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Postoperative radiotherapy in perivascular epithelioid cell tumors (PEComas): A narrative review

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ABSTRACT
Perivascular epithelioid cell tumor (PEComa), which is relatively new to the literature, is a rare mesenchymal tumor containing perivascular epithelioid cells. The immunohistochemical features of the disease must be considered for diagnosis. The disease contains melanocytic differentiation markers such as HMB45 and MelanA/Mart1, and myogenic markers such as actin, but does not express markers such as epithelial membrane antigen, keratin, or S-100. The disease can be seen in almost every organ. Most PEComas are benign. Malignant PEComa can follow an aggressive course, capable of recurrence and metastasis. The primary treatment approach for localized disease is surgical resection. Adjuvant systemic therapy can be administered to high-risk patients. It is noteworthy that the literature on postoperative radiotherapy in PEComa is limited with studies focusing primarily on gynecological cases. Most of the patients remained disease-free during follow-up, suggesting radiotherapy may be effective for local control. Integration of molecular profiling and mTOR-targeted approaches alongside radiotherapy may further define optimal management strategies.
Keywords: PEComa, Rare Tumor, Postoperative Radiotherapy, Local Control, mTOR inhibitors.

1. INTRODUCTION

Perivascular epithelioid cell tumor (PEComa), which is relatively new to the literature, is a rare mesenchymal tumor containing perivascular epithelioid cells [1,2]. The disease is considered to be in the same tumor family as angiomyolipoma, sugar cell tumor of lung, lymphangioleiomyomatosis, and clear cell myomelanocytic tumor of the falciform ligament [3]. Because it's a rare disease, it's difficult to diagnose. It can be confused with tumors such as gastrointestinal stromal tumor, clear cell sarcoma, leiomyosarcoma, epithelioid sarcoma, and malignant melanoma [4-6]. The immunohistochemical features of the disease must be considered for diagnosis. The disease contains melanocytic differentiation markers such as HMB45 and MelanA/Mart1, and myogenic markers such as actin, but does not express markers such as epithelial membrane antigen, keratin, or S-100. Some types have been reported to express progesterone receptors. Pathologically, neoplastic cells typically contain slightly eosinophilic, granular cytoplasm. PEComa can occur in association with tuberous sclerosis complex, an autosomal dominant disease caused by loss of the tuberous sclerosis complex 1 (TSC1) or TSC2 genes [4-10]. The disease can be seen in almost every organ, including the uterus and retroperitoneum, as well as the bladder, colon, gallbladder, skin, bone, heart and adrenal gland [10-24].

The primary treatment approach for localized disease is surgical resection. Adjuvant systemic therapy can be administered to high-risk patients [25,26]. However, studies in the literature regarding postoperative radiotherapy outcomes in PEComa cases are far from providing a clear recommendation on this matter. Given the locally aggressive potential of malignant PEComas and occasional positive surgical margins, postoperative radiotherapy may be considered for improved local control, though supporting data are limited. In this review, we aimed to compile the results of postoperative radiotherapy for PEComa.

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2. METHODS

This article is structured as a narrative review of the literature with keywords 'PEComa', 'sugar cell tumor', 'postoperative radiotherapy'. Data were obtained from articles published in English from journals indexed in PubMed, Google scholar. No time criteria were applied in the literature review.

3. DISCUSSION

Postoperative Radiotherapy in PEComa

Most PEComas are benign. Although the criteria for malignancy have not been definitively established, tumors with histologically extensive necrosis, infiltrative growth patterns, vascular invasion, pleomorphism, and a high mitotic rate can be considered malignant. In addition to these histological features, the tumor's large size suggests that the disease may have a more aggressive clinical course [27,28]. Malignant PEComa can follow an aggressive course, capable of recurrence and metastasis. The most common sites of metastasis are lymph nodes, lungs, and bones, although this can vary depending on the primary location of the tumor [8,27].

The primary treatment approach for localized disease is surgical resection. Adjuvant anthracycline-based chemotherapy regimens may be administered to high-risk patients based on pathological risk factors that help determine the risk of postoperative recurrence. The most important of these risk factors are tumor size >5 cm and a high mitotic rate [25,26]. Since the disease may occur in association with tuberous sclerosis complex, an autosomal dominant disease caused by loss of the TSC1 or TSC2 genes, mechanistic target of rapamycin (mTOR) inhibition-based treatment is thought to be beneficial in some cases [29,30].

It is noteworthy that the literature on postoperative radiotherapy in PEComa is limited, with studies focusing primarily on gynecological cases. Jeon et al.'s study examined a 9-year-old patient with uterine PEComa that was metastatic at the time of diagnosis [27]. Following systemic chemotherapy, the patient underwent a transabdominal hysterectomy, lymph node dissection, and postoperative radiotherapy. A dose of 45 Gy was administered to the primary site. The patient remained disease-free 1.5 years after initial diagnosis. In Fukunaga's study reporting the treatment outcomes of four cases of uterine PEComa, one case underwent postoperative chemotherapy and radiotherapy [31]. This patient, with a primary tumor size of 30 cm and mitotic activity of 15/10 on a high power field (HPF), died of lung and bowel metastases 16 months after total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH+BSO), and omentectomy. Folpe's study examined 26 cases of PEComa originating from various anatomic locations, including the cervix, uterus, scalp, forearm, abdominal wall, shoulder, and mesentery [32]. Four of these cases received postoperative radiotherapy. In Vang's study of eight uterine PEComa cases, one case received postoperative radiotherapy after hysterectomy and bilateral salpingo-oophorectomy [33]. In a study by Bonetti, presenting four cases of abdominopelvic PEComa, one case originating from the uterus received postoperative chemotherapy and radiotherapy [7]. The case was last seen 18 months after surgery, and the general condition of the patient, who had multiple lung and bone metastases, was noted to be poor. In the study by Akay et al., a case of adrenal PEComa received postoperative radiotherapy of 46.8 Gy/26 fractions after adrenal tumor excision [22]. The patient continues to live a disease-free life during the 1.5-year follow-up period following surgery. Fink's study examined a case of broad ligament-induced PEComa [34]. The patient underwent TAH + BSO + omentectomy followed by postoperative pelvic radiotherapy with 50.4 Gy. Fifteen months after diagnosis, the patient remains disease-free. Bradshaw's study examined a case of cervical PEComa [35]. The patient received postoperative immunotherapy and postoperative radiotherapy. The patient has been disease-free for 3.5 years since the initial diagnosis. In a Taiwanese study, postoperative radiotherapy was administered to two cases of gynecologic PEComa [36]. One case was diagnosed with vaginal PEComa and underwent total vaginectomy and debulking surgery followed by mTOR inhibitors and radiotherapy. The patient remains disease-free during a 7-month follow-up. The other case underwent complete staging surgery for uterine PEComa and did not receive adjuvant therapy due to her advanced age. The patient, who developed a recurrence during follow-up, underwent total vaginectomy and stump tumor resection. Following re-excision, the patient received mTOR inhibitors and radiotherapy. The patient remains disease-free during a 4-year follow-up.

Studies have not sufficiently included information on why postoperative radiotherapy is applied. Most of the patients remained disease-free during follow-up, suggesting that radiotherapy may be effective for local control in high risk patients. Radiotherapy doses ranged between 45-50.4 Gy across reported cases. Postoperative radiotherapy should be considered in patients with high risk factors for recurrence. Overstimulation of the mTOR pathway is known to cause radiosensitization and chemoresistance in cancer cells, so it can be said that mTOR inhibitors have a radiosensitizing effect [37]. The use of mTOR inhibitors in the patient group considering radiotherapy has the potential to improve treatment response [37,38]. Integration of molecular profiling and mTOR-targeted approaches alongside radiotherapy may further define optimal management strategies. Studies involving cases treated with postoperative radiotherapy for PEComa and the characteristics of these cases are shown in Table I.

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Table I. *Studies involving cases in which postoperative radiotherapy applied for PEComa*

Studies	Patients Applied Radiotherapy	Tumor Localization	Patient Age-Gender	Systemic Therapy	Type of Chemotherapy	Radiotherapy Dose	Last Control	Result
Bonetti [7]	1	Uterus	19-F	Yes	Adriamycin + Ifosfamide		18 m	Multiple lung and bone Metastases
Akay [22]	1	Adrenal	24-F	No		46,8 Gy/26 fr	18 m	**Disease Free**
Jeon [27]	1	Uterus	9-F	Yes	Vincristine, Ifosfamide, and Doxorubicin	45 Gy	18 m	**Disease Free**
Fukunaga [31]	1	Uterus	40-F	Yes			16 m	Dead
Folpe [32]	4	Cervix, Uterus, Forearm, Neck	48-F, 56-F, 71-M, 77-F	Uterus: Yes, Others: No			Cervix: 21 m, Uterus: 11 m, Forearm: 10 m, Neck: 6 m	**Cervix, Forearm and Neck: Disease Free**, Uterus: Lung and Bone Metastases
Vang [33]	1	Uterus	75-F	No			2,6 y	**Disease Free**
Fink [34]	1	Broad Ligament	51-F	No		50,4 Gy	15 m	**Disease Free**
Bradshaw [35]	1	Cervix	F	Immunotherapy			3,5 y	**Disease Free**
Liu [36]	2	Vagina, Uterus	51-F, 80-F	mTOR inhibitor			Vagina: 7 m, Uterus: 4 y	**Disease Free**

F: Female, M: Male, m: Months, y: Years

Conclusion

Given the paucity of data, multicenter registries and collaborative case reporting are needed to clarify indications for postoperative radiotherapy in PEComa. Based on current data, radiotherapy may be effective for local control in high risk patients. Integration of mTOR-targeted approaches alongside radiotherapy may further define optimal management strategies.

Compliance with Ethical Standards

Conflict of interest: The authors declare that there is no conflict of interest.

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Authors' contributions: All authors contributed equally to the study conception, design, and literature search. All authors read and approved the final manuscript.

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