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Small Cell Neuroendocrine Cervical Carcinoma: A Review

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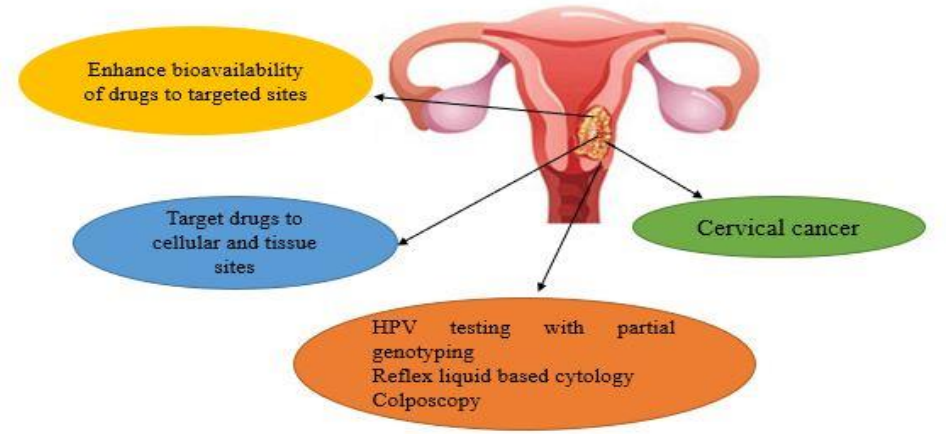
ABSTRACT

Small cell neuroendocrine cervical carcinoma (SCNCC) are neuroendocrine tumors neoplasms (NEN), an intrusive and rare disease originating from neuroendocrine cells that is basically linked with poor treatment or prognosis. Postoperative adjuvant peripheral radiotherapy has been described as a routine treatment. In spite of violent and unusual remedies, high mortality rate was observed in patients with earlier stage of neuroendocrine cervical carcinoma (NECC). The understanding was studied during the early stage of this malignancy, considered the desired work for the identification of predictive issues and optimum multi-modality treatment was concluded. By illustrating cytological elements along with reassessing the consequences of cytological smudges of cervix towards disease manifestations, the investigative specificity might be increased along with patient outcomes. Thus, a unique and novel methodology needs to be introduced to comprehend and cure this malignancy.

Keywords: carcinoid tumors, cervical cancer, chemotherapy, cytological features, radiotherapy

GRAPHICAL ABSTRACT



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Highlights

1. Small Cell Cervical Carcinoma (SCCC) is a rare and a very aggressive tumor.

2. It originates from neuroendocrine cells, linked with poor treatment or prognosis.

3. Combination surgery, chemotherapy, and radiotherapy treatment are usually used to treat SCCC, although evidence of their efficacy remains inconclusive.

1. INTRODUCTION

Small cell cervical carcinoma (SCCC) was firstly reported in 1957 by Regan and his colleagues [1]. Far ahead in 1972, Albores-Saavedra [2] described neuroendocrine tumors (NET). Cervical cancer has been ranked as the third most common cancer of which SCCC constitutes 1-3% tumors of cervix [3]. It is known as neuronal-endocrine cancer having some of the features of small cell carcinoid of lungs also termed as “extra pulmonary” small cell carcinoid [4]. In spite of inclusive failures in occurrence rates, cervix cancer has been regarded as the second or third utmost popular malignancy in women with somehow ~0.5 million cases globally [5]. Cervical neuroendocrine tumors are now classified by the World Health Organization (WHO) 2014, as either low-grade (carcinoid or atypical carcinoid tumor) or high-grade neuroendocrine carcinomas (small-cell carcinoma or large-cell neuroendocrine carcinoma) [6].

It is an aggressive sub-type of cervical tumor that is limited to the pelvis and its outcomes are poor. It is extremely lethal and is linked with lesser survival of the cervical malignancies. It proceeds quickly to lymphogenous and hematogenous metastasis and with reduced diagnosis. Patients having early-stage small cell carcinoma (SmCC) might be vulnerable to treatment failure due to high rates of lympho-vascular invasion that may affect lymph node metastasis and hematogenous spread [7]. Patients with SCCC often experience sensory management failures associated with early local recurrence or distant metastases, which are typically found in the brain, lung, liver, and bone [8, 9].

Patients mostly detected with small cell neuroendocrine carcinoma (SCNEC) have lymph vascular space invasion and lymph node metastasis [10]. A radical hysterectomy and lymphadenectomy with platinum-based therapy and adjuvant etoposide were also advised by the Society of Gynecologic Oncology (SGO) for patients with cervical malignancies less than four cm in size [11, 12]. Due to the rarity of the disease, clinical research has been constrained and treatment guidelines for both primary and recurrent cervical tumors are entirely based on research for lung cancer that resembles small cell cervical tumor in both histology and aggressive behavior [12, 13]. The diagnosis of primary carcinoma of cervix is conducted by cervix biopsy by considering the histopathological characters that are the distinctive features of SCC in addition to primary lung carcinoma [4].

Though, histopathology is considered as a backbone of diagnosis, immunohistochemistry (IHC) also plays a critical role to confirm both the identification and to determine the primary site of the tumor origin [14, 15]. Chemotherapy, surgery, and radiation therapy are the three main treatment options for SCNEC [16, 17]. Even after a full surgical resection of the SCNEC, the

condition can recur within a few months. The 5-year survival rates for SCNEC still range from 25% to 39% despite comprehensive treatment [18, 19]. Thus, there is a dire need for novel approaches to understand and treat this tumor..

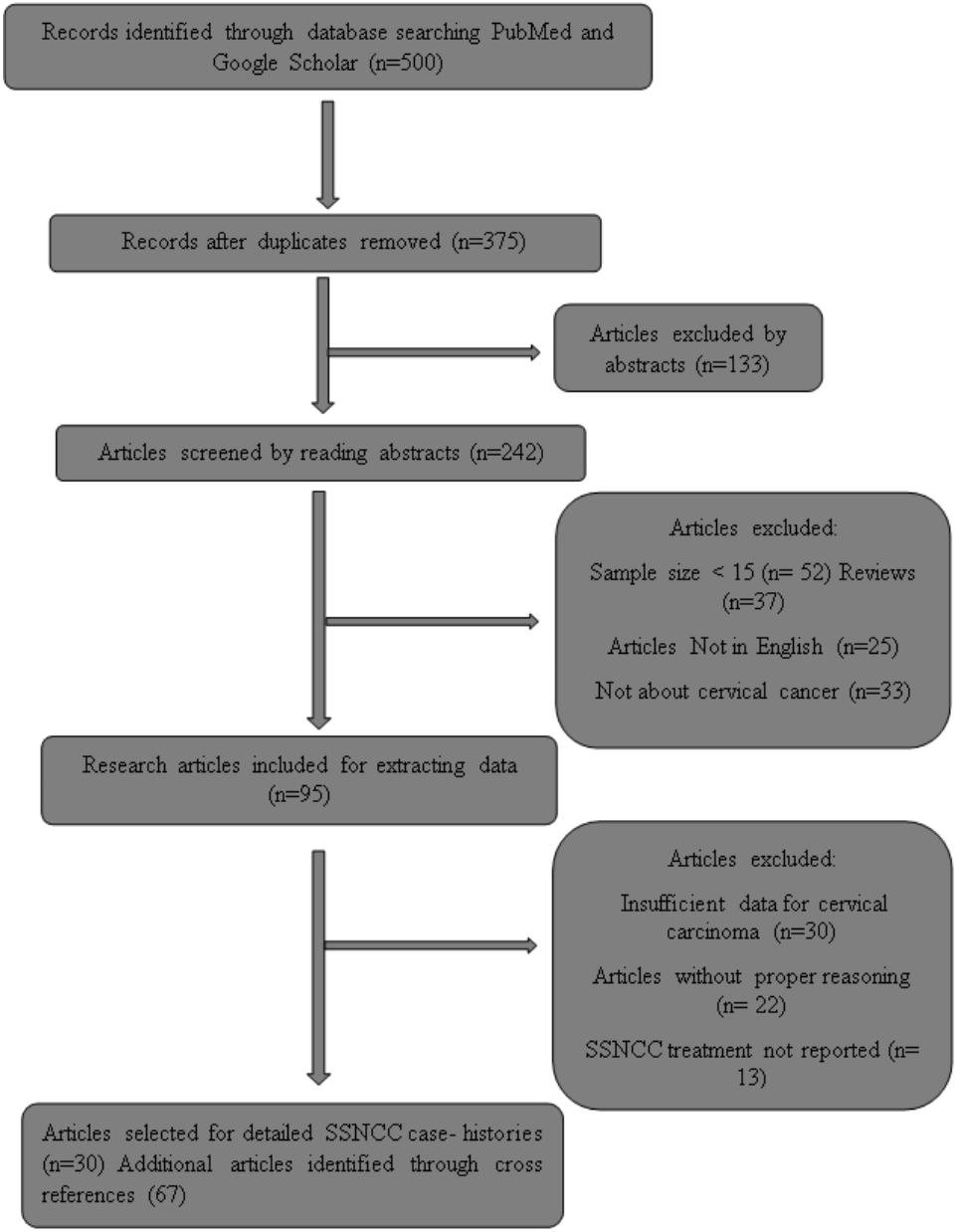

Figure 1. Flow Chart for the Selection Strategy and Inclusion / Exclusion Criteria for Small Cell Neuroendocrine Cervical Carcinoma

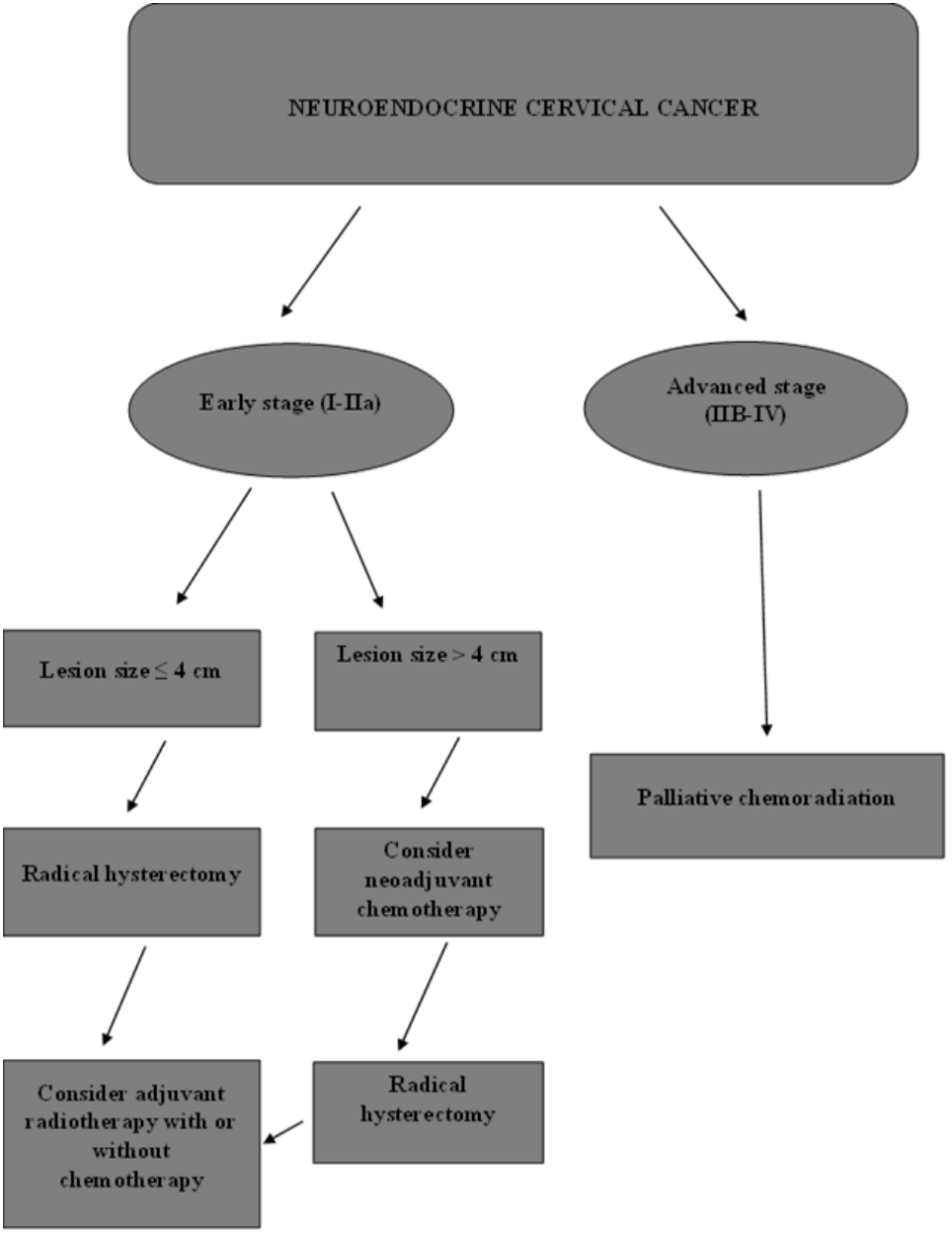

Figure 2. Management Scheme for Neuroendocrine Cervical Carcinoma

2. METHODOLOGY

Systematic literature search was conducted by database PubMed and Google Scholar using search terms "neurosecretory systems, neuroendocrine, neoplasms, carcinoid tumors, cervical cancer, cervical

carcinoma, uterine cervical neoplasms, small cell neuroendocrine cervical carcinoma, and therapeutics". After searching the published data pertaining to small cell neuroendocrine cervical cancer, some repeated records were eliminated after reading the abstracts and further screening was conducted by considering their sample size along with the data regarding cervical cancer. Some studies were excluded which lacked proper reasoning about cervical cancer and its treatment. Articles selected for detailed small cell neuroendocrine cervical carcinoma case studies were thirty in number. Remaining studies (sixty-seven articles) were retrieved along with their cross reference searching. Moreover, further appropriate work regarding the neuroendocrine cervical cancer (NECC) was also added to the study. Detailed explanation of literature for the selection strategy, inclusion or exclusion criteria for small cell neuroendocrine cervical carcinoma is mentioned in Figure 1. While, Figure 2 indicates general management scheme for neuroendocrine cervical carcinoma

3. CYTOLOGICAL CHARACTERISTICS AND TREATMENT OF CERVICAL SMALL CELL CARCINOMA (SCC)

Proper evaluation of both quality and amount of neoplasm is necessary for the best management of cervical cancer patients. The current study provided the findings of a systematic review of literature which comprised case histories of females with small cell neuroendocrine cervical carcinoma in order to emphasize some clinical aspects, therapy, and prognosis of women with small cell neuroendocrine cervical cancer. Common therapies along with their outcomes of this malignancy were also discussed.

Medical histories, histology, and most recent smears of all cases of SCC of the uterine cervix were investigated in the British Columbia Cancer Agency between the time period 1985 and 1997. Cervical smears were discovered in 11 out of 13 infamous instances. Out of these, 6 cases had a pre-treatment smear that showed a variety of malignant cells in it. In contrast to six malignant smears, none of the seven cases with negative smears were diagnosed as SCC on cervical smears due to missing high grade squamous intraepithelial lesions in one case and uncommon suspicious epithelial cells in other patients [20].

Behind pelvic lymphadenectomy or essential abdominal hysterectomy having neuroendocrine tumor confirmed by immune histochemical staining or electron microscopy, two patients were provided adjuvant complete chemotherapy with synchronized pelvic radiotherapy using treatments against SCC of lungs having neuroendocrine origin. Both patients were alive without any clinical sign of disease in spite of harsh myelotoxicity and obstinate neuropathy at twenty eight and forty seven plus months [21]. Another study reported 188 patients with different stages, that is, 135 (I-IIA), 45 (IIB-IVA), and 8 (IVB) who underwent different treatments, for instance, surgery, chemotherapy, and chemoradiation, respectively. Survival rate during 5-years was 36.8% (I-IIA), 9.8%, (IIB-IVA), and 0% (IVB). Chemoradiation has increased survival rate for IIB-IVA stage patients as compared to others with no chemotherapy treatment (17.8% vs 6.0%) [16].

In another study of Federation of International Gynecology and Obstetrics (FIGO), 11 women with initial stage (IB-IIA) of neuroendocrine cervical cancer were successfully treated with

chemotherapy and surgery. According to the findings, the overall two-year survival rate for these thirty-four individuals was 38% and 15 out of 29 individuals had lymph node metastases. Just seven of these patients underwent Vincristine Adriamycin cyclophosphamide (VAC), two received alternate phases of VAC and postoperative platinum or etoposide (PE) and 10 were treated with alternative chemotherapy. Among these patients, 15 received postoperative platinum or etoposide (PE). Radiation therapy helped in the recovery of twenty ladies. Resultantly, VAC chemotherapy was linked to an improved survival rate, however, platinum-etoposide was not strongly connected with the existence of lymph node metastases [22].

Twenty-one out of forty-five cases examined between the time period 1980 and 2000 had small cell neuroendocrine carcinoma as determined by the presence of positive chromogranin, CD56 or synaptophysin staining. Radiation therapy was used as the local treatment for fifteen patients and a radical hysterectomy for six of these individuals. Chemotherapy was a component of initial care for 13 patients. According to the findings, 14 out of twenty-one patients' conditions were found to be worse. In radioactivity fields, just two of the fifteen patients who had radiation therapy showed a recurrence. However, two patients experienced a relapse distal to the pelvic fields in the vagina and five patients experienced a recurrence above the radiation fields in the para-aortic lymph nodes. This is because, brain is the only site of first recurrence, no patient had brain metastases. On the other hand, in two individuals, lung and brain metastases occurred simultaneously. Although, none of the patients with disease more advanced than stage IB1 or lymph node metastases had survived and the overall-survival rate (OS) at 5 years was 29% [23].

Retrospective analysis of all patients between 1990 and 2007 was conducted to investigate progression-free and overall survival in patients with small cell neuroendocrine cervical cancer and to determine whether platinum-based treatment is beneficial for this population. In the early-stage, the three-year recurrence-free survival rate was 83% as compared to 0% in the group of patients who did not get chemotherapy as part of their first treatment. Overall, three year survival rate was eighty-three percent (83%) for patients receiving chemotherapy. While, twenty percent (20%) for patients who did not have chemotherapy exposure as a primary treatment [24].

Patients identified with SCC of the uterine cervix between the time period 1997 and 2007 were signed up at medical centers contributing in Kansai Clinical Oncology Group/Intergroup. Seventy-one patients were registered at twenty-five medical centers in Japan. Of these, only fifty-two patients were identified with SCC of the uterine cervix. The average follow-up period was fifty-seven months. To check post-operative adjuvant therapy, post-operative chemotherapy was associated to non-chemotherapy. Four-year progression-free rate was sixty-five (65) and fourteen percent (14%), while the four-year overall survival (OS) was sixty-five percent65% and twenty-nine percent (29%), respectively. Progression-free survival rate was significantly better, while the overall survival rate (OS) had a tendency to be better in the group having postoperative chemotherapy [25].

To assess how well surgery, chemotherapy, and radiation therapy work to control SCCC, medical records and histological reports of one hundred and forty-four (144) patients from 1987 to 2009 having FIGO stages IA–IIB SCC of uterine cervix cured in eleven (11) main hospitals in Taiwan were observed. Of these, one hundred and ten patients (110) had primary surgery, while thirty-four (34) had primary radiation therapy. Eighty-nine (89%) of thirteen (13) surgically treated patients with cervical tumors larger than or equal to two cm survived for five years. While, no lymph vascular space was noted in two out of four patients not having adjuvant chemotherapy and no one in the nine patients who had chemotherapy experience. A five-year overall survival rate (OS) of 78% was achieved with primary radiation therapy, excluding these thirteen patients, and at least five cycles of platinum-based chemotherapy when the patient count was fourteen. This was significantly better than the 46% achieved with primary surgery when the patient count was ninety-seven and forty stages IB2-IIB [8]

In another study conducted on women with SCCC, thirteen patients received topotecan, paclitaxel, and bevacizumab (TPB), while twenty-one (21) received non-TPB chemotherapy. The median progression free survival (PFS) with TPB was 7.8 months as compared to non-TPB regimens' for four months. The median OS rate with TPB was 9.7 months as compared to 9.4 months for non-TPB therapies. Eight women with TPB and four with non-TPB regimens received treatment for six months each. Whereas, four patients in the topotecan, paclitaxel, and bevacizumab group and two in the non-TPB group received treatment for twelve months. In TPB group, it was noted that three patients responded completely towards therapy, two had a complete response outside the brain, two had stable disease, three had a partial response, and three had progressive disease after the therapy [26].

Patients with FIGO stages I–IV neuroendocrine small cell cervical cancer received treatment at member hospitals of the Taiwanese Gynecologic Oncology Group between the time period 1987 and 2009. About 104 patients out of 179 were in FIGO stage I, 19 were in stage IIA, 23 in stage IIB, 9 in stage III, and 24 were in stage IV. The median failure-free survival rate was 16 months, whereas the median cancer specific survival (CSS) was 24.8 months. In contrast to other treatments (n=40), the initial regimen of etoposide platinum for at least five cycles (EP5+) (n=16) was linked with a five-year failure-free survival rate of 42.9% and a cancer-specific survival rate of 45.6%. Moreover, concomitant chemotherapy and radiation with at least 5 cycles of EP5+ was linked to a five-year failure-free survival rate of 62.5% vs. 13.1% of other treatments (surgery and chemotherapy, surgery and radiotherapy, radiotherapy, and chemotherapy) and a higher cancer-specific survival rate of 75.0% vs. 16.9% of other treatments [27].

Another study showed the treatment of 15 patients, diagnosed with undifferentiated SmCC of the cervix. Their clinical record comprised symptoms in offspring’s, site of metastasis, type of chemotherapeutic agent, recurrence, age of patients, and their survival. The age of studied females ranged between 28 to 83 years with an average of 47 years. Two of the studied females were nulliparous (‘a female that has not borne offspring’) and two were primiparous (‘a female that has borne only one offspring’). While,

remaining eleven were multiparous (‘producing many or more than one at a birth’). Five patients were stage I, three were stage II, one was stage III, and six were stage IV at analysis time. Five patients grew without treatment and seven had a recurrence of cancer after fifteen months. Treatments included chemotherapy, radiation, surgery or even their combination. Extra pelvic metastases were in five patients having stage I or stage II disease. Three patients had brain metastasis. Tumor lysis syndrome occurred in one patient. Death of thirteen patients occurred due to their disease, one remained alive even eighty months after diagnosis, and one was lost to follow-up [28].

Brachytherapy is a crucial component of definitive concurrent chemo-radiotherapy for neuroendocrine small cell cervical cancer and should not be overlooked according to a new National Cancer Database investigation of patients with SCC of cervix. In 100 patients with locally advanced SCC of the cervix, brachytherapy was linked with a median survival of twenty-seven (27) months as compared to external beam radiation therapy (EBRT) alone (48.60 versus 21.60 months, HR: 0.475, 95% CI: 0.255-0.883) [29]. Prophylactic cranial irradiation for extra-pulmonary SCC was noticed by Naidoo et al [30] who studied two hundred and eighty (280) patients, of which one hundred and eighty-six (186) had extensive-stage disease. On the other hand, sixty (60) patients had limited stage disease and twenty-nine (29) patients had an unidentified stage. 18 cases (6.4%) out of 280 examined patients had brain metastases. In comparison to SCC of the lungs, only 2.5% of the patients had brain metastases at initial diagnosis. Overall, Naidoo et al. suggested that prophylactic cranial irradiation (PCI) is not necessary due to the lower incidence of brain metastases in small cell cervical cancer.

Another study focused on the clinical diagnosis of SCCC published in China and abroad during 1st March 2017. Twenty cohort studies along with one thousand nine hundred and four (1,904) patients were examined. Meta-analysis exhibited statistical significance for the subsequent factors, that is, FIGO hazard ratio = 2.63, tumor size hazard ratio 1.64, resection margin hazard ratio 4.09, lymph node metastasis hazard ratio 2.09, depth of stromal invasion hazard ratio 1.99, parametrial involvement hazard ratio 2.40, neoadjuvant chemotherapy hazard ratio 2.06, and adjuvant chemotherapy hazard ratio 1.63. FIGO staging, parametrial involvement, tumor size, depth of stromal invasion, resection margin, and lymph node metastasis can be used as clinical treatment for SCCC. Neoadjuvant chemotherapy showed improved diagnosis. Thus, both neoadjuvant chemotherapy and adjuvant chemotherapy may be the desired approaches for treatment [31].

In another study of rare endometrium tumor, case one was based on a 54 years old woman, while the third case belonged to a 58 years old woman. Both of them had vaginal bleeding. On the other hand, case two was of a 53 years old woman with no symptoms, however, she had a vaginal-cervical smear cautious for malignancy. All patients underwent surgery and had their tumors initiated in the endometrium. SCCE and the immunohistochemical reactivity for neuroendocrine markers were keenly observed and studied in all these cases [32].

In one report, the medical record and cervical smears from twenty cases of

squamous cell carcinoma in situ (SCIS), thirteen different cases of SmCC, 4 cases of malignant lymphoma, and five cases of cholangiolocellular carcinoma were examined. The basic diagnosis facts of SCCC were salt and pepper chromatin and nuclear molding and smearing (100%), exudative and necrotic background (91.7%), tight clusters (75%), architectures individual cells (83.3%), feathering about 50%, and discreet nucleoli (75%). Hence, initial diagnosis of the cervical carcinoma by cytology and its cure is vital for the betterment of patients [33].

A 65-year-old postmenopausal Japanese woman's case with unusual vaginal hemorrhage was observed. The smear of cervix revealed the occurrence of two different neoplastic constituents in an inflammatory contextual. One constituent consisted of combination of small round cells with a high nuclear/cytoplasmic ratio, round to oval nuclei with powdery chromatin, and discrete nucleoli. Specific nuclear moulding was used. The other component comprised unevenly arranged overlapping groups of tall columnar cells with big, ovoid to spherical nuclei, abundant cytoplasm, and coarse chromatin. Resultantly, it was hypothesized that small cell cervical neuroendocrine cancer and cervical adenocarcinoma in situ (AIS) were present together. Despite the fact that cervical cancer has distinct cytological subtypes, its rarity makes cytodiagnosis of the tumor a challenge [34].

In order to treat small cell cervical neuroendocrine carcinoma, use of fertility-sparing cure is perplexing due to its violent nature. A nulligravida woman of 25 years with stinking vaginal ejection was observed to have exophytic cervical neuroendocrine tumor. No sign of parametrial invasion or distant metastasis was observed by magnetic resonance imaging. Clinical treatment owed her to have stage IB1 disease. For reproductive purpose, she was exposed to radical abdominal trachelectomy. Pre-operative chemotherapy followed by post-operative chemotherapy with etoposide/cisplatin combined with gonadotropin-releasing hormone was overseen. A spontaneous ordinary pregnancy was observed and a baby by cesarean section was delivered seven years after her treatment [35]. In another study, 25 patients having SmCC were treated using radical radiotherapy and brachytherapy. The OS and PFS at 5-years was 48% and 46.4%, respectively. Patients with I-IIA stage had more PFS (67.3%) and OS (62.5%). Distant metastasis is the major failure pattern for SmCC patients when treated by radical chemo-radiotherapy [36].

The clinicopathological records of thirty patients of cervical carcinoma were examined. The analysis concluded that out of thirty patients with cervical SCC, fifteen patients had other types of epithelial tumors, such as adenocarcinoma squamous cell carcinoma, adenocarcinoma in situ. Twenty-seven (27) cases had 90% harbored type 18 and fifteen (50%) revealed multiple HPV18 and HPV16 (high-risk human papillomavirus). The occurrence of HPV18 infection in SCC was greater than those in glandular epithelial neoplasms and cervical squamous. Both SCC and all other epithelial tumors exhibited nuclear and cytoplasmic staining for p16 in all these cases. Three cases showed absolutely negative p53 immunohistochemical expression in fifteen of these composite tumors which put forward TP53 non-sense type mutation patterns. On the other end, the pure SCC of uterine cervix indicated

related mutation or wild-type form for TP53 in contrast to composite tumor [37].

Clinicopathological characteristics of ten cervical neuroendocrine carcinomas were reported. Most of the studies involved immunohistochemical estimation of p53, p16, synaptophysin, chromogranin expression, in situ hybridizations, and polymerase chain reaction for high-risk HPV and HPV18 along with next-generation sequencing based on a six-hundred and thirty-seven (637) gene panel. The median age of patients was 40.5 years. All of these tumors had p16 and synaptophysin expression. Only one tumor showed positivity for chromogranin, while six tumors had HPV18 and just one tumor had HPV35. Only single driver mutation was observed in eight tumors and four had TP53 somatic mutations. In four tumors, mutations were observed in tumor suppressors PTEN, RB1, ARID1B, BRCA1, and BRCA2 that activate oncogenic mutations [38].

It was reported that fourteen thirty-eight (38) years old patients had SmCC. Various stages observed among them included Ib1, Ib2, IIa, and IIb. The OS rate at 2 and 5 years was 65% and 43% [39]. Small cell neuroendocrine cervix carcinoma was noticed in 80.4% of the studied cases. Their primary treatment for forty-eight (48) cases involved radical surgery chemotherapy in forty-two (42) cases, while radiotherapy and radio chemotherapy was also noticed in fifteen cases. Generally, the diagnosis for cervical carcinoma was poor with 40 months of OS rate [40]. Another study indicated small cell cervical cancer in 62 years old patient where IB1 stage of FIGO was reported [41]. The patient got benefit form radiotherapy, chemotherapy, and brachytherapy as he was checked every 3 months for 2 years. In another study, a 45 years old woman was diagnosed with IIA stage of uterine cervix. She was treated with radical surgery, chemo radiotherapy, and chemotherapy, however, no proper treatment is still known to cure the disease [42].

Another study reported that 11 out of 14 patients having SCNCC were treated with radical surgery, radiotherapy, and chemotherapy. About 3 patients had IB1 stage, 6 had IB2, 4 had IIA2, and a single patient had stage IVB. Among these patients, the average survival rate was about 43.6 months [43]. According to other findings, 621 cervical cancer cases were reported from 2004-2014. It was noticed among those patients that brachytherapy might enhance the OS for II-IVA cervical cancer, however, only 38% patients received brachytherapy [44]. In another study, small cell neuroendocrine carcinoma was observed in a pregnant woman. She was identified with FIGO III stage and was treated with chemotherapy, however, refused to undergo radiotherapy and died [45].

A study conducted between the time period 1993 and 2017 reported that 47 patients with FIGO stage (IB1-IIA1) of high grade NECC were initially treated with radical hysterectomy. IB1 stage was common (70.2%). About 29 patients (61.7%) experienced radical hysterectomy through minimally invasive surgery. Their survival and disease-free survival rates were 63.8% and 38.3%, respectively. Lymph-node metastasis and resection margin were poor prognostic aspects of survival in surgically cured early-stage high grade NECC [46]. Additionally, clinical, histological, and cytological results of different cases of SCC were also clearly reported along with patient's survival rate (Table 1).

Table 1. The cytological, histological, and clinical findings of several reports of small cell carcinoma of cervix

Study author's	Age (years)	Stage	Tumor size (cm)	Histology	Lymph node metastasis	Chemotherapy regimen	XRT	Overall survival (months)	Follow up status
[47]	23	IB	6.00	SC	Negative	PE	YES	17	ALIVE
[47]	39	IB	3.00	SC	Negative	VAC	NO	61	ALIVE
[47]	49	IB	3.00	SC	Negative	PE	NO	30	Deceased
[48]	35	IB	4.00	SC	Positive	PE	YES	20	Deceased
[48]	75	IB	2.00	SC	Positive	PE	YES	62	ALIVE
[48]	50	IB	2.00	SC	Positive	PE	YES	8	Deceased
[49]	27	IB	11.00	SC	Positive	OTHER	YES	2	Deceased
[50]	50	IB	LARGE	SC	Not done	OTHER	YES	15	Deceased
[50]	34	IB	3.20	SC	Not done	OTHER	YES	4	ALIVE
[51]	25	IB	6.00	SC	Positive	OTHER	YES	18	Deceased
[52]	29	IB	-	SC	Positive	OTHER	NO	6	Deceased
[53]	31	IB	5.00	SC	Negative	PE	NO	51	ALIVE
[54]	38	IB	-	SC	Negative	OTHER	NO	31	Deceased
[55]	50	IB	4.00	SC	Negative	PE	NO	60	ALIVE
[55]	31	IB	1.00	SC	Negative	PE	NO	54	ALIVE
[55]	32	IB	2.00	SC	Positive	PE	YES	14	Deceased
[21]	62	IB	2.00	SC	Negative	PE	YES	47	ALIVE
[21]	41	IB	-	SC	Negative	PE	YES	28	ALIVE
[56]	23	IB	4.50	SC	Not DONE	-	YES	15	Deceased
[57]	37	IB	2.50	SC	Positive	VAC	YES	24	Deceased

Study author's	Age (years)	Stage	Tumor size (cm)	Histology	Lymph node metastasis	Chemotherapy regimen	XRT	Overall survival (months)	Follow up status
[58]	54	IB	-	SC	Not done	VAC or PE	NO	15	ALIVE
[59]	26	IB	2.50	SC	Positive	VAC	NO	9.3	Deceased
[22]	40	IB	5.00	LC	Negative	VAC	YES	118	ALIVE
[22]	44	IB	1.00	SC	Negative	VAC	YES	30.8	Deceased
[22]	33	IB	5.00	SC	NOT DONE	VAC	NO	5.75	Deceased
[22]	38	IB	2.00	SC	Negative	VAC or PE	YES	19	Deceased
[22]	32	IB	2.00	SC	Negative	-	NO	27	Deceased
[22]	20	IB	5.10	SC	Positive	-	NO	19	Deceased
[22]	25	IB	0.50	SC	Negative	PE	NO	12	Deceased
[22]	49	IB	8.00	SC	Positive	PE	YES	11.25	Deceased
[22]	37	IB	5.00	SC	Positive	PE	YES	9	ALIVE
[22]	62	IB	6.00	AtCarc	Positive	-	YES	4.5	Deceased
[22]	53	IB	3.00	SC	Positive	PE	YES	13.75	Deceased
[20]	23	IB	-	Small 1 focal AIS	NOT DONE	IC/ Br	YES	118	ALIVE
[20]	28	IB	-	Intermediate	NOT DONE	IC/ Br	YES	11	Deceased
[20]	28	IB	-	Small	NOT DONE	IC/ Br	YES	16	ALIVE
[20]	29	IB	-	SMALL	NOT DONE	IC/ Br	YES	21	Deceased
[20]	36	IB	-	SMALL	NOT DONE	IC	YES	15	Deceased
[20]	36	IB	-	Intermediate	NOT DONE	IC/ Br	YES	2	ALIVE
[20]	37	IIIA	-	Intermediate	NOT DONE	IC/ Br	YES	97	ALIVE
[20]	43	IIA	-	Intermediate	NOT DONE	IC/ Br	YES	28	ALIVE

Study author's	Age (years)	Stage	Tumor size (cm)	Histology	Lymph node metastasis	Chemotherapy regimen	XRT	Overall survival (months)	Follow up status
				1adenocarcinoma					
[20]	45	IB	-	Intermediate 1 focal SIL	NOT DONE	IC/ Br	YES	26	ALIVE
[20]	48	IIIB	-	Intermediate	NOT DONE	IC/ Br	YES	8	ALIVE
[20]	50	IIB	-	SMALL	NOT DONE	IC	YES	105	ALIVE
[20]	69	IB	-	Intermediate	NOT DONE	IC/ Br	YES	5	ALIVE
[20]	63	IB	-	Intermediate 1 MMMT	NOT DONE	IC	YES	12	ALIVE
[20]	31	IB1	1.00	SC	NOT DONE	NONE	NO	209	ALIVE
[20]	42	IB1	3.00	SC	NOT DONE	Post-operative PE	NO	12	Deceased
[20]	50	IB1	3.00	SC	NOT DONE	NONE	NO	25	ALIVE
[20]	45	IB1	3.00	SC	NOT DONE	Post-operative PAE	NO	83	ALIVE
[20]	34	IB1	3.00	SC	NOT DONE	NONE	YES	12	Deceased
[20]	29	IB1	3.00	SC	NOT DONE	Concurrent P, 5-FU	YES	29	ALIVE
[23]	46	IB1	3.50	SC	NOT DONE	Neo-adjuvant PAE	YES	155	ALIVE
[23]	50	IB1	4.00	SC	NOT DONE	Post-operative PAE	NO	136	ALIVE
[23]	47	IB1	4.00	SC	NOT DONE	NONE	YES	6	Deceased
[23]	60	IB1	4.00	SC	NOT DONE	NONE	YES	31	Deceased
[23]	30	IB2	5.00	SC	NOT DONE	Post-operative	NO	21	Deceased

Study author's	Age (years)	Stage	Tumor size (cm)	Histology	Lymph node metastasis	Chemotherapy regimen	XRT	Overall survival (months)	Follow up status
						PAE			
[23]	26	IB2	5.00	SC	NOT DONE	Neo-adjuvant PAE	YES	16	Deceased
[23]	29	IB2	5.50	SC	NOT DONE	Neo-adjuvant PAE	YES	8	Deceased
[23]	48	IB2	5.50	SC	NOT DONE	Neo-adjuvant PE, concurrent P	YES	9	Deceased
[23]	61	IB2	6.00	SC	NOT DONE	Neo-adjuvant PAE	YES	16	Deceased
[23]	40	IIA	4.00	SC	NOT DONE	Neo-adjuvant PAE	YES	27	Deceased
[23]	49	IIA	5.50	SC	NOT DONE	Neo-adjuvant PAE	YES	10	Deceased
[23]	59	IIB	7.00	SC	NOT DONE	NONE	YES	17	Deceased
[23]	46	IIIB	≥8	SC	NOT DONE	NONE	YES	12	Deceased
[23]	50	IIIB	10.00	SC	NOT DONE	Neo-adjuvant PAE	YES	26	Deceased
[23]	78	IIIB	10.00	SC	NOT DONE	NONE	YES	13	Deceased

† **NOTE:** - Represents**:** Not Reported; **SC**, Small Cell subtype; **LC**, Large Cell subtype; **AtCarc**, Atypical Carcinoid subtype; **AIS**, Adenocarcinoma *In Situ;* **VAC**, Vincristine/Adriamycin/Cyclophosphamide; **PE**, Platinum/Etoposide; **XRT**, Radiation Therapy; **IC**: Initial Chemotherapy; **Br**: Brachytherapy; **SIL**: Squamous Intraepithelial Lesion; **MMMT**: Malignant Mixed Mullerian Tumor; **PAE**; P, Cisplatin; **A**, (Adriamycin) Doxorubicin; **E**, Etoposide.

4. EPIDEMIOLOGY

It is a well-documented fact that human papillomavirus is the prominent cause of manifesting infection related cancers worldwide [60]. Generally, in western civilizations, the most prevalent gynecological malignancy among females is uterine cancer. The second most documented malignancy is ovarian cancer and cervical cancer is the third most common type of cancer [61]. Moreover, invasive cervical cancer (ICC) is the fourth dominant cancer among females worldwide and about 85% incidence of ICC is reported in developing countries. Pakistan, with its 92 million females in 2015, is the sixth most populated country of the world. However, this number is likely to increase upto 151 million by 2050. The incidence of cervical carcinoma is quite difficult to assess in third world countries as they lack national cancer registries. According to statistics, cervical cancer is the third leading cause of death among Pakistani women. About 5233 newly diagnosed cases and 2876 ICC related deaths with prevalence and mortality rates of 5.9 and 3.2 per 100,000 were recorded in 2012. However, the ratio was expected to increase in upcoming years [60, 62].

Cervical cancer is the most prevalent malignancy followed by ovarian cancers [63]. As far as gynecological cancers are concerned, cervical cancer continues to be the most common followed by ovarian and uterine cancers [61]. Neuroendocrine (NE) tumors typically make up less than 1% of all the cancers. These malignancies can arise in numerous areas, such as esophagus, stomach, lungs, pancreas, ovary, cervix, and many more [64]. A pathogenic form of gynecological neuroendocrine lesions, small-cell neuroendocrine carcinoma (SCNC) of the gynecological tract have prevalence rates that range from high to low as follows: small cell neuroendocrine carcinoma of the cervix (SCNCC), ovarian, endometrial, vaginal, and vulvar [65].

5. CONCLUSION

Small cell cervical neuroendocrine carcinoma is an intermittent or aggressive tumor in the uterine cervix with poor diagnosis and no traditional cure. Recent investigation on this ailment had imperfect reconsideration. The studies conducted had small sample sizes due to the scarcity of this disease. Due to fewer cases of cervical carcinoma, considerable usage of concurrent chemoradiation (CCRT) with adjuvant etoposide/platinum (EP) chemotherapy for management of locally progressive cervical carcinoma is preferred. With various imaging modalities and development in chemotherapy treatments along with uterine conservancy techniques related to surgery, gynecologists/oncologists might offer multimodality treatment for young women having cancer of rare histology with a desire to reserve their efficacy. In inference, fertility-sparing operation may be modified in precise ways after comprehensive assessment and suitable therapy. This method justifies forthcoming inquiry to inspect its possibility in patients having carcinoma stage I SCNEC.

In short, neuroendocrine cervical cancer has a bad prognosis and is uncommon. Conclusions can only be drawn from a small number of these instances, although early stage disease is treated using a multimodal approach that includes major surgery and adjuvant or neoadjuvant chemotherapy with etoposide and cisplatin. In addition, women with locally advanced or recurrent NECC can benefit from both radiotherapy and

chemotherapy. While, primary RT with brachytherapy appears to be a better course of treatment for individuals with advanced stage SCNEC. Surgery is still thought to be the best local therapeutic strategy for people diagnosed with early-stage SCNEC. Combination therapy is likely the most appropriate course of action when small cell histology is known (chemotherapy and radiation therapy). If small cell histology is known, it is probably most appropriate to proceed with combined modality therapy (chemotherapy and radiation therapy). Despite the limitations of retrospective studies that covered numerous lengthy administrations, the results provided a valuable foundation to plan next modifications. Worldwide multicenter approaches of dynamic causes for SCNEC of whole body put on numerous groupings of dynamic chemotherapeutic mediators and marked remedies are necessary to expand the diagnosis of small cell cervical cancer. Therefore, a strong association between researchers, medical oncologists, and physicians considering neuroendocrine tumors (NETs) is necessary to create a phase, accelerative to cure these aggressive and violent diseases.

CONFLICTS OF INTEREST

The author of the manuscript has no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVALIABILITY STATEMENT

The data associated with this study will be provided by the corresponding author upon request.

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