External beam radiation therapy in treatment of malignant pheochromocytoma and paraganglioma

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Purpose: Pheochromocytomas (PCCs) are neuroendocrine tumors arising from the adrenal medulla or as paraganglioma (PGL) from extra-adrenal sites. While usually benign, a small fraction is malignant. Multi-modality therapy is used in treating malignant disease; however, little data exist on the role of external beam radiation therapy (EBRT). In this retrospective review, we assessed response to EBRT in malignant PCCs or PGLs.

Methods and Materials: Records of patients treated at the National Institutes of Health who received EBRT between 1990 and 2012 were studied. Patients were assessed for symptomatic control, biochemical response, local and distant control by response evaluation criteria in solid tumors v1.1 or stable disease on imaging reports, toxicity by radiation therapy oncology group (RTOG) criteria, and survival.

Results: There were 24 patients treated who received EBRT to lesions of the abdomen (n=3), central nervous system (n=4), and bone (n=40). Lesions were treated with 3D conformal EBRT to a mean dose of 31.8 Gy in 3.3 Gy fractions, or fractionated stereotactic radiosurgery to 21.9 Gy in 13.6 Gy fractions. Patients experienced acute (n=15) and late (n=2) RTOG toxicities; no patient experienced acute toxicity ≥4 or late toxicity ≥2. Symptomatic control was achieved in 81.1% of lesions. Stable radiographic response was achieved in 86.7% of lesions with progression in 13%. Distant progression was observed overall in 75% of patients and average survival was 52.4 months.

Conclusion: Malignant PCC and PGL often do not respond well to current systemic therapies. In these cases, EBRT can be considered in patients with symptomatic, localized disease progression.

Keywords: radiation, pheochromocytoma, paraganglioma, malignant, neuroendocrine

INTRODUCTION

Pheochromocytomas (PCCs) are neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. Closely related tumors of the extra-adrenal paranganglia are termed as paragangliomas (PGLs). Adrenal PCCs are the most common chromaffin tumors, occurring in about 80–85% of cases. The remainder occur as PGLs, which may be classified as branchiogenic, including glomus jugulare and carotid body tumors; intravagal; aorticosympathetic; and visceral-autonomic. These tumors are rare, with an annual reported incidence of two to eight per million population and prevalence in 0.2–0.4% of hypertensive patients. They are characterized by their ability to synthesize, store, and secrete catecholamines although some, especially those of branchiogenic or intravagal origin, are non-functional. Elevated urinary fractionated and plasma free metanephrines have been shown to be sensitive markers of disease and are therefore often used in diagnosis. Although less sensitive for diagnosis, chromogranin A levels are also valuable in following response to therapy and monitoring for recurrence (1).

While most occur as sporadic tumors, about 30–35% is associated with hereditary syndromes. These include multiple endocrine neoplasia type 2 arising from mutations in the rearranged during transfection (RET) proto-oncogene; von Hippel–Lindau (VHL) syndrome caused by mutations of the VHL gene; and von Recklinghausen’s disease due to mutations of the
Table 1 | Malignant PCC/PGL cases treated to known total dose.

| Reference | N | Site | Dose (Gy) | Results |
|-----------|---|------|-----------|---------|
| Fishbein et al. (11) | 17 | Malignant PCC/PGL outside the head and neck | Median 40 | 76% local control or significant symptomatic relief |
| Pham et al. (10) | 7 | Bony metastasis (5) and abdominal primary (2) | Mean 44 ± 0.04 | 71% effective in relieving pain (5/7) |
| Yoshida et al. (12) | 3 | Pelvic, para-aortic, left inguinal lymph nodes | Median 55 | Control of catecholamines, hypertension, and swelling |
| Elder et al. (13) | 4 | Osseous metastases | Median 20 | 100% with decreased urine catecholamines and temporary alleviation in pain |
| Teno et al. (14) | 2 | Sacral and vertebral metastases | Mean 30 | No significant change, exacerbated hypertension |
| Brodkey (15) | 2 | Vertebral metastasis | Mean 47 | Resolution of myelopathy |
| Hamilton (16) | 4 | Bony metastasis | Median 40 | Symptomatic improvement (50%); distant progression (100%) |
| Jindel (17) | 2 | Bony metastasis | Mean 38.7 | Resolution of myelopathy and swelling |
| Yu (18) | 3 | Various | Median 25 | Higher doses may have resulted in sustained remission |
| Olson (19) | 2 | Bony metastasis | Mean 30 | Resolution of pain and weakness; distant progression |
| Siddiqui (20) | 3 | Abdominal primary, femur, spinal cord | Median 25 | Resolution of pain and neurologic symptoms; distant progression |
| Drasin (7) | 2 | Vertebral metastasis | Mean 36.5 | Resolution of pain, slowed progression |
| James et al. (21) | 10 | Various | Median 25 | 50% treated with <2500 Gy without symptomatic or survival benefit |
| Scott (6) | 15 | Various | Median 32.5 | Some control of pain and BP, complicated by leukopenia |
| Holati (22) | 6 | Various | Median 44.5 | 66% survival at 2 years |
| Moloney (9) | 6 | Various | Median 30.75 | Pain control at bony metastasis; poorly tolerated at primary |

neurofibromatosis type 1 (NF1) gene. In addition, mutations in genes encoding succinate dehydrogenase subunits (SDHD, SDHC, and SDHB) are associated with familial PGL syndromes (PGL1, PGL3, and PGL4), respectively.

Currently, the only diagnostic criterion for malignant disease is the presence of metastasis. The proposed incidence of malignant disease ranges from 3 to 36% with generally lower rates of malignancy in PCC compared to PGL. However, rates of malignancy have been reported as high as 50% in patients with SDHB mutation. Overall 5-year survival in the setting of benign disease is between 90 and 95%. Prognosis of malignant PCC and PGL is poor, with a 5-year survival between 34 and 72%. While benign disease can generally be definitively treated with surgical resection, malignant PCC and PGL currently have no cure. Patients are treated with multi-modality therapy, which may include surgical resection, radiopharmaceutical therapy, chemotherapy, and radiofrequency ablation. Within these treatment options for malignant disease, the role of external beam radiation therapy (EBRT) remains largely undefined.

Ascribing a role to EBRT in the treatment of malignant PCC/PGL is difficult given limited numbers of patients and reports in the literature. There have been case reports on malignant PCC/PGL in which EBRT was delivered to unknown total doses. In these cases, irradiation was delivered to the primary tumor or metastatic sites with varying symptomatic control and most often with progression of local and distant disease (2–6). However, these reports may be of limited utility especially in PCC/PGL, given results from a 1978 literature review, which concluded that radiation therapy is beneficial for symptomatic relief of bone and lymph node metastases only at high doses (7).

Use of high-dose EBRT outside of bone and lymph node metastases was associated with significant normal tissue toxicity in older case reports, limiting its utilization for malignant PCC/PGL (8, 9). More recent case reports in which intensity
modulated radiation therapy (IMRT) or stereotactic radiosurgery and fractionated stereotactic radiosurgery (SRS/FSRT) are used, however, have allowed delivery of higher doses of radiation without significant normal tissue toxicity, resulting in durable local radiographic and symptomatic control at broader sites of metastatic disease (10). However, all of these reports are based on limited numbers of patients and lesions with the exception of a recent study on the role of EBRT and $^{131}$I-MIBG in non-head-and-neck PCC or PGL (11) (Table 1). In addition, this is the only study utilizing radiographic and biochemical responses to measure outcomes following EBRT in a subset of the patients reviewed. In the majority of case reports, patient characteristics as well as radiation techniques and outcomes are incompletely documented and direct comparison of the patients across these reports is difficult.

The objective of this study was to better characterize the utility of EBRT within multi-modality therapy by performing a retrospective review analyzing symptomatic, radiographic, and biological responses to treatment of patients with malignant PCC or PGL.

**MATERIALS AND METHODS**

A retrospective chart review of endocrinology patients treated at the National Institutes of Health between 1990 and 2012 was performed. Patients were selected if they received EBRT for pathologically confirmed malignant PCC/PGL. Irradiation was performed using either $^{60}$Co machine or 4- to 23-MV photons from a linear accelerator. Patient charts were assessed for: age, sex, familial syndromes, pre-treatment and post-treatment plasma and urinary metanephrine (PMNs, UMN$s$), and chromogranin A (CgA) levels within 5–6 months of radiation therapy, total radiation dose and fraction size, radiation technique, symptomatic response, local and distant radiographic response or control, radiation toxicities, additional therapies after treatment, and survival time.

Radiographic response was determined by response evaluation criteria in solid tumors (RECIST) v1.1 based on computed tomography (CT) or magnetic resonance imaging (MRI) reports for a subset of eight patients with 12 lesions with pre and post-treatment imaging available for evaluation (Figure 1). The criteria were applied to these patients for both local and distant, or non-target, disease. For the remainder of patients without imaging available, local and distant control was defined as stable lesion size and progression defined as any increase in size or number as documented by imaging reports. Given the retrospective nature of this study, imaging was performed at variable intervals based on physician discretion. Local and distant control was determined at the time of last available post-treatment imaging. Time to progression (TTP) was defined in months beginning on the first day of EBRT to first progression of local or distant disease in both subsets of patients. Toxicity was graded according to the radiation therapy oncology group (RTOG) acute and late criteria extrapolated from documentation in charts and on-treatment notes. Survival time was defined as months from ERBT to death or to last follow-up.

**RESULTS**

Treatment courses for 24 patients with a total of 47 lesions who met these criteria were reviewed. Patients were an average age of 34.1 years at diagnosis (range 12–59 years). Eight patients presented with metastases and 16 recurred with metastases an average of 6.2 years (2–264 months) after resection of the primary tumor.
One patient had a RET mutation, one had SDHD mutation, and nine had SDHB mutations. Prior to EBRT, 16 patients underwent surgical resection alone; 3 received resection followed by systemic chemotherapy (CVD, 3–26 cycles); 1 underwent resection with RFA to liver metastases; 1 underwent resection with systemic yttrium-90 therapy; and 1 underwent resection, systemic chemotherapy (CVD, 2 cycles), and RFA to iliac crest lesions. Only two patients received biopsy alone prior to EBRT (Table 2).

Patients received EBRT to abdominal, CNS, and bone lesions. Bone lesions were treated with 3D conformal EBRT to a mean dose of 32.6 Gy in 3.9 Gy fractions, CNS tumors to a mean of 30.3 Gy in 2.1 Gy fractions, and abdominal disease to a mean of 54 Gy in 1.8 Gy fractions. The overall mean was 31.8 Gy in 3.3 Gy fractions. Treatments were delivered by SRS to a single bony lesion to 24 Gy; by SRS to a CNS lesion at a dose of 14 Gy; and by FSRT to two abdominal masses to 24.0 and 25.5 Gy in 8.0 and 8.5 Gy fractions, respectively. Of the 47 sites treated, 37 were symptomatic. Of lesions which were symptomatic, improvement in symptoms was reported in 81.1% (n = 30), with response of two symptomatic lesions included in analysis lost to follow-up.

Following RT, 13 patients received systemic chemotherapy for an average of 8.7 cycles (CVD; cytoxan and adriamycin; temozolomide; MS275, 6–18 cycles). Patients were treated with radiopharmaceutical therapy: nine were treated with 131I-MIBG therapy, one received radioactive octreotide, and one received radioactive Yttrium-90. Patients received additional surgery (n = 8) and RFA (n = 2). Only three patients died from progressive disease (PD) and mean follow-up time was 52.4 months.

For lesions evaluated by RECIST response, stable disease (SD) was achieved in 83.3% and PD in 16.7% (n = 2) with an average TTP of 22.47 months. For non-target disease, 28.6% of patients (n = 2) achieved complete response (CR), 14.2% had non-PN/PN-CR (n = 1), and 71.4% had PD with an average TTP of 13 months. Of the lesions not evaluable by RECIST, local control was achieved in 82.8% of lesions, with 11.4% progressing (n = 4) at an average of 14.8 months. For non-target disease, 16.7% of patients had no distant disease progression while 83.3% progressed at an average of 17.6 months. Overall, local control was observed in 86.7% of patients and progression in 13.3%; distant control observed in 25% of patients and progression in 75% (Table 3).

Of patients with familial syndromes (n = 11), 78.5% of symptomatic lesions improved following radiation therapy. Patients with familial syndromes evaluated by RECIST criteria had 84.6% local SD with 15.3% local PD (n = 2) at an average of 13.43 months TTP. They had 92.3% distant PD with 7.6% distant SD and an average TTP of 25.85 months. Of those not evaluated by RECIST criteria, 75% had local control and 25% (n = 1) local progression at 28.63 months TTP. Distal CR was achieved in 33.3% (n = 1) and distal progression occurred in 66.7% with an average TTP of 42.7 months.

Patients who received 3D conformal or IMRT responded best symptomatically at a higher average dose of 33.7 Gy while average dose for patients without improvement was 31.7 Gy (P = 0.39). Local SD was achieved at an average of 34.75 Gy compared to 31 Gy for those with PD (P = 0.15). Progressive distal disease was observed at an average dose of 33.3 Gy with stable distal disease observed at an average of 36.0 Gy (P = 0.34). In our study, 100% of patients treated with SRS/FSRT achieved local control (n = 4) compared to 85.3% (n = 35) of those treated with standard fractionation.

All 24 patients were evaluated for biochemical response by chromogranin A, free plasma metanephrines, and fractionated urine metanephrines. Six patients had chromogranin A levels before and after radiation; four of these showed a positive biochemical response. Six patients had free plasma metanephrine levels, three with a decrease after radiation. Four patients had fractionated urine metanephrine levels, three with a decrease in value after radiation therapy (Table 4).

Toxicities from treatment were both acute and late. Patients experienced RTOG grade 1 acute skin (n = 3), esophageal (n = 4), and upper gastrointestinal (n = 2) toxicity, as well as grade 2 upper gastrointestinal (n = 4), and grade 3 upper gastrointestinal (n = 1) and esophageal (n = 1) toxicities. There were two reported late toxicities, one esophageal which subsequently resolved and one spinal cord which was permanent in one patient treated by SRS to C3 to 2400 cGy. No patient suffered RTOG acute toxicity grade ≥4 or any RTOG late toxicity grade ≥2.

**DISCUSSION**

In this retrospective analysis, we evaluated patients with malignant PCC/PGL with primary lesions in the head, neck, and abdomen.
| Patient | Primary | Field site | Dose (cGy) | Fractions | Radiation technique | Outcome | Months follow-up |
|---------|---------|------------|------------|-----------|---------------------|---------|------------------|
| 1       | PGL     | R iliac fossa | 3000       | 15        | 3D conformal       | Decreased pain. Stable LD, DP at 8 months | 40     |
|         |         | L pubic symphysis | 3000       | 15        | 3D conformal       |         |                  |
| 2       | PCC     | C1-C6       | 3000       | 10        | 3D conformal       | Pain resolved. Stable LD, DP at 18 months | 110    |
| 3       | PGL     | T6-L1       | 3000       | 10        | 3D conformal       | Decreased pain. Stable LD, DP at 2.4 months | 5.9    |
| 4       | PGL     | L abdomen   | 4500       | 25        | 3D conformal       | Decreased pain. Stable LD, DP at 7 months | 23     |
|         |         |             | 900        | 5         | 3D conformal       |         |                  |
| 5       | PCC     | T9-T11      | 3500       | 14        | 3D conformal       | Improved pain. Stable LD, DP at 4 months | 20     |
|         |         | R femur     | 2000       | 5         | 3D conformal       |         |                  |
| 6       | PCC     | L SI joint  | 3500       | 14        | 3D conformal       | Continued pain. Stable LD, DP at 11.2 months | 7      |
|         |         | R femur     | 3500       | 14        | 3D conformal       |         |                  |
| 7       | PGL     | R glomus jugulare | 1400       | 10        | Gamma Knife       | Asymptomatic. Stable LD, distant CR | 56.4   |
| 8       | PGL     | R skull base | 5400       | 30        | TomoTherapy       | Continued symptoms. Stable LD, distant CR | 6.7    |
| 9       | PCC     | Thoracic/lumbar spine | 4050       | 29        | 3D conformal       | Decreased pain. Stable LD; DP at 188.1 months | 220   |
| 10      | PGL     | C3          | 2400       | 1         | SRS                | Asymptomatic. Stable local/distant disease | 39     |
| 11      | PGI     | T3-T7       | 2000       | 8         | 3D conformal       | Resolution of symptoms T3-T7; unchanged C6-T2. Stable LD, DP at 9 months | 64     |
|         |         | T3-T7       | 3600       | 18        | IMRT               |         |                  |
|         |         | C6-T2       | 3000       | 12        | 3D conformal       |         |                  |
| 12      | PCC     | L1-L5       | 3825       | 17        | 3D conformal       | Lessened pain. Stable LD, DP at 6 months | 51     |
| 13      |         | L hip       | 3000       | 10        | 3D conformal       | Pain resolved. Stable LD, DP at 4.13 months | 9.9    |
|         |         | L4          | 3000       | 10        | 3D conformal       |         |                  |
| 14      | PCC     | T10         | 2100       | 1         | IMRT               | Improved pain. LP at 24 months, DP at 8 months | 33     |
| 15      | PCC     | T6-T12      | 3000       | 10        | 3D conformal       | Improved pain; asymptomatic at R/L femur, occipital, and frontal lobes. LP at T6-T12 at 15 months otherwise stable. DP at 2 months. | 68     |
|         |         | Sacrum      | 3000       | 10        | 3D conformal       |         |                  |
|         |         | C5-T2       | 3000       | 10        | 3D conformal       |         |                  |

(Continued)
Our patients had metastatic lesions to bones, to the abdomen, and to the CNS. This series is the largest on the response of PCC/PGL to EBRT and, unlike many previous case series and case reports, utilizes newer technologies of 3D conformal radiation therapy including IMRT as well as SRS/FSRT. In addition, a subset of our patients was evaluated using standardized radiographic criteria and assessed for biochemical responses to localized radiation therapy. We found an overall symptomatic improvement in 81.1% of patients after radiation therapy regardless of site or radiation technique, with overall local control of 86.7% in patients treated to mean doses of 31.8 Gy in 3.3 Gy fractions by 3D conformal radiation therapy and 21.9 Gy in 10.4 Gy fractions by FSRT.

Our study shows a trend of greater symptomatic responses as well as local and distant control in patients who received higher...
Table 4 | Biochemical responses to EBRT.

| Patient | Biochemical test | Pre-EBRT measurement | Post-EBRT measurement |
|---------|------------------|----------------------|----------------------|
| 2       | PMN (nl: 12–61 pg/mL) | 132                  | 207                  |
| 6       | Chg A (nl: 0–225 ng/mL) | 296                  | 257                  |
| 7       | Chg A (nl: 0–225 ng/mL) | 278                  | 540                  |
| 14      | PMN (nl: 12–61 pg/mL) | 32                   | 36                   |
| 19      | Chg A (nl: 0–225 ng/mL) | 2160                 | 1780                 |
| 20      | UMN (nl: 44–261 µg/24 h) | 73                   | 89                   |
| 22      | UMN (nl: 44–261 µg/24 h) | 96                   | 89                   |
| 23      | PMN (nl: 12–61 pg/mL) | 25                   | 23                   |
| 23      | PMN (nl: 12–61 pg/mL) | 93                   | 84                   |
| 23      | UMN (nl: 44–261 µg/24 h) | 93                   | 110                  |
| 23      | PMN (nl: 12–61 pg/mL) | 51                   | 18                   |
| 23      | Chg A (nl: 0–225 ng/mL) | 65,000               | 137,000              |

Radiation therapy remains a local therapy, and the majority of patients in this study progressed systemically through their radiation treatments, reinforcing the need for concurrent systemic therapy to control distant metastasis. In spite of this, for patients who were able to be evaluated for biochemical responses after radiation there was a decrease in chromogranin A and catecholamine levels, suggesting a decreased overall disease burden after radiation therapy.

As with other reports on the use of EBRT in malignant PCC/PGL, this study is limited by its retrospective nature and the small number of patients treated. However, we have found both 3D conformal EBRT and SRS/FSRT to be effective in controlling symptoms and local progression in patients with both sporadic and familial malignant PCC/PGL. Patients achieved better responses at higher doses in general, although the optimal dose and radiation technique may vary depending on the site treated and size of the lesion. In addition to currently available systemic therapies, EBRT may play a significant role in the control of local disease for these patients.

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