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Scientific Article

External beam radiation therapy for advanced/unresectable malignant paraganglioma and pheochromocytoma

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Abstract

Purpose/Objectives: To evaluate the role of external beam radiation therapy (EBRT) for treatment of malignant paraganglioma (PGL) and pheochromocytoma (PCC).

Methods and materials: A retrospective review was performed of all patients with malignant PGL/PCC treated with EBRT at our institution between 1973 and 2015. Local control (LC) per treated lesion and overall survival were estimated using the Kaplan-Meier method. Toxicities were scored using the Common Toxicity Criteria for Adverse Events (AE), version 4.

Results: The cohort included 41 patients with 107 sites treated. Median (range) age at EBRT was 33 (11-80) years. Treatment intention was curative in 20 patients (30 lesions) and palliative in 21 patients (77 lesions). The primary tumor was PGL (63%) and PCC (37%). Previous local therapies were surgical resection (90%) and percutaneous ablation (19%). Indications for EBRT were local control (66%), pain (22%), or spinal cord compression (12%). Treatment site included bone (69%), soft tissue (30%), and liver (1%). Median (range) EBRT dose was 40 (6.5-70) Gy. Median biologic effective dose using $\alpha/\beta = 10$ (BED_{10}) was 53 (9-132). Median follow-up was 3.8 years (0.04-41.5), and mean follow-up was 9.7 years. Overall survival at 5 years was 65%: 79% for curative- and 50% for palliative-intention patients ($P = .028$). LC at 5 years was 81% for all lesions; 91% for lesions receiving $BED_{10} \geq 53$, and 62% for lesions receiving $BED_{10} < 53$ ($P = .001$). All 11 lesions treated with stereotactic body RT or radiosurgery had LC at a median of 3.0 (0.2-5.4) years. For the symptomatic lesions, symptoms improved in 94%. There were no acute grade ≥3 treatment-related AEs, including no hypertensive crises. Two patients developed a late grade ≥3 AE.

Conclusions: EBRT is a useful treatment modality for malignant PGL and PCC. Higher RT dose was associated with improved LC.

Conflicts of interest: None.

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Introduction

Paraganglioma (PGL) and pheochromocytoma (PCC) are rare neuroendocrine tumors arising from chromaffin cells in the adrenal medulla (PCC) or in extra-adrenal sites (PGL). Most PGL and PCC are benign and remain localized; however, a small fraction of patients develop distant metastases, which defines malignant PGL/PCC.[1] Many patients with malignant PGL/PCC experience disease progression at a relatively slow rate.

A variety of management strategies have been used for metastatic PGL/PCC, although cure is rare. For asymptomatic patients with nonimminently threatening disease, observation may be a reasonable option. For symptomatic patients, local or systemic therapies may be used to control tumor burden and improve quality of life. According to the 2017 National Comprehensive Cancer Network guidelines, management options for malignant PGL/PCC include cytoreductive surgery (when feasible), systemic chemotherapy (often cyclophosphamide, vincristine, and dacarbazine or temozolomide), or I-131 metaiodobenzylguanidine (MIBG).[2] Percutaneous ablation has also been used as a minimally invasive local treatment option.[3]

Small retrospective series have suggested that external beam radiation therapy (EBRT) may be a useful local treatment modality in some patients with advanced/unresectable malignant PGL/PCC[4-9]; however, because of the rarity of malignant PGL/PCC, the role of EBRT is incompletely defined. The purpose of the present study was to review outcomes of patients with PGL/PCC treated at our institution with EBRT. We hypothesized that EBRT would be associated with a high rate of local tumor control and symptom reduction and a low rate of treatment-related toxicity.

Methods and materials

Our institutional review board approved the conduct of this retrospective study.

Patient selection

Patients with PGL/PCC were identified from an institutional endocrinology database and an institutional radiation oncology database. Medical records were reviewed for all patients who received RT for PGL/PCC at our institution between January 1973 and September 2015. Patients with malignant PGL and PCC treated with EBRT were included. Patients with malignant PGL of the head and neck region with regional lymph node metastases were included (n = 4). Exclusion criteria were histology other than PGL/PCC, nonmetastatic (benign) disease, or inadequate follow-up or documentation.

Patients were divided into "curative" and "palliative" intention cohorts. The curative intention cohort consisted of patients being treated at all known sites of macroscopic disease. All others were considered palliative.

Patient evaluation and treatment

Because this was a retrospective study, all patients had been treated per attending physician discretion. Evaluation and treatment approaches for malignant PGL/PCC at our institution have evolved over time but generally are consistent with those included in contemporary National Comprehensive Cancer Network guidelines. Clinical evaluation included 24-hour urine and serum catecholamines and metanephrines. Imaging included computed tomography, magnetic resonance imaging, bone scan, ^{123}I-MIBG scintigraphy, octreotide scintigraphy, and/or 18F-fluorodeoxyglucose positron emission tomography. Resection was performed of primary and metastatic tumors when anticipated morbidity was low.[10] Alpha-adrenergic blockade was typically performed preoperatively before attempted resection. Percutaneous ablation techniques using ethanol, radiofrequency ablation, or cryoablation have recently been used for small, localized tumors amenable to such treatment.[3] For patients with multifocal or progressive metastatic disease not amenable to local therapies, systemic therapies including cytotoxic chemotherapy, ^{131}I-metaiodobenzylguanidine, or bone-directed therapies have been used.

EBRT has been used for patients with localized disease not amenable to other local therapies (surgical resection or percutaneous ablation) or for patients with widespread disease with symptoms from local tumor burden. From 1973 through approximately 1985, most patients were treated with 2-dimensional conformal megavoltage photon or electron RT techniques (including intraoperative electron RT). More recently, 3-dimensional conformal, intensity modulated RT, and stereotactic body RT (SBRT) megavoltage photon techniques have been used. Stereotactic radiosurgery (SRS) was used for brain metastases.

Following EBRT, patients were typically reevaluated for response and adverse events 1 to 3 months after RT with clinical examination and/or imaging, as appropriate. Subsequent follow-up and additional therapies undertaken were as deemed appropriate by involved expert providers.

The biologic effective dose (BED) was calculated for the delivered EBRT regimen, using the equation $BED = nd[1 + d/\alpha/\beta]$ with n = number of fraction, d = dose per fraction, and $\alpha/\beta = 10$ or 3. Accordingly, this is denoted as BED_{10} and BED_3.

Outcomes assessment

Acute (within 90 days from completion of RT) and chronic (>90 days after completion of RT) adverse events