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Radical Surgery After Neoadjuvant Chemotherapy for Locally Advanced Neuroendocrine Cancer of the Cervix

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Abstract. *Background/Aim: Although still controversial, the current treatment for locally advanced neuroendocrine carcinoma of the cervix (NECC) relies on chemoradiation (CRT). The aim of this study is to evaluate the alternative role of combined chemotherapy and surgery in treating NECC. Patients and Methods: This is a retrospective series of patients undergoing radical surgery after neoadjuvant chemotherapy (NACT) for locally advanced NECC (stages IIB-IVA). Histological examination and immunohistochemistry were performed on surgical specimens to confirm diagnosis. Systematic literature search was conducted to identify other cases treated with chemotherapy and surgery. Results: Seven patients with a mean age of 49 years were identified. The mean greatest diameter at diagnosis was 59.3±24.7 mm. FIGO stage was IIB in 14.3% of patients, IIIB in 28.6%, IIIC in 42.9%, and IVA in 14.3%. The response to NACT was partial, ranging from 50% to 80%. Neuroendocrine markers were expressed in all cases. The mean progression-free survival (PFS) and overall survival (OS) were 15.0±30.6 months and 26.3±36.4 months, respectively. Eleven studies encompassing a total of 27 patients met eligibility criteria for the systematic review. Conclusion: Surgery after NACT for locally advanced NECC may yield similar outcomes compared to CRT. The benefit of performing surgery as a primary approach could lie in the possibility of reserving CRT for recurrences. Since randomized clinical trials are difficult to be designed, an expert consensus is required to address the non-inferiority of radical surgery over CRT.*

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Key Words: Locally advanced cervical cancer, neuroendocrine carcinoma, radical surgery, chemoradiation.

The neuroendocrine carcinoma of the cervix (NECC) is an extremely rare and aggressive tumor, accounting for 1-2% of all gynecological malignancies (1). It is generally diagnosed in younger women and shows a poorer prognosis compared to the squamous cell counterpart (2, 3). Approximately 50-60% of cases present at early stages while around half of the patients show positive lymph nodes at diagnosis (4-6). The 5-year overall survival (OS) ranges from 14% to 67% for all stages, with 30-60% for early stages and 0-17% for advanced stages (2, 7-9).

The recommended treatment for NECC is based on a multimodal strategy, including surgery, chemotherapy (CHT), and/or radiotherapy (RT) (1, 10). Historically, chemoradiation (CRT) has represented the mainstay of treatment for all non-metastatic stages. Whilst the latest evidence has established surgery as the mainstay of treatment for early stages (11-14), the treatment of locally advanced stages (FIGO IIB-IVA) still relies on definitive CRT (7). The prognosis is extremely poor, especially in the recurrent setting, and there is an urgent need to develop alternative strategies.

In the wake of early stages, radical surgery after neoadjuvant chemotherapy (NACT), in order to enhance resectability, may yield non-inferior clinical outcomes for locally advanced stages. However, currently available data are scant and all published studies of NECC included only few cases of locally advanced stages treated with CHT and surgery (15-25). Moreover, the optimal time sequence of CHT and surgery has not yet been established.

The aim of the present study is to share our single-institution experience in treating locally advanced NECC with a three-step strategy: NACT, radical surgery and adjuvant CHT.

Table I. *Demographic, oncological and surgical data of included patients.*

Case	Age (years)	BMI (kg/m^2)	Size (mm)	Clinical FIGO stage at diagnosis	Positive lymph nodes	Peritoneal carcinosis	NACT	Response to NACT	Surgery (laparotomy)	Surgical complications	Adjuvant CHT
1	52	23.3	89×107×78	IIIC1	Pelvic	Yes	EP (3 cycles)	PR	RH+BSO+PLND, omentectomy, appendicectomy, bowel resection	None	EP (3 cycles)
2	34	19.8	60×60×48	IIIC1	Pelvic	No	EP (2 cycles)	PR	RH+BSO+PLND	None	EP (4 cycles)
3	39	29.1	50×52×60	IIIC2	Pelvic and paraortic	No	TIP (3 cycles)	PR	RH+BSO+PPLND	None	TIP (3 cycles)
4	59	22.6	38×19×25	IIIB	-	No	PT (3 cycles)	PR	RH+BSO+PLND, bladder resection	Vesicovaginal fistula	PT (3 cycles)
5	77	20.5	23×15×30	IIIB	-	No	EP* (3 cycles)	PR	RH+BSO+PLND	None	EP (3 cycles)
6	49	27.8	53×40×42	IVA	Pelvic and paraortic	Yes	EP (3 cycles)	PR	RH+BSO+PLND, right ureteral distalresection, uretero-vesical reimplantation, partial omentectomy	Wound dehiscence, DVT of the common femoral and external iliac	EP (3 cycles)
7	32	19.7	67×55×30	IIB	-	No	EP (2 cycles)	PR	RH+BSO+PLND	None	EP (4 cycles)

EP: Etoposide 100 mg/mq on days 1-3 and cisplatin 75 mg/mq on day 1 every 21 days. TIP: topotecan 0.75 mg/mq on days 1, 7 and 14, ifosfamide 5 g/mq on day 1 and cisplatin 75 mg/mq on day 1 every 21 days. PT: cisplatin 75 mg/mq and paclitaxel 175 mg/mq on day 1 every 21 days. BMI, Body mass index; BSO, bilateral salpingo-oophorectomy; CHT, chemotherapy; EP, etoposide/cisplatin; DVT, deep vein thrombosis; FIGO, International Federation of Gynecology and Obstetrics; NECC, neuroendocrine carcinoma of the cervix; PLND, pelvic lymph node dissection; PPLND, pelvic and paraaortic lymph node dissection; PT, paclitaxel/cisplatin; RH, radical hysterectomy; SCC, squamous cell carcinoma; TIP, topotecan, ifosfamide, cisplatin.

Patients and Methods

Case series. From January 2015 to October 2020, data from consecutive patients undergoing radical surgery for locally advanced NECC at the Department of Gynecologic Oncology of Policlinico Umberto I (Sapienza University of Rome) were collected. The study was approved by the local Ethics Committee. Informed consent was obtained from all patients.

Inclusion criteria were as follows: 1) histologically confirmed diagnosis of NECC; 2) locally advanced stage (IIB-IVA); 3) radical surgery (hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy) after NACT. Exclusion criteria included: 1) early stage (IA-IIA); 2) radiotherapy; 3) concomitant neoplasms; 4) incomplete medical records. Preoperative magnetic resonance imaging (MRI) was used to determine the tumor size and parametrial involvement, while positron emission tomography/computed tomography (PET/CT) to evaluate the presence of lymph node or distant metastases. All surgeries were performed by the same highly experienced surgical team.

The following items were extracted from each patient: age, tumor size, histology, FIGO stage, response to NACT, recurrences, PFS (progression-free survival) and OS. The following immunohistochemical (IHC) markers were performed: synaptophysin (clone MRQ-40; Roche Ventana Medical Systems, Tucson, AZ, USA), chromogranin (clone LK2H10; Roche Ventana Medical Systems), and CD56 (clone 123C3; Dako, Denmark A/S) (18). IHC markers were quantified as negative (absence of staining), focal (staining in ≤50% of tumor cells) or diffuse (>50% of tumor cells).

Descriptive statistics were performed for clinical and pathologic data evaluation. Ordinal variables were calculated as medians with range, while interval level variables as arithmetic means with standard deviation. Survival was calculated using Kaplan–Meier tables. Statistical analysis was performed by SPSS software (version 27.0, IBM Corp, Armonk, NY, USA).

Systematic review of the literature. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used for this study (26). A systematic search was performed up to March 31, 2021 by two authors (G.C., R.G.) independently within several electronic databases (Medline/Pubmed, Embase, Cochrane library, Google scholar) to identify all relevant studies on the role of radical surgery in treating locally advanced NECC.

The process of evidence acquisition combined the following MESH terms: “locally advanced”, cervical cancer”, “cervix”, “neuroendocrine”, “hysterectomy”, “small cell”, “surgery”. Key criteria for inclusion were: (a) original studies published in English in peer-reviewed journals; (b) locally advanced NECC treated with radical hysterectomy; (c) availability of surgical, oncological and survival data. Two authors (G.C., R.G.) carried out data extraction and quality assessment. Discrepancies between the investigators were resolved by consensus.

Table II. *Overview of the histological and immunohistochemical features.*

Case	Histology	Tumor pathology	Necrosis	Hemorrhage	Inflammatory infiltrate	Growth pattern	Ki-67 (%)	CgA	Syn	CD56
1	LCNECC	Pure	+++	–	Mild peritumoral	Nesting	80	+/–	+/–	++
2	SCNECC and LCNECC	Pure	+++	–	No	Nesting and pseudorosette	90	+	++	++
3	SCNECC	Pure	++	+	No	Nesting	80	+	++	++
4	SCNECC	Mixed with G3 squamous cell carcinoma,	+	–	No	Diffuse	90	+	++	++
5	LCNECC	Pure	+++	–	No	Nesting	80	–	++	++
6	SCNECC	Pure	+	–	No	Nesting	80	+/–	+	+
7	SCNECC and LCNECC	Pure	+	++	No	Nesting	80	+	++	++

CgA, Chromogranin A; LCNECC, large cell neuroendocrine carcinoma of the cervix; SCNECC, small cell neuroendocrine carcinoma of the cervix; Syn, synaptophysin.

Results

Case series. Overall, seven patients were included in the present series. Demographic, oncological and surgical data are detailed in Table I. Briefly, the mean age was 49 years (range, 34-77 years) and the mean BMI (±SD) was 23.3 kg/m2 (± 3.8). Vaginal bleeding was the most common symptom at diagnosis.

Three patients (42.8%) had small cell NECC (SCNECC), two (28.6%) had large cell NECC (LCNECC), while two patients (28.6%) had both small and large cells. The histology was pure neuroendocrine in 6 cases (86%) and mixed with squamous cell carcinoma in one case (14%). The mean±SD greatest tumor diameter at diagnosis was 59.3±24.7 mm. All patients underwent 2-3 cycles of platinum-based NACT before surgery. The response to NACT was partial ranging from 50% to 80%. All patients underwent radical surgery and tumors were completely removed. FIGO stage at diagnosis was IIB in one case (14.3%), IIIB in 2 (28.6%), IIIC in 3 (42.9%), and IVA in one (14.3%). All patients received 3-4 cycles of adjuvant CHT based on etoposide and cisplatin. Histological and immunohistochemical data are described in Table II. Figure 1 shows the histological characteristics of the neuroendocrine tumors consisting of a monomorphic population of neoplastic cells, with oval or elongated nuclei with finely dispersed chromatin and scant cytoplasm, with solid (Figure 1A), nested (Figure 1B) and diffuse growth patterns (Figure 1C). Molding features, necrosis and crush artifacts were frequently observed, while inflammatory infiltrates were reported only in one case. The proliferative index was high, ranging from 80% to 90%.

No patient was lost to follow-up. The recurrence of disease and the prognosis of included patients are detailed in Table III. Briefly, the median follow-up time was 26 months (range=3-108 months). The mean PFS was 15.0±30.6 months. The mean OS was 26.2±36.4 months. The cumulative 5-year survival rate was 14%.

Systematic review of the literature. The systematic search resulted in 766 relevant articles. Of these studies, 18 were removed as they were duplicates and 735 were excluded based on title and abstract review. Full manuscripts were evaluated for 13 studies. Two studies were excluded because surgical data for locally advanced stages were not reported separately from the whole NECC cohort of patients. Ultimately, 11 studies fulfilled the inclusion criteria, including a total of 27 patients with a mean age of 49.9±9.4 years (Figure 2). No prospective or randomized studies were found. The characteristics of the included studies and the clinical data are detailed in Table IV.

Discussion

Recognizing the lack of randomized controlled trials, the Society of Gynecologic Oncology (SGO) (1) and the Gynecologic Cancer Intergroup (GCIG) (10) recommend a multimodal treatment algorithm for all stages of NECC. These guidelines are retrieved from retrospective studies and the treatments available for more traditional histologic subtypes and other similar neuroendocrine tumors (1, 9, 10). Whilst historically concurrent CRT has represented the cornerstone of treatment for all non-metastatic stages of NECC, the alternative role of surgery has only recently emerged and has been mainly addressed for early stages.

The current treatment relies on concurrent CRT with or without prior NACT, followed by adjuvant CHT (7). However, despite the initial high response rate to CHT

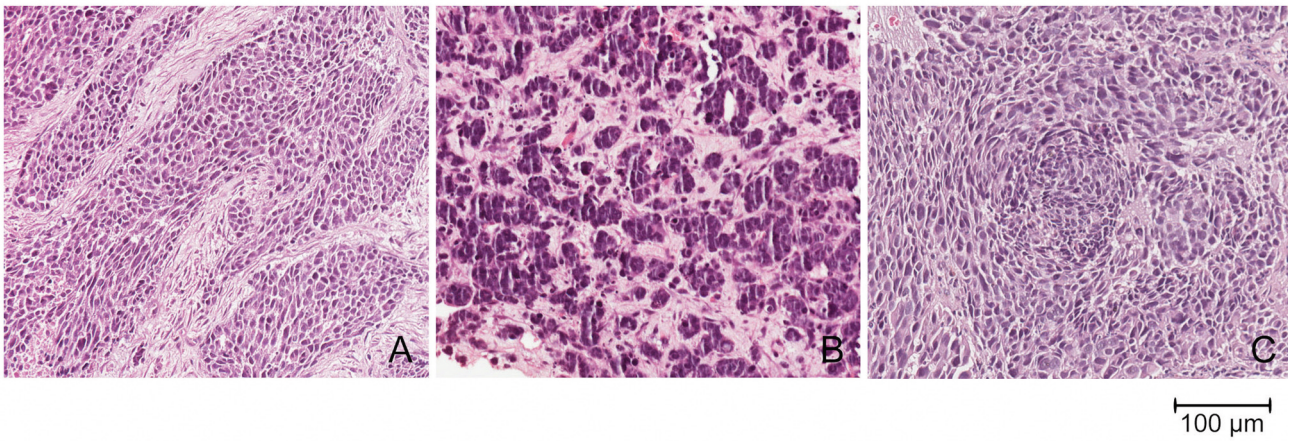

Figure 1. *Neuroendocrine carcinoma, small cell component with different growth patterns: solid (A), nested (B) and diffuse with spindle cell (C). Hematoxylin-eosin staining.*

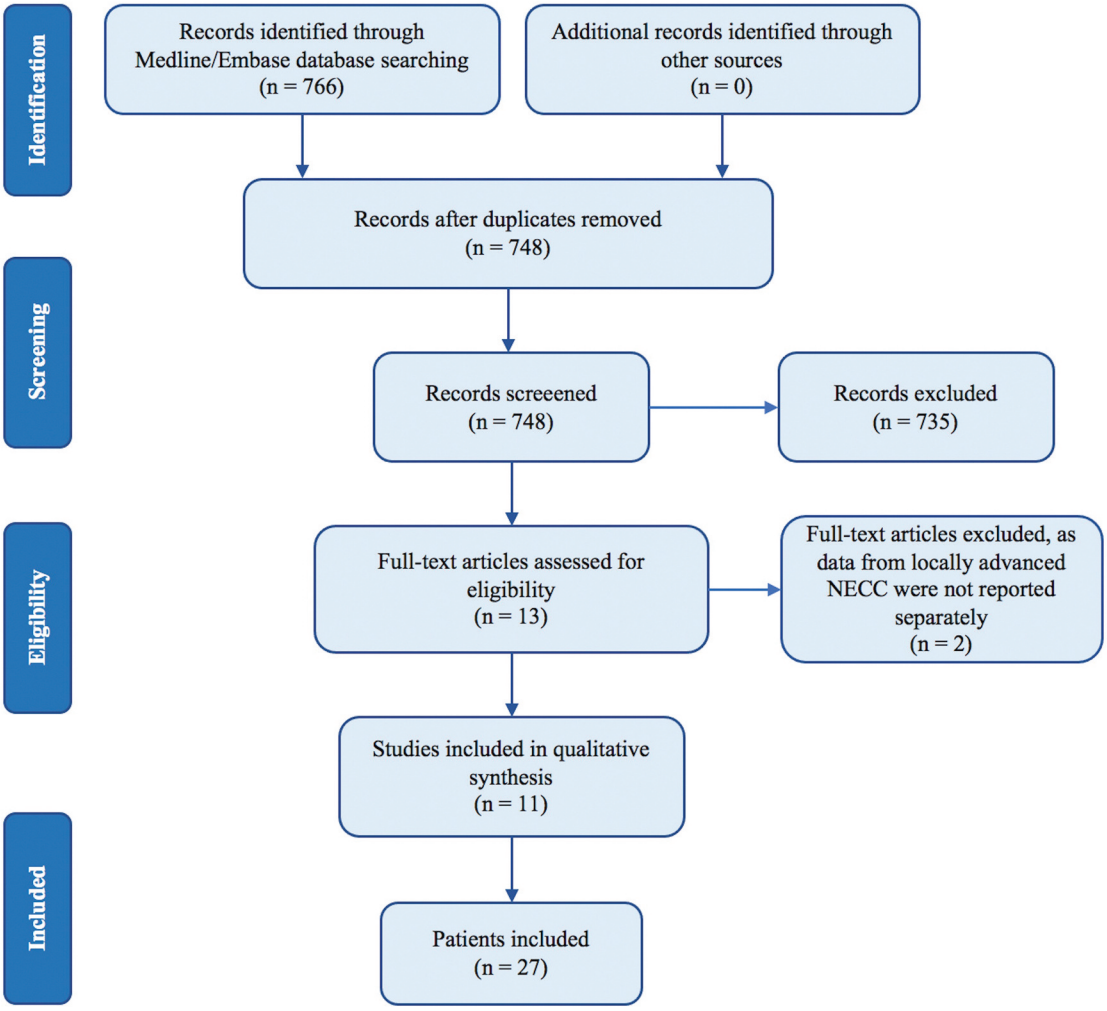

Figure 2. *PRISMA flow diagram. The systematic search resulted in 766 relevant articles: 18 were duplicates and 735 were excluded based on title and abstract review. Full manuscripts were evaluated for 13 studies and 11 studies fulfilled the inclusion criteria, including a total of 27 patients.*

Table III. *Cancer recurrences and prognosis of included patients.*

Case	PFS (months)	Recurrence	Sites of recurrence	Treatment of recurrence	Status	OS (months)
1	4	Local	LNs (bilaterally iliac, lomboaortic)	Surgery + CHT (EP 6 cycles)	DOD	16
2	10	Local	LNs (bilaterally iliac, lomboaortic), pelvis	Surgery + CHT (EP 4 cycles)	DOD	14
3	84	Local and distant	LNs (latero-cervical, submandibular, mediastinal, cardiophenic), lung, pancreas, rectum	CHT: - EP 3 cycles - IP 2 cycles - PT 3 cycles - 5-FU 2 cycles	DOD	108
4	2	Local and distant	LNs, (bilaterally iliac, lomboaortic, intercaval, paraaortic, celiac, pancreatic), bones, right lung	CHT: PT plus denosumab 1 cycle	DOD	13
5	1	Local	LNs (bilaterally iliac, lomboaortic), pelvis	Surgery + CHT (EP 4 cycles)	DOD	7
6	2	Local and distant	LNs (supraclavicular, paracardiac, esophageal, bilaterally iliac, lomboaortic), pelvis, diaphragm, bladder, massive carcinosis	CHT: EP 2 cycles	DOD	6
7	3	Local	LNs (bilaterally iliac, lomboaortic)	Surgery + CHT (EP 6 cycles)	DOD	20

5-FU, 5-Fluorouracil; CHT, chemotherapy; DOD, dead of disease; EP, etoposide/cisplatin; IP, ifosfamide/cisplatin; LNs, lymph nodes; OS, overall survival; PFS, progression-free survival; PT, paclitaxel/cisplatin.

(usually over 90%), recurrences are frequent and the 5-year OS is around 10-15% (8, 27, 28). Increasing interest has been raised on the potential role of radical surgery for locally advanced NECC. Despite the limits of the small sample size, our single-institution experience in treating locally advanced NECC suggests that radical surgery after NACT, followed by adjuvant CHT, could represent a potential alternative at least warranting further investigation.

Since complete resection with free margins is the cornerstone of a successful surgical treatment, we argue that NACT should be highly considered for locally advanced NECC, as it allows to shrink the tumor size and increase the resectability, especially when tumors are greater than 4 cm. In our series, all patients underwent NACT regardless of tumor size, with an overall response of 50-80%. Complete resection was successfully achieved in all patients. However, whether NACT can improve the survival rates remains controversial (2, 9, 29, 30).

The usefulness of surgery as a primary treatment approach for NECC appears more evident when considering the high recurrence rate of these malignancies. Using RT as the primary treatment may prevent performing surgery as recurrence treatment, due to alteration of the normal pelvic anatomy and loss of tissue planes. On the other hand, the adoption of surgery as the primary approach more likely allows for re-treating patients surgically and sparing the possibility of using CRT in the recurrence setting.

These tumors are highly aggressive, with a higher rate of distant recurrences when compared to the squamous cell counterpart, in which recurrences are frequently pelvic. In our series, local recurrences (57%) were treated with surgery and adjuvant chemotherapy, while chemotherapy alone was administered in case of distant relapses (43%). In our opinion, surgery should be pursued also for treating local recurrences with no evidence of distant metastasis. The natural history of these rare carcinomas predicts an incessant number of relapses. Therefore, at least until relapses are localized and can be completely resected by highly experienced surgeons, surgery should be preferred over chemoradiation, sparing the latter for further recurrences when surgery becomes no longer feasible. In the recurrent setting, chemotherapy regimens were platinum-based and no targeted agents (*e.g.*, immune checkpoint inhibitors, bevacizumab) were added, since there is no sufficient evidence of their efficacy to justify the increase in toxicity.

Finally, since the NECC is frequently misdiagnosed at initial cervical biopsy, especially in case of mixed tumors in which neuroendocrine components could be poorly represented, the diagnosis should be made by an expert gynecologic pathologist and IHC should be performed in suspicion of neuroendocrine differentiation. This is extremely important for the prognosis considering that NACT in cervical carcinoma does not usually include etoposide, which is the drug with the highest response rate in neuroendocrine histology. In our series, the case of mixed tumor was initially misdiagnosed with poorly differentiated squamous cell carcinoma and the patient received cisplatin/paclitaxel instead of the more effective cisplatin/etoposide.

Conclusion

Due to the lack of standardized guidelines, the management of locally advanced NECC poses a real clinical challenge for gynecologic oncologists. The current treatment relies on

Table IV. *Comprehensive review of literature cases of locally advanced NECC managed with surgical treatment.*

Author, year of publication	Study design	Histologic subtype	Age (years)	FIGO stage	Treatment	Type of CHT	Prognosis (status, months)
Tsunoda *et al.*, 2005 (15)	Retrospective Monocentric	SCNECC	50	IIB	RH + RT	-	DOD, 14
			52	IIB	RH + RT		DOD, 16
			48	IIB	NACT + RH + CHT	EP	DOD, 11
			36	IIIB	NACT+ RH	EP	DOD, 13
Bermudez *et al.*, 2001 (16)	Retrospective Monocentric	NA	NA	IIB	NACT + RH + CHT	VBP	5-year OS: 16%
				IIB	NACT + RH + CHT		
				IIB	NACT + RH + CHT		
				IIB	NACT + RH + CHT		
				IIIB	NACT + RH + CHT		
				IIIB	NACT + RH + CHT		
				IVA	NACT + RH + CHT		
				IVA	NACT + RH + CHT		
Straughn *et al.*, 2001 (23)	Retrospective Monocentric	SCNECC	53	IIIB	EBRT + PE + CHT	NA	DOD, 43
	Case series	SCNECC	45	IVA	RH + CHT	NA	DOD, 18.5
Delaloge *et al.*, 2000 (17)		SCNECC	28	IIIB	EBRT + RH + BRT	-	DOD, 14
		SCNECC	43	IVA	BRT + RH + CRT + CHT	CRT: CDDP Adj CHT: EP	DOD, 10
Lewandowsky *et al.*, 1993 (24)	Case series	SCNECC	57	IIB	NACT + RH + CHT	NACT: EAP Adj CHT: E	NED, 12
Inzani *et al.*, 2020 (18)	Retrospective Monocentric	SCNECC	33	IIB	RH + CHT + BRT	CE	AWD, 28
		SCNECC	50	IIB	RH + CHT + BRT	EP	DOD, 48
		SCNECC	50	IIB	RH + CHT + BRT	EP	DOD, 26
		LCNECC	62	IVA	RH + CHT + BRT	EP	DOD, 10
		SCNECC	62	IVA	RH + CHT + BRT	EP	NED, 60
Peng *et al.*, 2012 (19)	Case series	NA	NA	IIB	RH + ?	NA	NA
Bifulco *et al.*, 2009 (22)	Case report	SCNECC	48	IIIB	RH + CRT	PT	NED, 12
Kasamatsu *et al.*, 2007 (20)	Retrospective Monocentric	NA	NA	IIB	RH + CHT	NA	AWD, 21
Tangjitgamol *et al.*, 2005 (21)	Case report	LCNECC	42	IIIC	RH + CHT	TC	DOD, 44
Nasu *et al.*, 2011 (25)	Case report	SCNECC	39	IIIB	NACT + RH + CHT	IP	DOD, 27

AWD, Alive with disease; BRT, brachytherapy; CE, carboplatin/etoposide; CHT, chemotherapy; CRT, chemoradiation therapy; DOD, dead of disease; E, etoposide; EAP, etoposide, doxorubicin, cisplatin; EBRT, external beam radiotherapy; EP, etoposide/cisplatin; FIGO, International Federation of Gynecology and Obstetrics; IP, irinotecan/cisplatin; LCNECC, large cell neuroendocrine carcinoma of the cervix; NA, not available; NED, no evidence of disease; OS, overall survival; PFS, progression-free survival; PE, pelvic exenteration; PT, paclitaxel/cisplatin; RH, radical hysterectomy; SCNECC, small cell neuroendocrine carcinoma of the cervix; TC, paclitaxel/carboplatin; VBP, vincristine, bleomycin, cisplatin; VIP, etoposide, ifosfamide, cisplatin.

definitive CRT; however, the prognosis is poor and recurrences are frequent.

Given the potentially similar outcomes, radical surgery after NACT could represent an alternative strategy, both in primary and local recurrence settings, as long as it is performed by highly experienced surgeons. Moreover, using surgery as a primary approach allows to potentially spare CRT for further recurrences, in case surgery becomes no longer feasible. Since

prospective trials are difficult to be designed because of the rarity, a solid international collaboration and a consensus expert opinion are required to further address the non-inferiority of radical surgery over CRT.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, G.C., I.P.; methodology, G.C., I.P., V.D.D., A.P., R.G., G.P.; data acquisition and interpretation, G.C., I.P., V.D.D., A.P., R.G., G.P., M.L.; discussion of the findings, G.C., I.P., V.D.D., A.P., R.G., G.P.; writing - original draft preparation, G.C., I.P., V.D.D., A.P., R.G., G.P.; review and final editing, G.C., I.P., C.D.R., L.M., P.B.P.; project administration and supervision, G.C., I.P., L.M., P.B.P.

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