (Chen et al., 2008). However, none of these studies described the ideal target volume of radiotherapy for these patients. Radiation target volume needs to be tailored depending on overall tumor stage including nodal involvement, use of chemotherapy and individual tolerance.

Our study shows improved distant control, intracranial disease control and a numerically superior overall survival with PCI. However, there are underlying confouding factors including non-random patient allocation and limited sample size. Moreover, the overall rate of intracranial failure is only 12% at 5-years which is comparable to other series on extra-pulmonary small cell carcinoma (EPSCC) (De Caluwé et al., 2017; Naidoo et al., 2013; Müller et al., 2012). However, these patients did not undergo serial brain imaging during their follow-up and therefore the failure rate should be interpreted with caution. Naidoo et al. (Naidoo et al., 2013) studied 280 patients of EPSCC. Approximately 66% belonged to extensive stage and 17 (6%) had primary cervical SmCC. They found an intra-cranial metastasis rate of 6.5%. Another study by De Caluwé et al. (De Caluwé et al., 2017) estimated the incidence of symptomatic brain metastasis from a cohort of EPSCC. The overall rate of brain metastasis was 12.5% at 3-years. In PCI Eligible patients, defined as patients with non-metastatic EPSCC who received local or systemic treatment, or metastatic EPSCC who responded to systemic treatment, the 3-year cumulative incidence of new brain metastases was 5.5% for non-metastatic cohorts and 26.3% for M1 disease. The 3-year cumulative incidence of brain metastasis in patients with cervical SmCC was 8.7%. In the absence of prospective studies, the findings of these large retrospective series allude to a relatively low rate of intra-cranial metastasis in EPSCC. Moreover, several studies have highlighted the long-term neurocognitive effect of PCI including significant decline in memory (both immediate and delayed recall) in patients with lung cancer (Sun et al., 2011; Wolfson et al., 2011). Therefore, PCI might be dispensable in primary SmCC, but should always be discussed as part of multi-modality management protocol.

In our cohort, the use of complex multi-agent chemotherapy regimen was reasonably well tolerated and outcomes were comparable to historic cohorts (Hoskins et al., 2003). A cisplatin/etoposide (EP) regimen similar to that used for small cell lung cancer, however, may be most widely used and is described in Gynecologic Cancer Inter Group (GCIG) Consensus Review (Tempfer et al., 2018; Satoh et al., 2014). In retrospective studies and systematic reviews, an addition of platinum-based chemotherapy in pre-operative or post-operative setting was associated with improved OS and PFS (Tempfer et al., 2018; Li et al., 2015b; Zhang et al., 2018). Similarly, concurrent chemotherapy may improve survival outcomes in conjunction with radiation therapy,

Table 2
Other studies of Small cell carcinoma of cervix.

Authors	Year of publication	Patients	Treatment used	Median follow-up	Survival outcome	Stage-wise survival
Boruta et al. (Boruta II et al., 2001)/USA	2001	34	Sx + Adj. CTx	–	OS at 2-years: 38%	–
Vishwanathan et al. (Viswanathan et al., 2004)/USA	2004	21	Mixed	83 mo. (surviving pts)	OS at 5-years: 29%	–
Zivanovic et al. (Zivanovic et al., 2009)/USA	2009	17	Mixed	21 mo.(surviving pts)	OS at 3-years: 30% PFS at 3-years: 22%	–
Cohen et al. (Cohen et al., 2010)/literature review	2010	188	Mixed	N/A	–	5-year DFS: I-IIA: 36.8% IIB-IV: 8.9%
Chen et al. (Chen et al., 2008)/SEER	2008	290	Mixed	14.5 mo.	OS at 5-years: 35.7%	–
Lee et al. (Lee et al., 2008)/Korea	2008	68 (stage IB-IIA)	Sx ± Adj. treatment	44 mo.	OS at 5-years: 46.6%	–
Wang et al. (Wang et al., 2012a)/Taiwan	2012	179	Mixed	51.2 mo. (surviving pts)	Median CSS: 24.8 mo. Median FFS: 16 mo.	I (51.1%) II (50.4%) III (13%) IV (6%)
Peng et al. (Peng et al., 2012)/China	2012	14 (NEC)	Sx ± Adj. treatment	10 mo.	Median OS: 32 mo. Median DFS: 6 mo.	–
Kuji et al. (Kuji et al., 2013)/Japan	2013	52	Mixed	57 mo.	–	4-year OS & PFS: IB1: 63%, 59% IB2: 67%, 68% IIB: 30%, 13% IIIB: 29%, 17% IVB: 25%
Stecklein et al. (Stecklein et al., 2016)/USA	2016	40 (NEC)	Mixed	21.5 mo.	OS at 5-years: 27% EFS at 5-years: 20%	Median OS: ≤ Stage IB1: 41 mo. ≥ Stage IB2: 17 mo.
Lan Fang et al. (Lan-Fang et al., 2012)/China	2012	43	–	–	OS at 5-years: 29%	Median OS: Early stage: 89.6 mo. Late stage: 34.4 mo.
Lee et al. (Lee et al., 2015)/Korea	2015	102	Mixed	–	–	Median OS & TTP: Early stage: 40.7 & 22.3 mo. Late stage: 21.4 & 13.3 mo.
Yuan et al. (Yuan et al., 2015)/China	2015	38 (Stage IA-IIA)	Sx ± Adj. CTx	–	OS at 5-years: 43% Median DFS: 36 mo.	–
Nagao et al. (Nagao et al., 2015)/Japan	2015	23	Mixed	24 mo.	5-year OS: Small cell NEC-19% Large cell NEC: 91%	–
Li et al. (Li et al., 2015a)/China	2015	22	Mixed	24.1 mo.	OS at 3-years: 55% DFS at 3-years: 50%	3-year OS: Early stage: 68% Late stage: 0%
Huang et al. (Huang et al., 2014)/China	2014	72	Mixed	–		4-year OS: IB1: 63% IB2: 67% IIB: 30% IIIB: 29% IVB:25%
McCann et al. (McCann et al., 2013)/USA	2013	26	Mixed	27 mo.	–	Median OS: Stage I: NR Stage II-IV: 12.1 mo
Lee et at (Lee et al., 2016)/Korea	2016	61	Sx ± Adj. Tx	–	–	5-year OS: Early-42.1%, Late-23.7%
Roy et al./current study	–	25	CTx + RT ± PCI	54 mo.	OS at 5-years: 48% PFS at 5-years: 46.4%	5-year PFS & OS: Stage I-IIA: 55.7% & 62.5% Stage IIB-IVB: 0% & 22.2%

Mo.: months; Sx: surgery; Adj: adjuvant; CTx: chemotherapy; RT: radiotherapy; NEC: neuro-endocrine carcinoma; pts.: patients; OS: overall survival; PFS: progression free survival; DFS: disease specific survival; CSS: cancer specific survival; FFS: failure free survival; EFS: event free survival; TTP: time to progression; NR: not reached; PCI: Prophylactic cranial irradiation.

although no level I evidence exists to demonstrate what constitutes an optimal regimen. In setting of concurrent chemoradiation, at least one retrospective study identified that receipt of 5 or more cycles of EP was associated with significantly better 5-year failure-free survival and cancer-specific survival (Wang et al., 2012b). In the absence of evidence from direct comparison, the addition of a platinum-based chemotherapy regimen is generally accepted as standard of care in this context.

Some of the limitations of the current study include its retrospective nature, limited patient number, lack of comprehensive information

about quality of life parameters including treatment related toxicities and neurocognitive effects of PCI among others.

Despite these caveats, we conclude that combined modality treatment using multi-agent platinum-based chemotherapy and loco-regional radiotherapy remains cornerstone of non-surgical management for patients with small cell carcinoma of the cervix. Role of PCI is controversial. With modern chemo-radiotherapy protocols we can expect a 5-year survival of around 50%. Stage and nodal involvement bear significant correlation with survival and these factors should be given consideration while customizing treatment.

Source of support

None.

Funding/disclosure

None.

Conflicts of interest

None.

Contribution of authors

Soumyajit Roy: Idea, Data collection, data analysis and interpretation, manuscript write up, critical appraisal and approval of the final content.

Jenny Ko: Data collection, data analysis and interpretation, manuscript write up, critical appraisal and approval of the final content.

Gaurav Bahl: Idea, Data collection, data analysis and interpretation, manuscript write up, critical appraisal and approval of the final content.

References

Albores-Saavedra, J., Gersell, D., Gilks, C.B., et al., 1976. Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. Cancer 38, 2328–2342.

Boruta II, D.M., Schorge, J.O., Duska, L.A., Crum, C.P., Castrillon, D.H., Sheets, E.E., 2001. Multimodality therapy in early-stage neuroendocrine carcinoma of the uterine cervix. Gynecol. Oncol. 81, 82–87.

Chan, J.K., Loizzi, V., Burger, R.A., Rutgers, J., Monk, B.J., 2003. Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer 97, 568–574.

Chen, J., Macdonald, O.K., Gaffney, D.K., 2008. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. Obstet. Gynecol. 111, 1394–1402.

Cohen, J.G., Kapp, D.S., Shin, J.Y., et al., 2010. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. Am. J. Obstet. Gynecol. 203 347.e1-6.

De Caluwé, A., Bowering, G., Nichol, A., Hsu, F., 2017. The incidence of symptomatic brain metastases from extra-pulmonary small cell carcinoma: is there a role for prophylactic cranial irradiation in a clinically relevant population cohort? Radiother. Oncol. 124, 31–37.

Hoskins, P.J., Swenerton, K.D., Pike, J.A., et al., 2003. 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. 21, 3495–3501.

Huang, L., Liao, L.M., Liu, A.W., et al., 2014. Analysis of the impact of platinum-based combination chemotherapy in small cell cervical carcinoma: a multicenter retrospective study in Chinese patients. BMC Cancer 14, 140.

Kuji, S., Hirashima, Y., Nakayama, H., et al., 2013. Diagnosis, clinicopathologic features, treatment, and prognosis of small cell carcinoma of the uterine cervix; Kansai Clinical Oncology Group/Intergroup study in Japan. Gynecol. Oncol. 129, 522–527.

Lan-Fang, L., Hai-Yan, S., Zuo-Ming, Y., Jian-Qing, Z., Ya-Qing, C., 2012. Small cell neuroendocrine carcinoma of the cervix: analysis of the prognosis and role of radiation therapy for 43 cases. Eur. J. Gynaecol. Oncol. 33, 68–73.

Lee, J.M., Lee, K.B., Nam, J.H., et al., 2008. Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study. Ann. Oncol. 19, 321–326.

Lee, S.W., Lim, K.T., Bae, D.S., et al., 2015. A multicenter study of the importance of systemic chemotherapy for patients with small-cell neuroendocrine carcinoma of the uterine cervix. Gynecol. Obstet. Investig. 79, 172–178.

Lee, D.Y., Chong, C., Lee, M., et al., 2016. Prognostic factors in neuroendocrine cervical carcinoma. Obstet Gynecol Sci. 59, 116–122.

Li, X., Yang, R., Jia, Y., Zhou, J., Ma, D., Li, S., 2015a. Prognostic risk factors for small cell carcinoma of the cervix and impact of platinum-based neoadjuvant chemotherapy. Int. J. Gynaecol. Obstet. 130, 31–35.

Li, X., Yang, R., Jia, Y., Zhou, J., Ma, D., Li, S., 2015b. Prognostic risk factors for small cell carcinoma of the cervix and impact of platinum-based neoadjuvant chemotherapy. Int. J. Gynaecol. Obstet. 130, 31–35.

McCann, G.A., Boutsicaris, C.E., Preston, M.M., et al., 2013. Neuroendocrine carcinoma of the uterine cervix: the role of multimodality therapy in early-stage disease. Gynecol. Oncol. 129, 135–139.

Miller, B., Dockter, M., el Torky, M., Photopulos, G., 1991. Small cell carcinoma of the cervix: a clinical and flow-cytometric study. Gynecol. Oncol. 42, 27–33.

Müller, A.C., Gani, C., Weinmann, M., et al., 2012. Limited disease of extra-pulmonary small cell carcinoma. Impact of local treatment and nodal status, role of cranial irradiation. Strahlenther. Onkol. 188, 269–273.

Nagao, S., Miwa, M., Maeda, N., et al., 2015. Clinical features of neuroendocrine carcinoma of the uterine cervix: a single-institution retrospective review. Int. J. Gynecol. Cancer 25, 1300–1305.

Naidoo, J., Teo, M.Y., Deady, S., Comber, H., Calvert, P., 2013. Should patients with extrapulmonary small-cell carcinoma receive prophylactic cranial irradiation? J. Thorac. Oncol. 8, 1215–1221.

Peng, P., Ming, W., Jiaxin, Y., Keng, S., 2012. Neuroendocrine tumor of the uterine cervix: a clinicopathologic study of 14 cases. Arch. Gynecol. Obstet. 286, 1247–1253.

Satoh, T., Takei, Y., Treilleux, I., et al., 2014. Gynecologic Cancer InterGroup (GCIG) consensus review for small cell carcinoma of the cervix. Int. J. Gynecol. Cancer 24, S102–S108.

Scully, R.D., Aguirre, P., DeLellis, R.A., 1984. Argyrophilia, serotonin, and peptide hormones in the female genital tract and its tumors. Int. J. Gynecol. Pathol. 3, 51–70.

Sevin, B.U., Lu, Y., Block, D.A., Nadji, M., Koechli, O.R., Averette, H.E., 1996a. Surgically defined prognostic parameters in patients with early cervical carcinoma. A multivariate survival tree analysis. Cancer 78, 1438–1446.

Sevin, B.U., MethodMW, Nadji M., Lu, Y., Averette, H.A., 1996b. Efficacy of radical hysterectomy as treatment for patients with small cell carcinoma of the cervix. Cancer 77, 1489–1493.

Stecklein, S.R., Jhingran, A., Burzawa, J., et al., 2016. Patterns of recurrence and survival in neuroendocrine cervical cancer. Gynecol. Oncol. 143, 552–557.

Sun, A., Bae, K., Gore, E.M., et al., 2011. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non–small-cell lung cancer: neurocognitive and quality-of life analysis. J. Clin. Oncol. 29, 279–286.

Tavassoli, F.A., Devilee, P., 2003. World Health Organization classification of tumours. In: Pathology and Genetics of Tumours of the Breast and Female Genital Organs, 3rd ed. IARC Press, Lyon, pp. 279.

Tempfer, C.B., Tischoff, I., Dogan, A., et al., 2018. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer 18, 530.

Viswanathan, A.N., Deavers, M.T., Jhingran, A., Ramirez, P.T., Levenback, C., Eifel, P.J., 2004. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. Gynecol. Oncol. 93, 27–33.

Wang, K.L., Chang, T.C., Jung, S.M., et al., 2012a. Primary treatment and prognostic factors of small cell neuroendocrine carcinoma of the uterine cervix: a Taiwanese Gynecologic Oncology Group study. Eur. J. Cancer 48, 1484–1494.

Wang, K.L., Chang, T.C., Jung, S.M., et al., 2012b. Primary treatment and prognostic factors of small cell neuroendocrine carcinoma of the uterine cervix: a Taiwanese Gynecologic Oncology Group study. Eur. J. Cancer 48, 1484–1494.

Wolfson, A.H., Bae, K., Komaki, R., et al., 2011. Primary analysis of a phase II Randomized Trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol 81, 77–84.

Yuan, L., Jiang, H., Lu, Y., Guo, S.W., Liu, X., 2015. Prognostic factors of surgically treated early-stage small cell neuroendocrine carcinoma of the cervix. Int. J. Gynecol. Cancer 25, 1315–1321.

Zhang, Q., Xiong, Y., Ye, J., Zhang, L., Li, L., 2018 Apr 11. Influence of clinicopathological characteristics and comprehensive treatment models on the prognosis of small cell carcinoma of the cervix: a systematic review and meta-analysis. PLoS One 13 (4), e0192784.

Zivanovic, O., Leitao Jr., M.M., Park, K.J., et al., 2009. Small cell neuroendocrine carcinoma of the cervix: Analysis of outcome, recurrence pattern and the impact of platinum-based combination chemotherapy. Gynecol. Oncol. 112, 590–593.