



Rationale for the avoidance of parametrectomy and systematic lymphadenectomy in patients with early stages of neuroendocrine cervical cancer

David Cibula

Department of Obstetrics and Gynecology, General University Hospital in Prague, First Faculty of Medicine, Charles University, Prague, Czech Republic

Correspondence to

Dr David Cibula, Department of Obstetrics and Gynecology, University of Prague, Prague 118 00, Czech Republic; dc@ davidcibula.cz

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Neuroendocrine tumors account for only 1–2% of cervical carcinomas, but they are known to have the worst prognosis of all. Given the low incidence, their management is based on retrospective series of small cohorts, and pharmacological treatment is adopted from experience with small cell lung cancer.^{1 2} Approximately 50% of neuroendocrine carcinoma is diagnosed in advanced metastatic stage.¹

The most significant prognostic factor, which almost all analysis is agreed on, is the disease stage. The prognosis of neuroendocrine carcinoma is substantially worse in comparison with common tumor types of cervical cancer (squamous cell and adenocarcinomas), irrespective of stage. The 5-year cancer specific survival oscillates in early stages at approximately 50%, while in advanced stages it drops to 5–15%.^{3 4} The most frequent subtype is small cell carcinoma, which accounts for up to 80%; it seems, however, that histological subtype is not a key factor for prognosis.

In this issue, the authors from MD Anderson under the leadership of Gloria Salvo present one of the largest cohorts of patients with early stage neuroendocrine carcinoma, which they collected from an international registry (NeCTuR: Neuroendocrine Cervical Tumor Registry).⁵ A total of 100 cases of neuroendocrine carcinoma in stages IA1-IB2 were treated by primary surgery between 1991 and 2020. All included cases had negative lymph nodes and parametria on preoperative staging, even though it is not stated whether imaging or just physical examination was carried out. Based on definitive pathology, positive lymph nodes were diagnosed in 21% of patients and positive parametria in 10%. With a median follow-up of 42 months, recurrence appeared in 52% of cases, of which 60% was distant. Progression-free survival at 5 years was 44%, but it reached only 13% in those with parametrial involvement. The risk of recurrence was 60% lower when adjuvant radiotherapy was administered. Surprisingly, 5% of cases underwent fertility-sparing treatment, which is not consistent with any recommendations in international guidelines.⁶

In a rare disease with such poor prognosis, which often occurs in young women with good performance status (median age in the study by Salvo et al is 35 years), it is not surprising that a combination of three main treatment modalities is recommended in the management of the disease. In early stages, radical hysterectomy with systematic lymphadenectomy is recommended, followed by chemoradiation with platinum concomitant chemotherapy; to lower the risk of distant spread an additional combined chemotherapy containing cisplatin and etoposide is also suggested.^{2 3} The data on toxicity of such treatment are generally missing in the majority of publications, but derived from the experience with common tumor types, a multimodal treatment is mostly associated with substantially increased risk of morbidity. Based on the results of their study, the MD Anderson team suggests altering the current recommendations for surgical management of early stages. They assume that neither lymphadenectomy nor parametrectomy are diagnostic in this group of patients, since all cases of neuroendocrine carcinoma are referred for adjuvant chemoradiotherapy. It is very unlikely that parametrial removal would improve the prognosis in patients who undergo pelvic radiotherapy. The same applies to imaging-negative lymph nodes. The recently published ABRAX (ABandoning RAd hyst in cerviX cancer) study has not shown any survival benefit resulting from a completion of radical hysterectomy in patients with common cervical cancer types, in whom positive pelvic lymph nodes were diagnosed intraoperatively.⁷ Taking into account the fact that neuroendocrine carcinoma is a very rare disease, it is not realistic to conduct prospective trials and come up with level I evidence on the significance of parametrectomy and systematic pelvic lymphadenectomy. Avoiding parametrectomy and limiting lymph node staging to sentinel lymph node biopsy only is, however, a logical step in patients with early stages of neuroendocrine carcinoma, which can decrease toxicity of the treatment, increase the chance that the multimodal treatment will be delivered, and improve quality of life in long-surviving patients.



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Editorial

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REFERENCES

- 1 Tempfer CB, Tischoff I, Dogan A, *et al.* Neuroendocrine carcinoma of the cervix: a systematic review of the literature. *BMC Cancer* 2018;18:530.
- 2 Salvo G, Gonzalez Martin A, Gonzales NR, *et al.* Updates and management algorithm for neuroendocrine tumors of the uterine cervix. *Int J Gynecol Cancer* 2019;29:986–95.
- 3 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:S102–8.
- 4 Ishikawa M, Kasamatsu T, Tsuda H, *et al.* A multi-center retrospective study of neuroendocrine tumors of the uterine cervix: prognosis according to the new 2018 staging system, comparing outcomes for different chemotherapeutic regimens and histopathological subtypes. *Gynecol Oncol* 2019;155:444–51.
- 5 Salvo G, Ramalingam P, Flores Legarreta A, *et al.* Role of radical hysterectomy in patients with early-stage high-grade neuroendocrine cervical carcinoma: a NeCTuR study. *Int J Gynecol Cancer* 2021. doi:10.1136/ijgc-2020-002213. [Epub ahead of print: 09 Feb 2021].
- 6 Cibula D, Pötter R, Planchamp F, *et al.* The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Radiother Oncol* 2018;127:404–16.
- 7 Cibula D, Dostalek L, Hillemanns P, *et al.* Completion of radical hysterectomy does not improve survival of patients with cervical cancer and intraoperatively detected lymph node involvement: ABRAX international retrospective cohort study. *Eur J Cancer* 2021;143:88–100.