Scholars Journal of Medical Case Reports

OPEN ACCESS

Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

Neuroendocrine Carcinoma of the Cervix: A Case Report and Review of the Literature

Sanae Chaouia[1*], Ghita Hadraoui[1], Youness El-Khadir[1], Oumayma Bounid[1], Tariq Igarramen[1], Rokkaya Iharti[1], Mouna Darfaoui[1], Abdelhamid El Omrani[1], Mouna Khouchani[1]

[1]Radiation Oncology Department, Mohammed VI Teaching Hospital, Marrakesh, Morocco

DOI: 10.36347/sjmcr.2021.v09i10.005 | **Received:** 21.08.2021 | **Accepted:** 29.09.2021 | **Published:** 05.10.2021

***Corresponding author:** Sanae Chaouia

Abstract **Case Report**

Small cell neuroendocrine carcinoma of the cervix (NECC) is a rare variant of cervical cancer. The prognosis of women with NECC is poor and there is no standardized therapy for this type of malignancy based on controlled trials. Here we report a case in which a 32 years old African female patient with an intermittent vaginal spotting and abdominal pain evolving for more than three months with complete preservation of the general condition. The clinical examination revealed only a bulky mass of the cervix, which turned out to be small cell neuroendocrine cervical carcinoma. We reviewed and discussed the features, diagnosis, and prognosis of small cell neuroendocrine carcinoma of the cervix.

Keywords: Neuroendocrine, Cervical cancer, Small cell cancer, Chemotherapy, Radical Surgery.

INTRODUCTION

Neuroendocrine uterine cervix tumors are an uncommon group of neoplasms characterized by a high incidence of early nodal and distant metastases, resulting in a worse prognosis than other subtypes of cervical cancer [1]. They represent only about 2% of all cervical malignancies. The College of American Pathologists and the National Cancer Institute suggested reducing the number of terms used to identify neuroendocrine tumors of the cervix in 1996, developing a classification system of 4 categories: Typical (classical) carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma, and small cell carcinoma are the four types of carcinoid tumors [2-6].

The prognosis of patients remains bleak despite multimodal treatments, and the majority of patients die within 2 to 3 years of diagnosis [7, 8].

Here, we report a case of small cell neuroendocrine carcinoma of the uterine cervix.

CASE PRESENTATION

We present a case of a 32 years old African female patient (G4 P4 A0 L4); with unremarkable medical history, who presented with intermittent vaginal spotting and abdominal pain evolving for more than three months with complete preservation of the general condition. The clinical examination revealed only a bulky mass of the cervix, with no other physical signs. The patient have had a cervical biopsy , which the histopathological examination showed a tumor proliferation arranged in lobules and clusters of poorly differentiated malignant tumor cells with a neuroendocrine appearance. The tumor cells have hyperchromatic nuclei with frequent mitoses. On immunohistochemistry, the tumor cells showed positivity for cytokeratin 7 (CK7), CD56 and chromogranin, and negativity for CK5/6 and P63. Those findings have led to retaining the diagnosis of small cell carcinoma of the cervix, and then the patient was referred to our institution for management.

She subsequently underwent an enlarged lymphadeno-colpohysterectomy with ovarian transposition. Morphological and immunohistochemical findings were in favor of neuroendocrine carcinoma, measuring 1.2 cm, with negative lymph node dissection.

The patient lost to follow-up for three years, and then she was reseen in consultation with an anemic syndrome resulting from vaginal bleeding, associated with dysuria and abdominal pain. The clinical examination showed pallor and poor general condition with a performance status equals 2. On vaginal

examination, she presented a bleeding circumferential budding process at the level of the vaginal collar.

A Thoraco-abdominopelvic Computed Tomography scan (TAP CT) revealed a Centro-pelvic recurrence infiltrating the bladder and the rectosigmoid with peritoneal mass infiltrating the abdominal wall, associated with multiple lymphadenopathy and an osteocondensing lesion of the vertebral body of C5 (Figure 1). A biopsy of the mass was performed, which the anatomopathological and immunohistochemical study concluded a neuroendocrine small cell carcinoma.

After managing the anemia and the electrolytes disturbances, the patient received hemostatic radiotherapy with a total dose of 20 Gray (Gy) in 5 fractions of 2 Gy per fraction, after that, she received chemotherapy based on etoposide and cisplatin. The clinical and radiological assessment showed a progression of the disease. The patient subsequently died after two months.

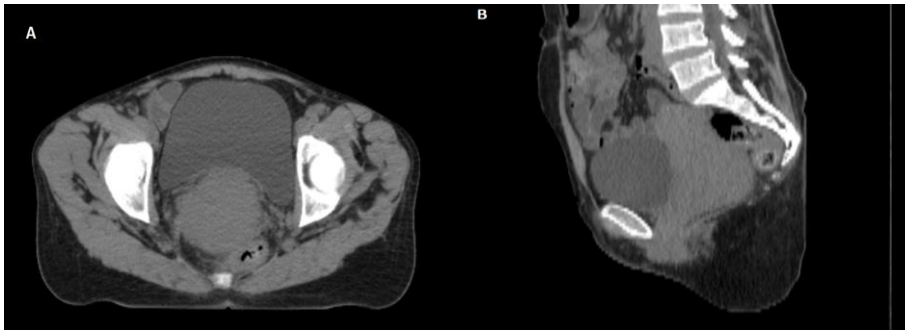

Fig-1: A: axial view of a Centro-pelvic recurrent tumor infiltrating the bladder and the rectosigmoid. B: sagittal view of the recurrent centro-pelvic tumor

DISCUSSION

Neuroendocrine carcinoma is a rare and aggressive malignant tumor that develops mainly in the lung and digestive tract, accounting for only up to 2% of all invasive cervical cancers, which are mostly squamous cell carcinomas [2, 6]. It was first identified in 1957 [9], but its true prevalence is likely underestimated. It is described under different terminologies such as carcinoid tumor, Argyrophilic tumour cells, APUDoma, small cell carcinoma, neuroendocrine carcinoma, atypical carcinoid, undifferentiated small cell carcinoma or intermediate cell carcinoma [6, 9, 10]. Throughout the last two decades, a rise in the incidence of neuroendocrine cancers in small cells has been observed, owing to the widespread use of this terminology, which has also allowed researchers to identify several distinguishing characteristics through the publication of retrospective studies.

Although the disease has been reported in women ranging in age from 22 to 87, the mean age at diagnosis of small cell neuroendocrine carcinoma of the cervix is about 45 [11, 12], which appears to be younger than uterine cervix squamous cell carcinoma.

Abdominopelvic symptoms are common in patients, such as vaginal bleeding or discharge, pelvic pain, or pelvic pressure. Only a few percentages of patients are asymptomatic or present only an abnormal Pap smear result. On clinical examination, a pelvic mass is frequently discovered. Due to the low quality of the data, it appears that the majority of patients had bulky disease at the time of diagnosis. Early (stage I to IIA), advanced (stage IIB to IVA), and metastatic (stage IVB) cancer were found in 135, 45, and 8 women, respectively, in a review of 188 patients with small cell neuroendocrine carcinoma of the cervix [13], moreover, 80% of the patients have had a tumor size more than 2 cm [13].

Patients may also manifest with a paraneoplastic syndrome, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing syndrome, hypercalcemia, or neurologic disease. The liver, adrenals, bone, bone marrow, and brain are the most commonly impacted organs.

Unlike squamous cell carcinomas of the uterine cervix, neuroendocrine carcinomas are consistently observed late due to the ineffectiveness of cervical smears in finding small cell neuroendocrine carcinomas [14, 15], for this reason biopsy is crucial for establishing the diagnosis. In the other side, pure small cell neuroendocrine carcinoma of the cervix is histologically indistinguishable from the small cell lung carcinoma and the extrapulmonary small cell carcinoma from other locations. The diagnosis relies mostly on the immunohistochemical study, which requires the presence of at least one neuroendocrine marker (synaptophysin, chromogranin A, neuron-specific enolase).

Histochemical research demonstrates a histological spectrum that ranges from a typical or atypical carcinoid tumor to a small cell carcinoma. The size, argyrophilia, immunocytochemical staining, and ultrastructure of endocrine cells differ considerably. On hematoxylin-eosin (H&E) stained sections, a little

differentiated, a diffusely infiltrating tumor composed of small blue cells with sparse cytoplasm, hyperchromatic nuclei with finely dispersed chromatin, and absent or inconspicuous nucleoli may be seen. The existence of prominent nucleoli, vesicular nuclei with a more granular chromatin pattern, and variable amounts of cytoplasm define the large cell variant of small cell neuroendocrine carcinoma. Pan-neuroendocrine markers such as chromogranin A (CGA), synaptophysin, and neuron-specific enolase can be used to demonstrate neuroendocrine differentiation. Almost all small cell neuroendocrine carcinomas are immunoreactive for keratin and epithelial membrane antigen due to their epithelial cellular origin. Furthermore, at least one neuroendocrine differentiation marker is expressed in 88 to 100 % of cases [11, 16]. Neuron-specific enolase (NSE), synaptophysin, CGA, and CD56 are one of these markers (neural cell adhesion molecule [NCAM]). The percentage of cases that are reactive with each varies in different studies [11, 16, 17].

The prognosis for women with small cell cervix carcinoma is less than for women with cervical squamous cell carcinomas or adenocarcinomas [10, 18], but significantly better than for women with small cell lung cancer. The major adverse prognostic factors are advanced tumour stage, larger tumour size, pure small cell histology, and smoking [19-22]. Patients with limited-stage cancer have a five-year survival rate of around 30%. However, few patients with more acute diseases survive for more than two years. Small cell neuroendocrine carcinomas have a higher risk of lymph node metastases and lymphovascular space invasion, and their clinical course is defined by early hematogenous dissemination [5, 13, 23, 24].

Small cell neuroendocrine carcinomas are often not confined to the cervix. Therefore, the workup should include abdominopelvic imaging, preferably magnetic resonance imaging [18]. Currently, guidance from the Society of Gynecologic Oncologists and with the aim of improving lymph node staging, PET (Positron Emission Tomography) has shown superiority in this indication both at the pelvic and lumbo-aortic level [18]. Allowing dual monitoring of target lesions from both a morphological and metabolic point of view is becoming the tool of choice when one wishes to assess the effectiveness of treatment better [18].

Small cell neuroendocrine carcinoma and other neuroendocrine variations are included in standard cervical cancer staging, and it is increasingly being used for disease staging. However, the increased risk of lymphatic and vascular invasion, as well as the high rate of extra pelvic recurrence, must be recognized. Early lymphatic invasion of locoregional adenopathies, for example, it was found in 40% of stage IB small cell tumours less than 3 cm in diameter. At the time of diagnosis, vascular and lymphatic invasion was observed in 60% of these tumours. The recurrence time was 19.9 months [19]. Metastases can occur at any age, including bone, lungs, and supraclavicular structures.

Given the rarity of the condition, there are limited data to recommend treatment of small cell neuroendocrine carcinoma. Most published series contain few patients, and there are no prospective trials. In general, survival after radical hysterectomy alone is poor, but there is no consensus as to optimal management [7, 10, 11]. Treatment considerations generally take into account the treatment options for cervical cancer and particularly for chemotherapy and have been largely extrapolated from the experience with small cell lung cancer [11, 13, 20-24].

For patients with early-stage disease (International Federation of Gynecology and Obstetrics [FIGO]) stage I to IIA, local treatment is not enough; the majority of patients developed metastases, the main cause of death within three years. According to two authors that have reported disappointing results, Sheet *et al*., first found an overall survival rate of 16 percent at three years and a progression-free survival rate of 0 percent at five years [25]. According to Sevin et al, that one was 36% [7].

Because of the high rates of hematogenous (67-90% of cases) and lymph nodes (34% of cases) metastases, a high incidence of adenopathy upon diagnosis (40-60%), and frequent vascular invasion, most authors recommend a combination of systemic and local treatment [26-28].

Three studies compared local treatment alone (surgery) or combined with adjuvant chemotherapy. Zivanovic *et al*., observed that patients who underwent cisplatin and etoposide-based chemotherapy had an 83% three-year recurrence-free survival rate compared to 0 % for local treatment alone [29]. A larger Japanese series of 52 patients showed that chemotherapy improved both progression-free and overall survival rates [26].

Finally, Cohen *et al*., showed a survival advantage of adjuvant chemotherapy (47.8% vs 38.7%), although this difference did not reach the significance threshold [13]. In advanced stages of the disease, metastases are treated with platinum-based combination chemotherapy. Although the initial response rate is relatively high (50-79%), recurrence or chemoresistance develops. Then, as a second-line therapy, vincristine/doxorubicin/cyclophosphamide and topotecan are started.

Due to the high incidence of early nodal and distant metastases in early stages, some authors recommended neoadjuvant chemotherapy. Chang demonstrated a complete response in 6 of 7 patients who received CAV/PE before hysterectomy; however,

microscopic residues were present in all cases, although some authors preferred neoadjuvant chemotherapy. Adjuvant chemotherapy was required. Therefore, three patients were covered of cancer at 16, 45 and 56 months of follow-up.

Morris and al. reported their experience with the chemotherapy of 10 stage IB-IIB tumors with surgery or radiation therapy preceded by chemotherapy. The response rate was 57%, with a median survival time of 28 months [27]. Bermudez *et al*., observed a partial response in 69.4% of cases and a complete response in 15.3% [30]. Lee and al; on either side; found no benefit in the six patients who received neoadjuvant chemotherapy [31].

Despite the lack of data comparing radiotherapy and surgery, some authors have preferred to include them into the framework of a multimodal treatment by combining surgery, radiotherapy, and chemotherapy. Chan et al. achieved a five-year survival rate of 32%, significantly higher than those reported in other various series. Patients with tumors less than 2 cm who had had radical surgery were considered long-term survivors [22]. According to the Hoskins *et al*., protocol, a combination of radiotherapy and chemotherapy is recommended for locally advanced tumors (stages IIB-IV) and inoperable patients [21]. In these stages, chemotherapy with at least five cycles of cisplatin and etoposide is associated with improved progression-free survival and overall survival.

Patients with widespread metastatic or recurrent disease are treated with chemotherapy regimens such as cisplatin and etoposide alone or with VAC (vincristine, adriamycin and cyclophosphamide).

A subsequent retrospective study concluded that the combination of topotecan, paclitaxel, and bevacizumab was superior to standard chemotherapy regimens in recurrent small cell carcinoma of the cervix [32].

The major adverse prognostic factors are advanced tumor stage, larger tumor size, pure small cell histology, and smoking [22, 24, 33, 34]. In one study, the only survivors were those with tumors <4 cm and no clinical evidence of nodal metastases [11]. However, these are small-scale series that do not allow us to draw any definitive conclusion.

CONCLUSION

Small cell neuroendocrine carcinomas of the uterine cervix are uncommon tumors with a poor prognosis, but due to multimodal treatment, encouraging results have been shown in recent series in early detection cases, even if the optimal treatment regimen still has to be defined.

REFERENCE

1. Alfsen, G. C., Thoresen, S. Ø., Kristensen, G. B., S kovlund, E., & Abeler, V. M. (2000). Histopatholo gic subtyping of cervical adenocarcinoma reveals i ncreasing incidence rates of endometrioid tumors i n all age groups: a population based study with revi ew of all nonsquamous cervical carcinomas in Nor way from 1966 to 1970, 1976 to 1980, and 1986 to 1990. *Cancer: Interdisciplinary International Jour nal of the American Cancer Society*, *89*(6), 1291-12 99.
2. Albores-Saavedra, J., Larraza, O., Poucell, S., & M artinez, H. A. R. (1976). Carcinoid of the uterine ce rvix. Additional observations on a new tumor entity . *Cancer*, *38*(6), 2328-2342.
3. Scully, R. E., Aguirre, P., & DeLellis, R. A. (1984) . Argyrophilia, serotonin, and peptide hormones in the female genital tract and its tumors. *Internationa l journal of gynecological pathology*, *3*(1), 51-70.
4. Miller, B., Dockter, M., El Torky, M., & Photopulo s, G. (1991). Small cell carcinoma of the cervix: a c linical and flow-cytometric study. *Gynecologic onc ology*, *42*(1), 27-33.
5. Van Nagell Jr, J. R., Donaldson, E. S., Wood, E. G. , Maruyama, Y., & Utley, J. (1977). Small cell canc er of the uterine cervix. *Cancer*, *40*(5), 2243-2249.
6. Albores-Saavedra, J., Gersell, D., Gilks, C. B., & H enson, D. E. (1997). Terminology of endocrine tum ors of the uterine cervix. *Archives of pathology & l aboratory medicine*, *121*(1), 34-39.
7. Sevin, B. U., Method, M. W., Nadji, M., Lu, Y., & Averette, H. A. (1996). Efficacy of radical hysterec tomy as treatment for patients with small cell carci noma of the cervix. *Cancer: Interdisciplinary Inter national Journal of the American Cancer Society*, *7 7*(8), 1489-1493.
8. Boruta II, D. M., Schorge, J. O., Duska, L. A., Cru m, C. P., Castrillon, D. H., & Sheets, E. E. (2001). Multimodality therapy in early-stage neuroendocrin e carcinoma of the uterine cervix. *Gynecologic onc ology*, *81*(1), 82-87.
9. Reagan, J. W. (1957). Analytical study of the cells i n cervical squamous-cell cancer. *Lab. Invest.*, *6*, 24 1-250.
10. McCusker, M. E., Coté, T. R., Clegg, L. X., & Tav assoli, F. J. (2003). Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. *Gynecolo gic oncology*, *88*(3), 333-339.
11. 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. *Gynecologic oncology*, *93*(1), 27-33.
12. Abeler, V. M., Holm, R., Nesland, J. M., & Kjørsta d, K. E. (1994). Small cell carcinoma of the cervix. A clinicopathologic study of 26 patients. *Cancer*, *7 3*(3), 672-677.
13. Cohen, J. G., Kapp, D. S., Shin, J. Y., Urban, R., S herman, A. E., Chen, L. M., ... & Chan, J. K. (2010

). Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *American journal of obstetrics and gynecology*, *203*(4), 347-e1.

14. Wang, P. H., Liu, Y. C., Lai, C. R., Chao, H. T., Yuan, C. C., & Yu, K. J. (1998). Small cell carcinoma of the cervix: analysis of clinical and pathological findings. *European journal of gynaecological oncology*, *19*(2), 189-192.
15. Zhou, C., Hayes, M. M., Clement, P. B., & Thomson, T. A. (1998). Small cell carcinoma of the uterine cervix: cytologic findings in 13 cases. *Cancer Cytopathology: Interdisciplinary International Journal of the American Cancer Society*, *84*(5), 281-288.
16. Straughn Jr, J. M., Richter, H. E., Conner, M. G., Meleth, S., & Barnes, M. N. (2001). Predictors of outcome in small cell carcinoma of the cervix—a case series. *Gynecologic oncology*, *83*(2), 216-220.
17. McCluggage, W. G., Kennedy, K., & Busam, K. J. (2010). An immunohistochemical study of cervical neuroendocrine carcinomas: Neoplasms that are commonly TTF1 positive and which may express CK 20 and P63. *The American journal of surgical pathology*, *34*(4), 525-532.
18. Bonardel, G., Chargari, C., Gontier, E., Bauduceau, O., Soret, M., Dechaud, C., ... & Foehrenbach, H. (2009). Positron emission tomography in the management of cervix cancer patients. *Cancer radiotherapie: journal de la Societe francaise de radiotherapie oncologique*, *13*(6-7), 490-498.
19. van Nagell Jr, J. R., Powell, D. E., Gallion, H. H., Elliott, D. G., Donaldson, E. S., Carpenter, A. E., ... & Pavlik, E. J. (1988). Small cell carcinoma of the uterine cervix. *Cancer*, *62*(8), 1586-1593.
20. Wang, K. L., Yang, Y. C., Wang, T. Y., Chen, J. R., Chen, T. C., Chen, H. S., ... & Wang, K. G. (2006). Neuroendocrine carcinoma of the uterine cervix: a clinicopathologic retrospective study of 31 cases with prognostic implications. *Journal of chemotherapy*, *18*(2), 209-216.
21. Hoskins, P. J., Swenerton, K. D., Pike, J. A., Lim, P., Aquino-Parsons, C., Wong, F., & Lee, N. (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. *Journal of Clinical Oncology*, *21*(18), 3495-3501.
22. 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: Interdisciplinary International Journal of the American Cancer Society*, *97*(3), 568-574.
23. 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. *Gynecologic oncology*, *81*(1), 82-87.
24. Chang, T. C., Lai, C. H., Tseng, C. J., Hsueh, S., Huang, K. G., & Chou, H. H. (1998). Prognostic factors in surgically treated small cell cervical carcinoma followed by adjuvant chemotherapy. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *83*(4), 712-718.
25. Sheets, E. E., Berman, M. L., Hrountas, C. K., Liao, S. Y., & DiSAIA, P. J. (1988). Surgically treated, early-stage neuroendocrine small-cell cervical carcinoma. *Obstetrics and gynecology*, *71*(1), 10-14.
26. Kuji, S., Hirashima, Y., Nakayama, H., Nishio, S., Otsuki, T., Nagamitsu, Y., ... & Yamada, T. (2013). Diagnosis, clinicopathologic features, treatment, and prognosis of small cell carcinoma of the uterine cervix; Kansai Clinical Oncology Group/Intergroup study in Japan. *Gynecologic oncology*, *129*(3), 522-527.
27. Morris, M., Gershenson, D. M., Eifel, P., Silva, E. G., Mitchell, M. F., Burke, T. W., & Wharton, J. T. (1992). Treatment of small cell carcinoma of the cervix with cisplatin, doxorubicin, and etoposide. *Gynecologic oncology*, *47*(1), 62-65.
28. Lewandowski, G. S., & Copeland, L. J. (1993). A potential role for intensive chemotherapy in the treatment of small cell neuroendocrine tumors of the cervix. *Gynecologic oncology*, *48*(1), 127-131.
29. Zivanovic, O., Leitao Jr, M. M., Park, K. J., Zhao, H., Diaz, J. P., Konner, J., ... & Aghajanian, C. (2009). Small cell neuroendocrine carcinoma of the cervix: analysis of outcome, recurrence pattern and the impact of platinum-based combination chemotherapy. *Gynecologic oncology*, *112*(3), 590-593.
30. Bermúdez, A., Vighi, S., Garcı, A., & Sardi, J. (2001). Neuroendocrine cervical carcinoma: a diagnostic and therapeutic challenge. *Gynecologic oncology*, *82*(1), 32-39.
31. Lee, J. M., Lee, K. B., Nam, J. H., Ryu, S. Y., Bae, D. S., Park, J. T., ... & Kang, S. B. (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. *Annals of Oncology*, *19*(2), 321-326.
32. Frumovitz, M., Munsell, M. F., Burzawa, J. K., Byers, L. A., Ramalingam, P., Brown, J., & Coleman, R. L. (2017). Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix. *Gynecologic oncology*, *144*(1), 46-50.
33. Hirahatake, K., Hareyama, H., Kure, R., Kawaguchi, I., Yamaguchi, J., Sakuragi, N., & Fujimoto, S. (1990). Cytologic and hormonal findings in a carcinoid tumor of the uterine cervix. *Acta cytologica*, *34*(2), 119-124.
34. Videtic, G. M., Stitt, L. W., Dar, A. R., Kocha, W. I., Tomiak, A. T., Truong, P. T., ... & Yu, E. W. (2003). Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. *Journal of Clinical Oncology*, *21*(8), 1544-1549.