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Review

Management of Recurrent and Metastatic Pheochromocytoma After Adrenalectomy: Reappraisal of the Role of ^{131}I-MIBG Therapy in the Contemporary Era

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ABSTRACT

Recurrent and metastatic pheochromocytoma (PCC) represents a rare but clinically challenging endocrine malignancy characterized by unpredictable biological behavior and limited curative options. Malignancy is defined exclusively by the presence of distant metastases rather than histopathological criteria. Recurrence may occur several years after apparently curative adrenalectomy, necessitating prolonged surveillance. The therapeutic armamentarium includes cytotoxic chemotherapy, temozolomide-based regimens, targeted agents, peptide receptor radionuclide therapy (PRRT), and iodine-131 metaiodobenzylguanidine (^{131}I-MIBG). Although PRRT has gained increasing attention in recent years, ^{131}I-MIBG remains a biologically rational and regulatory-approved targeted therapy for MIBG-avid disease. This review synthesizes current evidence on recurrence patterns, therapeutic sequencing, and the contemporary role of ^{131}I-MIBG therapy, with emphasis on patient selection and the durability of disease control.

1. Introduction

Pheochromocytomas are catecholamine-secreting neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. Approximately 10-20% demonstrate malignant behavior, defined solely by the presence of distant metastases or invasion into non-chromaffin tissues, as histopathological features alone cannot reliably distinguish benign from malignant disease[1,2]. Metastases most commonly involve bone, liver, lung, and lymph nodes. These may present either synchronously at diagnosis or metachronously following an apparently curative adrenalectomy.

Recurrence after primary surgical resection presents a distinct clinical challenge. Late recurrence, occurring five to ten years after adrenalectomy, is well documented and highlights the unpredictable biological behavior of pheochromocytoma[3,4]. Lifelong biochemical and radiological surveillance is therefore recommended for all patients, regardless of initial tumor characteristics.

Management of recurrent or metastatic PCC requires a multidisciplinary approach. While complete surgical resection remains the only potentially curative modality for localized disease, systemic therapies are necessary in patients with

unresectable recurrence or distant metastases. Available options include cytotoxic chemotherapy (most commonly the cyclophosphamide-vincristine-dacarbazine regimen), temozolomide, tyrosine kinase inhibitors, PRRT, and ^{131}I-MIBG therapy[5-8]. Although PRRT has gained momentum in neuroendocrine tumor management, ^{131}I-MIBG remains the only regulatory-approved radiopharmaceutical specifically indicated for metastatic or unresectable PCC and paraganglioma, following the phase II trial of high-specific-activity (HSA) ^{131}I-MIBG[9].

The optimal sequencing of these therapies remains undefined. In this context, the contemporary role of ^{131}I-MIBG warrants reappraisal, particularly in recurrent MIBG-avid disease.

2. Biology and Patterns of Recurrence

Recurrence following adrenalectomy occurs in approximately 6–23% of patients, with higher rates observed in individuals harbouring SDHB mutations, large primary tumors, extra-adrenal disease, or capsular invasion[3,4,10]. The interval between initial surgery and recurrence is highly variable, reflecting the biological heterogeneity of pheochromocytoma. Some patients exhibit indolent progression over many years, whereas others develop rapidly progressive metastatic disease.

Bone metastases are among the most frequent sites of distant spread and are associated with significant morbidity, including pain, pathological fractures, and spinal cord compression[11]. Hepatic and pulmonary metastases are also common. Importantly, recurrence may be biochemical before it becomes radiologically evident, reinforcing the importance of structured long-term surveillance.

Advances in molecular characterization have demonstrated that distinct genetic clusters exhibit different metabolic and imaging phenotypes[10]. SDHB-associated tumors, in particular, are linked to aggressive behavior and a higher risk of metastatic dissemination. These biological differences directly influence imaging findings and, consequently, therapeutic decision-making.

3. Imaging and Patient Selection

Functional imaging plays a central role in therapeutic stratification. ^{123}I-MIBG scintigraphy identifies tumors expressing the norepinephrine transporter, which is the molecular target of ^{131}I-MIBG therapy[12]. In contrast, ^{68}Ga-DOTATATE PET evaluates somatostatin receptor expression, thereby identifying candidates for PRRT[13].

In recurrent disease, imaging discordance is not uncommon. Some lesions may demonstrate avid uptake on MIBG imaging, whereas others may preferentially express somatostatin receptors or show high glycolytic activity on FDG-PET. Consequently, imaging phenotype rather than institutional preference should guide radionuclide therapy selection.

In patients with strong and homogeneous MIBG avidity, ^{131}I-MIBG remains a biologically rational first-line radionuclide therapy. Conversely, patients with MIBG-negative but somatostatin receptor–positive disease may benefit more from PRRT. This individualized imaging-based approach is central to modern endocrine-oncology practice.

4. Systemic Treatment Landscape

Surgical resection remains appropriate in cases of isolated or oligometastatic recurrence when technically feasible. However, complete cure in metastatic settings is rare, and surgery is frequently palliative or cytoreductive.

The cyclophosphamide–vincristine-dacarbazine (CVD) regimen has historically demonstrated objective response rates ranging from 37% to 55%, although responses are often transient and associated with systemic toxicity[6]. Temozolomide has shown particular activity in SDHB-mutated tumors and may offer improved tolerability in selected patients[7].

Targeted therapies such as sunitinib have demonstrated disease stabilization in small prospective studies, but robust randomized data are limited[8]. Thus, radionuclide therapy remains an important component of the treatment algorithm in appropriately selected patients.

5. ^{131}I-MIBG Therapy

^{131}I-MIBG exploits active uptake through the norepinephrine transporter, allowing targeted beta radiation delivery to tumor cells (13). Clinical experience with MIBG therapy spans several decades.

The pivotal phase II trial evaluating high-specific-activity (HSA) ^{131}I-MIBG included 68 patients with advanced pheochromocytoma or paraganglioma[9]. Durable reduction of at least 50% in baseline antihypertensive medication use was achieved in 25% of patients. Among evaluable patients, 92% achieved either partial response or stable disease within 12 months. Median overall survival was 36.7 months. The most common adverse events were nausea, fatigue, and myelosuppression. Notably, no acute hypertensive crises were reported during treatment. These findings led to regulatory approval and re-established ^{131}I-MIBG as a validated therapeutic option.

Prior to the development of high-specific-activity formulations, fractionated moderate-dose regimens (100–200 mCi per cycle) were widely used. Systematic analyses demonstrate objective response rates of approximately 20–30% and disease stabilization in up to 50% of patients[14,15]. Importantly, repeated moderate-dose administration may allow cumulative tumor control while maintaining acceptable hematologic safety profiles in carefully selected individuals.

Long-term follow-up studies confirm that meaningful survival outcomes can be achieved, particularly in patients with indolent MIBG-avid disease[15]. These data suggest that ^{131}I-MIBG remains a valuable modality rather than a historical therapy superseded by newer approaches.

6. ^{131}I-MIBG Versus PRRT

PRRT with ^{177}Lu-DOTATATE has demonstrated promising activity in metastatic pheochromocytoma and paraganglioma (16). However, no randomized head-to-head trials compare PRRT directly with ^{131}I-MIBG.

Therapeutic selection should consider molecular target expression, renal function, bone marrow reserve, prior radiation exposure, and disease kinetics. PRRT carries a recognized risk of nephrotoxicity and cumulative marrow suppression, whereas ^{131}I-MIBG toxicity is primarily hematologic and dose-dependent.

In patients with clearly MIBG-avid recurrence, bypassing ^{131}I-MIBG solely due to contemporary enthusiasm for PRRT

may not be evidence-based. Rather, radionuclide therapy should be tailored to the dominant imaging phenotype.

7. Is ^{131}I-MIBG Underutilized?

Despite regulatory approval and demonstrated efficacy, utilization patterns vary considerably across institutions. Factors contributing to this variability include limited access to specialized nuclear medicine facilities, logistical considerations, and growing familiarity with PRRT in neuroendocrine tumor programs.

Nevertheless, phase II data, systematic reviews, and long-term outcome studies consistently demonstrate clinically meaningful biochemical control, tumor stabilization, and acceptable safety in appropriately selected patients (9,14,15). These findings support continued integration of ^{131}I-MIBG within modern therapeutic algorithms.

8. Conclusion

Recurrent and metastatic pheochromocytoma remains a rare endocrine malignancy requiring individualized, multidisciplinary management. While therapeutic options have expanded in recent years, ^{131}I-MIBG therapy continues to offer durable biochemical and radiologic disease control in patients with MIBG-avid tumors. In the contemporary endocrine-oncology landscape, imaging-guided patient selection rather than therapeutic trends should determine radionuclide sequencing. Further comparative studies are needed to clarify the optimal integration of ^{131}I-MIBG and PRRT in recurrent disease.

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