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External Beam Radiation Therapy (EBRT) for Patients with Malignant Pheochromocytoma and Non-Head and Neck Paraganglioma: Combination with ¹³¹I-MIBG

Lauren Fishbein^{1,2}, Lara Bonner³, Drew A. Torigian⁴, Katherine L. Nathanson^{1,5}, Debbie L. Cohen^{1,6}, Daniel Pryma^{4,7}, and Keith Cengel³

¹Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

²Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

³Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

⁴Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

⁵Division of Medical Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

⁶Renal and HTN Division, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

⁷Division of Nuclear Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia PA 19104

Abstract

In patients with malignant pheochromocytoma and paraganglioma, ¹³¹I-MIBG radiotherapy can achieve an objective response rate of 30–50% with the dose limiting toxicity being hematologic. Patients with disseminated disease, who also have a few index bulky or symptomatic lesions, may benefit from the addition of targeted external beam radiotherapy alone or in combination with systemic ¹³¹I-MIBG. The records of patients with malignant paraganglioma who were treated with external beam radiotherapy at the University of Pennsylvania from February 1973 to February 2011 were reviewed in an institutional review board approved retrospective study. Of the 17 patients with tumors in the thorax, abdomen, or pelvis, 76% had local control or clinically significant symptomatic relief for at least one year or until death. As expected, the predominant toxicity was due to irradiation of tumor-adjacent normal tissues without clinically significant hematologic toxicity. Due to widespread systemic metastases with areas of bulky, symptomatic

Corresponding Author: Keith Cengel, Hospital of the University of Pennsylvania, Department of Radiation Oncology, 3620 Hamilton Walk, 180 H John Morgan Building, Philadelphia, PA 19104, Phone: 215-898-0062, Fax: 215-349-5445, keith.cengel@uphs.upenn.edu.

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tumor, five of the 17 patients were treated with sequential ^{131}I -MIBG (2 mCi/kg per treatment) and external beam radiotherapy to nine sites. In these patients, all areas that were irradiated with external beam radiotherapy showed durable objective response despite all patients eventually experiencing out-of-field systemic progression requiring other treatment. Four of these patients remain alive with excellent performance status 16, 18, 23, and 24 months after external beam radiotherapy. External beam radiotherapy can be highly effective in local management of malignant paraganglioma and can be used in conjunction with ^{131}I -MIBG due to non-overlapping toxicities with excellent control of locally bulky tumors.

Keywords

metastatic; pheochromocytoma; paraganglioma; external beam radiotherapy; combined modality treatment

Introduction

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare tumors of the autonomic nervous system derived from chromaffin tissue in the adrenal medulla or extra-adrenal ganglia, respectively (1). PCC/PGL are often benign, but are associated with high morbidity secondary to mass effect and increased levels of circulating catecholamines which can lead to severe hypertension, stroke, and even death. About a quarter of tumors become malignant, defined as the presence of chromaffin tissue at sites where it is not normally found such as in bone, lymph nodes, lungs, and liver (1). Malignant PCC/PGL are associated with a 50% five year survival rate, and treatment often includes surgical debulking, chemotherapy, or ^{131}I -meta-iodobenzylguanidine (^{131}I -MIBG) systemic radiotherapy.

The role of external beam radiotherapy (EBRT) in the management of malignant PCC/PGL has been controversial with a limited number of small case series published in the medical literature. A 1978 review of series in which EBRT was used as treatment modality concluded that malignant PCC/PGL are generally radioresistant (2). In that review of 19 published reports, a total of 39 patients with malignant PCC/PGL had received EBRT with doses ranging from 20–40 Gy. EBRT was judged to be at least partially effective in 10 of these reports. However, closer examination of the treatment techniques and patient follow-up in these older reports suggests that doses less than 40 Gy are relatively ineffective. In addition, it appeared that EBRT was more effective for treatment of osseous or nodal metastases, which were locations where technology before computed tomography (CT) based anatomic imaging allowed for adequate targeting of radiation beams. Moreover, radioresistance often was judged by failure of tumors to regress following EBRT rather than by overt in-field disease progression. Several case reports published since then have demonstrated benefit of EBRT for specific patients (3–7). In addition, multiple modern series treating head and neck PGLs suggest that while EBRT may not significantly shrink tumors, doses of 45–50 Gy can affect long term local control in the overwhelming majority of head and neck PGL cases (8–13). However, case reports do indicate that EBRT, especially at higher doses with older technology, can produce significant toxicity particularly in the retroperitoneum (8). These data combined with the treatment response

data of malignant PCC/PGL to radionuclide-based radiotherapy with ^{131}I -MIBG (14) suggest that while malignant PCC/PGL may not be radioresponsive in terms of tumor volume reduction, these tumors are by no means highly radioresistant.

We hypothesize that EBRT can provide durable local control of disease with limited side effects even in patients with non-head and neck malignant PCC/PGL. Therefore, we present a case series describing the treatment and results for all non-head and neck malignant PCC/PGL treated at the University of Pennsylvania with EBRT. In addition, we describe a subset of five patients who received combined ^{131}I -MIBG with EBRT as a strategy to promote both long term local control of bulky tumors with focal EBRT and systemic control of disease with ^{131}I -MIBG.

Methods

A retrospective chart review was performed on Radiation Oncology patients from the Hospital of University of Pennsylvania Radiation Oncology Database between February 1973 and February 2011. IRB approval for the retrospective chart review was obtained through the University of Pennsylvania. Patients were selected if they had received external beam radiation treatment for malignant PCC/PGL where the primary tumor was not a head and neck paraganglioma. In other words, to be included in the study, primary PCC/PGL tumors must have originated within the adrenal gland or within extra-adrenal ganglia in the thorax, abdomen, or pelvis. Seventeen patients met this criterion.

Radiotherapy was delivered using a variety of technologies given the wide study period, but all used megavoltage beams following simulation imaging with fluoroscopy or CT for all patients. Local control was defined as clinically significant symptomatic relief or arrested progression of disease at the treatment site for at least one year or until death if this occurs before one year.

For the subset of five patients treated to the abdomen or pelvis with both ^{131}I -MIBG and EBRT, intensity modulated radiotherapy (IMRT) was used to spare normal tissues, including bone marrow where clinically appropriate, by identifying marrow containing tissues on the planning CT likely to receive radiation and placing a dose limit into the reverse planning IMRT algorithm. This causes IMRT planning software to choose beamlets that minimize marrow dose and create sharp dose gradients to irradiate the target of interest while sparing the dose to the specified normal tissue. ^{131}I -MIBG was given at a dose of 2 mCi/kg, with a median of two treatments given three months apart.

Response evaluation criteria in solid tumors (RECIST) v1.1 was used to define disease progression or stability in the subset of five patients treated with combined ^{131}I -MIBG and EBRT (15). For time to progression or for survival times, the first day of radiation treatment was considered time zero. Time to progression was defined as months from the first day of EBRT to first progression of either local or distant disease. Survival time was defined as months from EBRT to death or to last follow up. Plasma and urine metanephrines and catecholamines measured both pre and post EBRT were used as markers of active disease burden. Paired sets of measurements were recorded at the closest time point within 4 months

prior to the first dose of EBRT and then after three to four months post EBRT. To evaluate blood pressure and heart rate as another marker of active disease burden, the average of two measurements from two different office visits were recorded both prior to and at least one month after the last EBRT treatment. Three of the five patients had genetic testing for mutations in one of the known PCC/PGL susceptibility genes, which was performed in a CLIA approved laboratory as part of routine clinical care.

Results

The cohort of 17 patients was given a median total dose of radiation of 40 Gy in a median of 17 fractions (Table 1). As expected, the predominant toxicity was due to irradiation of tumor-adjacent normal tissues without clinically significant hematologic toxicity, with the most common toxicity being mild nausea or diarrhea due to the predominately abdominal-pelvic location of most treatments in this series. None of the patients required interventions or hospitalization for any toxicities experienced. Seventy-six percent of patients (13 of 17) had local control, with arrested progression or symptomatic relief, at one year or until death if this occurred in less than one year. The one year local control rate among patients who survived at least one year after EBRT was 90% (9 of 10) with one patient of the nine experiencing in-field disease progression at two years.

Five of the 17 patients were treated with a temporally combined ^{131}I -MIBG and EBRT treatment (Table 2). Two of the five patients presented with spinal cord compression and were treated with EBRT prior to the first cycle of ^{131}I -MIBG (patients 2 and 5). The other three patients received ^{131}I -MIBG cycle 1 before EBRT. In these patients, the ^{131}I -MIBG scan was used to assist in EBRT planning and IMRT was used to spare normal tissues, including bowel and bone marrow, where clinically appropriate (Figure 1). Four patients had in-field stable disease by RECIST v1.1 criteria and one had partial response at the site of radiation treatment. A typical treatment response is documented in serial magnetic resonance imaging (MRI) scans in Figure 2, in which a pelvic tumor that had a dramatic increase in size prior to EBRT demonstrated prolonged disease stability following EBRT. All five patients had progressive disease outside the radiation field and one patient died. However, the remaining four patients were treated with additional therapies and remain alive with good performance status 16, 18, 28, and 37 months after EBRT.

Other markers of disease activity, such as blood pressure (BP), heart rate (HR), plasma and urine metanephrines and catecholamines, were examined in the five patients who received combined ^{131}I -MIBG and EBRT treatment. Only two of five patients required antihypertensive medications prior to EBRT. The average blood pressure and heart rate before treatment was not different than after treatment (pretreatment: BP 126/79; HR 93 and post treatment: BP 129/76; HR 92); however, one of the two patients taking antihypertensive medications (patient 3) was able to reduce the dose of blood pressure medication significantly. Three of the five patients had paired biochemical assessments within four months pre and post treatment (Table 3). For all three patients, EBRT treatment was associated with at least short term decreased plasma metanephrines or catecholamines.

Discussion

This work represents the largest single series of irradiated patients with non-head and neck malignant PCC/PGL. In contrast to other multi-patient series published in the past, this work is the first to apply standardized radiologic criteria (RECIST v1.1) to determine the EBRT response of these rare tumors. In addition, all patients in this series were treated with megavoltage radiotherapy and all patients were treated with some form of 3-dimensional image guidance to determine treatment volumes. This work demonstrates that the in-field local control after EBRT for patients with a median dose of 40 Gy in 2.25 Gy fractions is 76%. However, unlike typical carcinomas and lymphomas, significant tumor volume reduction following EBRT is uncommon and most of the local control is attributable to disease stabilization. This is evident in intra-osseous metastases, as demonstrated by the arrest of pelvic tumor growth in Figure 2, which is clearly clinically significant. Finally, in three patients with elevation of plasma catecholamines and metanephrines, there was a marked biochemical response, suggesting that patients with a dominant disease mass could benefit from local irradiation for both local and systemic symptoms of malignant PCC/PGL.

The 30–50% systemic disease response observed in patients with ^{131}I -MIBG therapy, in addition to concerns over inadequate treatment of bulky tumor deposits using single modality radionuclide radiotherapy and the experience in prostate cancer with combined EBRT and radionuclide treatments (16), led us to explore combining EBRT with ^{131}I -MIBG therapy in select patients. The potential advantages of this therapy are multi-fold. Since the dose limiting toxicity of ^{131}I -MIBG is bone marrow suppression and the dose limiting toxicity of EBRT is peri-tumoral normal tissue damage, these non-overlapping toxicities can allow a higher dose of radiation to tumor tissue with a lower level of toxicity. Moreover, by using the ability of intensity modulated radiotherapy (IMRT) to provide bone marrow sparing radiation, toxicity can be further minimized. There is also the possibility of increased tumor radiosensitivity due to interactions of low dose rate radiation from radionuclide therapy and high dose rate radiation from EBRT. Both of these effects lead to increased therapeutic index for EBRT in the abdomen and pelvis, where significant complications of high dose EBRT can occur (8). Finally, the post- ^{131}I -MIBG therapy scan can be used to aid treatment planning in radiotherapy.

Our study is a retrospective case series with some recognized limitations. We can not make direct comparisons between the results of EBRT treatment alone verses combined EBRT and ^{131}I -MIBG therapy in controlling malignant PCC/PGL disease. Nevertheless, the combined treatment appeared safe with minimal side effects and was effective at offering pain relief, especially to intra-osseous metastases. In addition, while this is the first study to our knowledge that uses the RECIST v1.1 criteria to assess tumor control, we only were able to apply these criteria to the subset of five patients treated with combined EBRT and ^{131}I -MIBG based on availability of follow up imaging in our retrospective review. In addition, local control or stable disease may be difficult to define for indolent tumors such as malignant PCC/PGL. We defined local control as clinically significant symptomatic relief or arrested progression at the treatment site for at least one year or until death if this occurs before one year. This is similar to the definition used for this same disease in other case series (8, 11). We believe this is acceptable in our population because most patients had

stable disease or arrested local progression at the EBRT treatment site in the face of future systemic progression of disease. Despite these limitations, this is the largest reported series of using EBRT to non-head and neck malignant PCC/PGL to date and suggests that further prospective studies are warranted.

The high rate of local control for bulky metastases that was achieved in our current patient cohort, despite eventual systemic progression, suggests that combining ^{131}I -MIBG with EBRT can be safely performed due to non-overlapping toxicities and can achieve excellent control of locally bulky tumors. These data are being used to develop a prospective protocol for multi-modality management of malignant PCC/PGL that includes combined ^{131}I -MIBG with EBRT.

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Figure 1.

A. Digitally reconstructed anterior radiograph from planning CT scan demonstrating tumor and normal tissue volumes and dose distribution. The patient underwent CT based treatment planning and the attending radiation oncologist identified normal and tumor tissues as shown on the left panel. Tumor tissues are identified with the aid of ^{131}I -MIBG scan that is combined with the treatment-planning scan. Normal tissue, including bone marrow, bowel, bladder, and rectum that are outside the tumor volume are outlined on axial CT slices within 1 cm of the anticipated superior and inferior treatment borders. The intensity modulated radiation therapy (IMRT) plan is then obtained by computer based inverse treatment planning, where a prioritization algorithm determines the optimal beam configuration to deliver the prescribed dose to the tumor while maintaining acceptably low doses to the normal tissues. B. The dose distribution as viewed from the posterior treatment portal is represented as a dose color wash image.

Figure 2.

Typical treatment response to combined EBRT and ^{131}I -MIBG by MRI appearance. The patient treated in Figure 1 had an MRI scan two and a half years prior to intensity modulated radiation therapy (IMRT) EBRT that demonstrated an asymptomatic osseous metastasis to the left posterior ilium (A). This demonstrated clear growth and extension into the subjacent left sacrum prior to EBRT (B). While the tumor experienced slight pseudoprogession at one year post EBRT (C), disease stabilization continued through to the last follow-up MRI (D).

Table 1

EBRT Summary for Patients with Non-head and neck PCC/PGL

Patient	Location of EBRT	Total Dose (Gy)	Dose per Fraction (Gy)	Fractions (N)	Follow Up Interval (months)	Disease Course
1*	lumbar spine metastasis	30	3	10	12	local control [†] and reduced pain; systemic progression
2*	thoracic spine metastasis	30	6	5	14	local control with pain relief; stable to slight increase of systemic disease
3*	multiple metastases left arm left glenoid	54 34 40	2 2 2.5	27 17 16	23	local control clinically with reduced pain; systemic disease slow progression
4*	right parietal skull metastasis abdomen right flank spine metastasis	49.5 50.4 37.5	2.3 1.8 2.5	22 28 15	27	local control at all sites with reduced pain; systemic progression elsewhere and then stability
5*	spine and pelvis metastases	35	2.5	14	9	local control with decreased disease; systemic progression; deceased 9 months after EBRT
6	thoracic spine/chest wall metastases	54	1.8	30	108	local control despite systemic progression for 2 years and then in field progression
7	abdomen	45	1.8	25	31	disease progression severe; difficult to assess in field disease; deceased 2.5 years after EBRT
8	left perirenal post op to primary site	45	1.8	25	120	local control at last follow-up
9	pelvis and cervical spine metastases sternum/ribs metastases	35 20	2.5 4	14 5	36	local control at all EBRT sites; died of progressive disease 3 years after EBRT
10	Sternum metastases	30	3	10	10	pain relief, no other info, irradiated ribs at 8 months post sternum.
11	hip metastasis	30	3	10	117	symptomatic relief; lost to follow up but known to be alive
12	abdominal aorta, post op residual primary disease	50.4	1.8	28	NA	local control at last follow-up
13	multiple metastases	20	4	5	8	symptomatic relief, died 8 months after EBRT
14	chest, paravertebral masses at primary site	50	2	25	8	died 8 months after EBRT; no information

Patient	Location of EBRT	Total Dose (Gy)	Dose per Fraction (Gy)	Fractions (N)	Follow Up Interval (months)	Disease Course
15	mediastinum recurrent disease at primary site	45	1.8	25	NA	lost to follow up
16	lumbar spine metastasis	50.4	1.8	28	84	local control; Lost to follow up at 7 years
17	abdomen at primary site	28.8	1.8	16	2	did not finish treatment; local control but died 2 months after EBRT
Mean		39.3	2.5	18.2		
Median		40	2.3	17.0		

* Patients included in the subset who received temporally related ¹³¹I-MIBG and EBRT.

[†] local control is defined as clinically significant relief of symptoms or apparently arrested progression of targeted EBRT site for at least one year or until death if it occurred sooner than one year
NA not available; PCC/PGL pheochromocytoma and paraganglioma

Table 2

Subset of Patients who Received Temporally Related ¹³¹I-MIBG and EBRT

A. Demographics										
Patient	Gender	Age at Initial Diagnosis	FHX	Survival	Primary PGL Location	Metastatic Disease Diagnosis	Location of Metastases	Genetics	Presenting Symptoms	Other Systemic Treatments
1	F	40	no	Alive	retroperitoneal against caudate lobe of liver	At diagnosis	liver, IVC, bone, lymph nodes	not tested	Headaches, anxiety, weight loss, nausea and vomiting	chemotherapy with CVD 2 months after for systemic progression
Hom Metab Res. Author manuscript	M	42	yes	Alive	left retroperitoneal and left para-aortic	3 years later	bone	SDHB	Palpitations and diaphoresis	chemotherapy with CVD 11 months after for systemic progression
	F	22	yes	Alive	para-aortic	At diagnosis	bone, soft tissue	SDHB	Unavailable	chemotherapy with CVD + doxorubicin 17 years earlier
	M	41	yes	Alive	right retroperitoneal	9 years later	bone, lymph nodes, and into IVC	SDHB	Night sweats	chemotherapy with CVD one year after for systemic progression
5	F	28	yes	Deceased	retroperitoneal near and in liver	At diagnosis	liver, bones	not tested	Back pain and numbness in both legs	no other systemic treatment

B. Local and Distant Disease Status									
¹³¹ I-MIBG*									
Patient	Location of EBRT	Disease Status					Time to Progression (months)	Survival	Survival Time [‡] (months)
		Cycle 1	Cycle 2	Cycle 3	Local Disease	Distant Disease			
1	lumbar spine	-1	NA	NA	SD	PD	11.9	alive	15.9
2	thoracic spine	+0.5	NA	NA	SD	PD	3.6	alive	17.7
3	pelvis/left humerus	-12.9	-3	0	SD	PD	21.9	alive	23.3
4	abdomen/skull	-6.5	-1.2	NA	SD	PD	15.2	alive	23.5
5	spine/pelvis	+2.1	NA	NA	PR	PD	3.7	deceased	3.7

FHX family history; F female; M male; IVC inferior vena cava; CVD cyclophosphamide, vincristine and dacarbazine; SDHB succinate dehydrogenase B subunit gene mutation

* Treatment dose 2mCi/kg MIBG Per Cycle;

[‡] months prior to EBRT are denoted by “-” while months after EBRT are denoted by “+”;

[§] Time from EBRT to end of study or death

NA not applicable; SD stable disease; PR partial response; PD progressive disease

Table 3
 Biochemistries Pre and Post EBRT for Patients who Received Temporally Related ^{131}I -MIBG and EBRT

Patient	Biochemical Test	Pre EBRT Measurement	Fold above ULN	Post EBRT Measurement	Fold above ULN
2	Pl MN (nl: 0–0.49 nmol/L)	0.41	NA	0.32	NA
	Pl NMN (nl: 0–0.89 nmol/L)	6.76	7.60	2.62	2.94
	CGA (nl: 0–50 ng/mL)	52	1.04	28	NA
3	Pl MN (nl: 0–0.49 nmol/L)	0.98	2.00	0.86	1.76
	Pl NMN (nl: 0–0.89 nmol/L)	11.20	12.58	6.92	7.78
	CGA (nl: 0–50 ng/mL)	259	5.18	205	4.10
5	Pl DA (nl: 0–20 pg/mL)	94	4.70	62	3.10
	Pl E (nl: 10–200 pg/mL)	31	NA	22	NA
	Pl NE (nl: 80–520 pg/mL)	759	1.46	359	NA

* Patients 1 and 4 were not included in this table because Patient 1 had no biochemical testing within 4 months prior to EBRT and Patient 4 had normal plasma metanephrines pre and post EBRT.

ULN upper limit of normal; nl normal range; Pl plasma; MN metanephrines; NMN normetanephrines; CGA chromogranin A; DA dopamine; E epinephrine; NE norepinephrine; NA not applicable