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# Successful multimodal management of a rare grade 3 primary hepatic neuroendocrine tumor: A case report

**Abstract**

A 54-year-old male was seen for abdominal discomfort and was subsequently diagnosed with a Grade 3 primary liver neuroendocrine tumor replacing the left lobe. Based on the aggressive nature of the diagnosis, the patient was treated with systemic therapy with minimal response. Due to concerns for progression due to biologic unfavorable features, and in addition to new onset of pulmonary embolism, the tumor was then managed with palliative Y90 radioembolization after multidisciplinary discussion. Post Y90 radioembolization imaging revealed significant reduction in both size and enhancement of the tumor. Six months post Y90 radioembolization, the extent of the favorable response allowed for left partial hepatectomy as the patient's next treatment option. Analysis of the resected specimen revealed total cell necrosis. The excellent pathological response from Y90 radioembolization serves as a unique integration of locoregional therapy for primary hepatic neuroendocrine tumors and warrants further research.

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## Introduction

Neuroendocrine tumors make up around 1-2% of all gastrointestinal malignancies, and while it is relatively common for neuroendocrine tumors to metastasize to the liver, only 0.3% of all neuroendocrine tumors originate in the liver [1]. A primary hepatic neuroendocrine tumor poses challenges with diagnosing, prognosis, and formulating treatment plans as data on the disease is limited, with only 200-300 cases of primary hepatic neuroendocrine tumors being documented in literature [2]. Advances in immunohistochemistry utilizing the protein marker ki-67 have been used to offer prognostic evaluations for gastroenteropancreatic neuroendocrine tumors by highlighting enhanced proliferation activity of cells [3,4]. World Health Organization benchmarks for ki-67 varies depending on the origin of the neuroendocrine tumor with a higher percentage of ki-67 positive cells overall indicating a more aggressive tumor or higher grade. World Health Organization guidelines for ki-67 indexing of gut and pancreas well differentiated neuroendocrine tumors demonstrate a grade 1 neuroendocrine tumor to be diagnosed by a ki-index of <3%, a ki-67 index between 3% and 20% to indicate a grade 2 neuroendocrine tumor, and a ki-67 index of >20% to indicate a grade 3 neuroendocrine tumor. [5]. Uncertainties arise with ki-67 indexing as metrics vary based on the type of tumor and site of origin, leading to inconsistent diagnoses and prognoses across different neuroendocrine tumor sites [4]. While multitudes of studies show ki-67 indexing to be effective as a prognostic marker in gastrointestinal neuroendocrine tumors, problems occur due to intra tumoral heterogeneity of the specimen and different counting methods [3,4].

Grade 3 Neuroendocrine Tumors (NET G3) pose pathological diagnostic dilemma primarily because they can mimic poorly differentiated Neuroendocrine Carcinomas (NECs) and are heterogeneous in behavior and morphology. Distinct gene mutations and pathways have been identified in G3-NETs and NECs, offering potential for developing a diagnostic gene panel. The 2022 WHO classification recognizes the use of immunohistochemistry for somatostatin receptors 2/5, TP53, Rb, Menin, P27, ATRX, and DAXX to distinguish G3-NETs and NECs. In particular, TP53 and ATRX immunohistochemistry may be useful in routine diagnostics [6] Misclassification has important treatment implications: NECs require platinum-based chemotherapy, while G3 NET can be treated with other regimens which may include targeting the somatostatin receptor depending on results of functional imaging.

Medical management of liver neuroendocrine tumors prioritizes restricting tumor growth and mitigating the symptoms of functional tumors. Radiofrequency ablation and trans arterial procedures provide disease control directly to the tumor but have inconsistent success rates [7]. Gastrointestinal neuroendocrine tumors overexpressing somatostatin receptors introduce additional treatment options such as somatostatin analogues which can reduce hormone production, resulting in adequate palliation of symptoms and delay in progression (improved progression free survival). Peptide receptor radionuclide therapy similarly exploits somatostatin receptors to deliver targeted radiotherapy to tumor cells. Both treatments play a significant role in tumor control focused on progression free survival rather than cure [7].

As of now, surgical resection of a liver tumor is considered the most effective and reliable treatment , and in conjunction with neoadjuvant Y90 radioembolization, can potentially induce a response [2]. Y90 radioembolization is a minimally invasive method of locoregional liver cancer treatment. It is offered as a treatment for cytoreduction or hormone control of hormone producing neuroendocrine tumors while surgical resection is recommended for tumors causing patient symptoms either due to size or compression [7]. An advantage of Y90 radioembolization is the long-term preservation of health-related quality of life, an important factor for patient experience [8]. The use of Y90 for unresectable liver masses can improve overall survival rate, however this improvement is very miniscule for metastatic grade 3 liver NETs with median survival around 28 months with treatment. When surgical resection of the liver tumor is not available, liver neuroendocrine tumors remain a clinical challenge with data on available options to have presumably poor survival outcomes [9].

## Case presentation

A 54-year-old white male was referred to a comprehensive cancer center for abnormal findings on a Dotatate Positron Emission Tomography/Computed Tomography and MRI abdomen after presenting with abdominal pain. Past medical history was significant for pulmonary embolism managed with anticoagulation. Past surgical history was significant for hernia repair and sigmoid colectomy due to diverticulitis. Patient reported recreational drinking habits and no personal or family history of cancer. Initial Computed Tomography of the abdomen and pelvis demonstrated a large mass approximately 10 centimeters replacing the left lobe of the liver not seen in an abdominal Computed Tomography scan 4 years prior (that was done preceding his sigmoid colectomy). Bland tumor thrombus was seen in the left hepatic vein and left portal vein. No primary source or evidence of metastatic disease has been seen in the patient's previous scans. Biopsy of left hepatic tumor identified a well differentiated Grade 3 neuroendocrine tumor with Ki67 30% and negative immunohistochemistry for hepatocellular carcinoma. This prompted Dotatate Positron Emission Tomography imaging, which was negative. No pertinent abnormalities were seen on patient's lab work.

A Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography performed 1 month after his initial Dotatate Positron Emission Tomography/Computed Tomography scan demonstrated only mild uptake within the hepatic mass. There was no evidence of metastases, confirming the primary hepatic grade 3 neuroendocrine tumor. While the tumor was respectable at presentation, given the grade 3 histology and associated poor anatomic/biologic features, treatment with systemic therapy was recommended as primary treatment. The patient received 3 cycles of capecitabine/Temozolomide.

Three months post-systemic therapy, Computed Tomography abdominal imaging demonstrated an increase in tumor size to 12.5 cm × 12.9 cm × 10.8 cm associated with pain. Further review at the multidisciplinary tumor board yielded consensus for Y90 radioembolization for cytoreductive purposes and to reduce patient abdominal discomfort due to the enlarging tumor's size. Further, the patient was found to have a new pulmonary embolism and started on anticoagulation as such non-surgical treatment was further supported by this finding given the timing required for anticoagulation.

Y90 radioembolization was carried out in a standard fashion: Lung shunt fraction was found to be 16.3% upon shunt study. Y90 resin microspheres were injected into two branches of hepatic arterial vasculature supplying the tumor. Patient tolerated the procedure without complications. A prescheduled Comput-

ed Tomography abdomen for tumor restaging was performed 1 week after Y90 radioembolization and demonstrated significant reduction in tumor bulk and enhancement with no new disease site. A 6-week surveillance imaging Computed Tomography post Y-90 radioembolization demonstrated a significant ongoing decrease in tumor size and a reduction of thrombus in the intrahepatic IVC. No new disease site was found.

With continuing excellent response to the Y90 radioembolization, and after completing a course of anticoagulation, left hepatectomy was considered: Seven-months post-Y90 radioembolization patient underwent explorative laparotomy, partial liver resection and cholecystectomy. Post resection ultrasound imaging exhibited adequate flow to and from the residual liver. Surgical specimens collected and submitted to pathology included a 7 mm entirely calcified fibrotic nodule within the liver, portal lymphadenectomy, and the gallbladder. The submitted resection margins and additional specimens were negative for cancer. Surgical pathology presented no viable residual tumor.

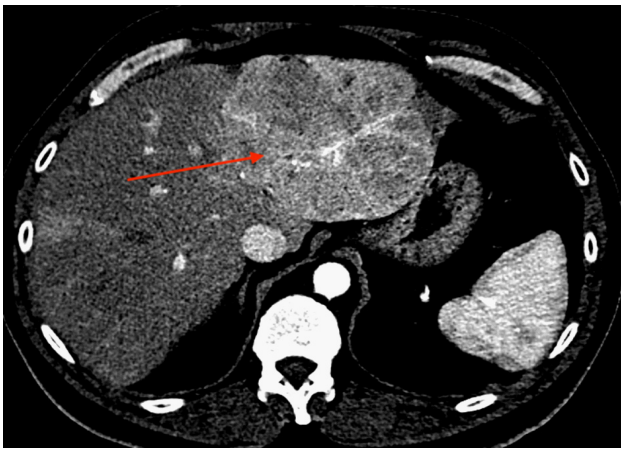

**Figure 1:** Arterial phase of computed tomography at presentation demonstrates a large hypervascular mass (Red arrow) replacing the left lobe of the liver and extending to the middle lobe.

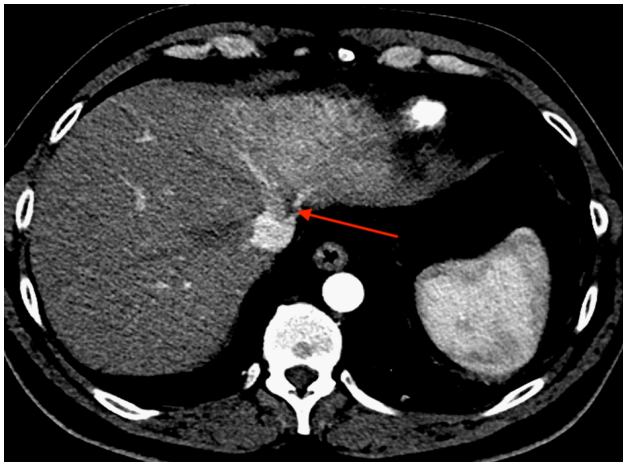

**Figure 2:** Computed tomography on a different level shows a small hypodense filling defect (Red arrow) in the left hepatic vein consistent with bland thrombus.

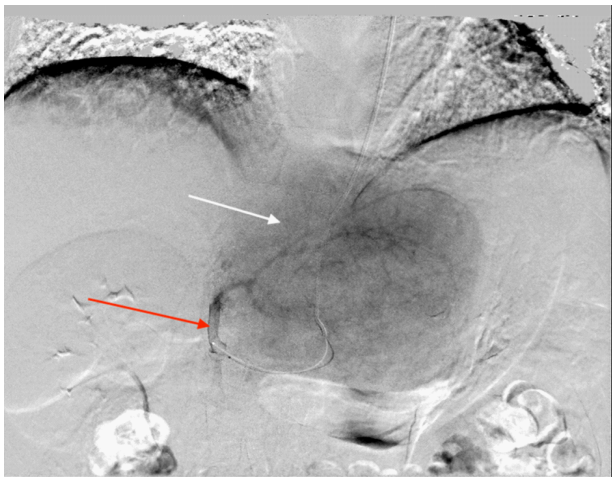

**Figure 3:** Hepatic catheter arteriogram through left radial approach obtained during Y90 mapping study demonstrates large area of tumor blush in the left lobe of the liver (White arrow) that is being supplied by the left hepatic artery (Red arrow).

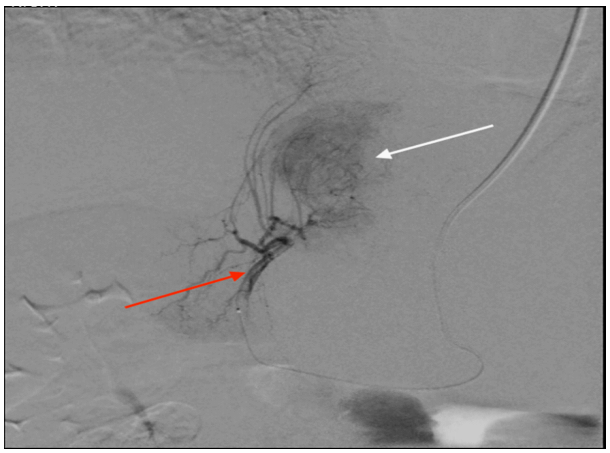

**Figure 4:** Hepatic arteriogram through left radial approach obtained during Y90 mapping study demonstrates additional area of tumor blush in the middle lobe of the liver (White arrow) that is being supplied by the middle hepatic artery (Red arrow).

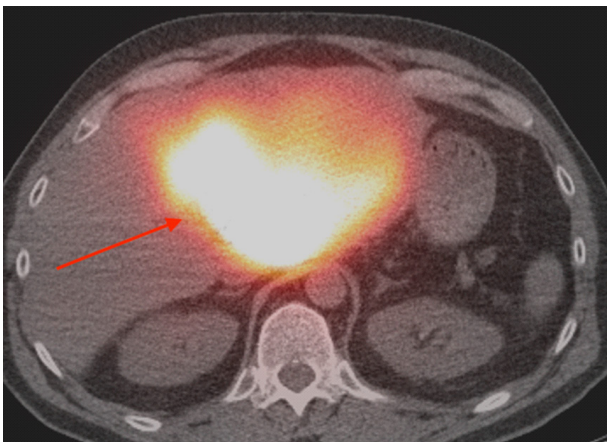

**Figure 5:** Scintigraphic imaging of Bremsstrahlung Radiation post Y90 delivery depicts the Y90 distribution corresponding to the pre-treatment extent of the tumor indicating complete coverage of the tumor.

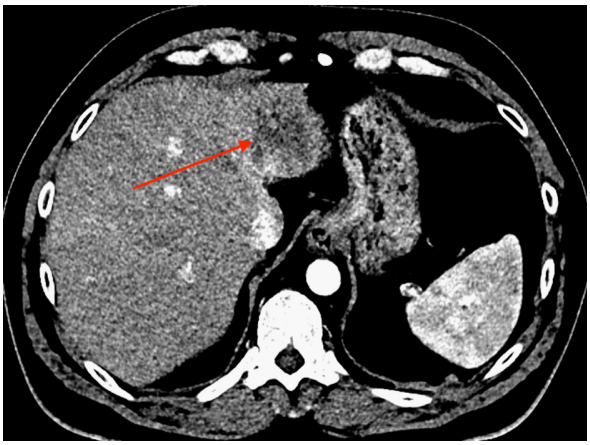

**Figure 6:** Arterial phase of an abdominal Computed Tomography six weeks post Y90 treatment demonstrates remarkable shrinkage and devascularization of the tumor (Red arrow) consistent with excellent response.

## Discussion/conclusion

Ki-67 indexing is a critical prognostic factor in patients with well-differentiated neuroendocrine tumors, and based on the World Health Organization classification, a tumor with Ki-67 >20% (as in this case – 30%) is classified as a high-grade tumor and portends the worse prognosis among those with neuroendocrine tumor histology.

Due to limited literature on grade 3 primary hepatic neuroendocrine tumors, constraints were immediate concerning treatment plans and prognosis. The current data on the effectiveness of direct-liver therapies as initial curative treatment for grade 3 liver neuroendocrine tumors were minimal and inconclusive as most studies investigate their effectiveness on tumors less aggressive than grade 3 or in conjunction with other therapies where the efficacy of each is difficult to measure. The initial approach of systemic therapy in a multimodal treatment plan proceeded as an attempt to control the disease, and in doing so helps select patients likely to benefit from surgery. When systemic therapy failed, subsequent treatments were further limited leading the multidisciplinary tumor board to evaluate locoregional therapies as a palliative care option to reduce patient symptoms. The minimal data currently present reports that patients undergoing local-regional therapies after failed systemic treatments have poor prognoses, however patients encounter a marginal improvement in symptoms and prolonged survival in comparison to no treatments. While Y90 radioembolization was recommended for a palliative care plan, it acted as a segment of a total treatment design that can preserve patient quality of life and deliver effective interventions.

Post Y90 radioembolization imaging demonstrated the locoregional therapy to provide symptomatic treatment while preserving the patient's quality of life which is not traditionally seen in more aggressive cancer therapies. Restaging Computed Tomography demonstrated significant reduction in tumor size 1 week after Y90 radioembolization procedure. Subsequent Computed Tomography imaging as part of IR surveillance 6 weeks post Y90 radioembolization demonstrated a further decline in tumor size. The tumor board's reassessment of resection after Y90 radioembolization furthers insight into the use of local-regional therapies as part of a patient's multimodal treatment plan for aggressive tumors.

Final pathology of the grade 3 primary hepatic neuroendocrine tumor after left hepatectomy demonstrated an excellent pathological response to Y90 radioembolization treatment. Immuno stains block C7 with AE1/3, Ki-67+CD5, synaptophysin, chromogranin, and INSM1 showed no residual neuroendocrine tumor in any submitted specimens including the liver tumor. Surgical pathology revealed the tumor bed was entirely replaced by fibrosis and scarring, demonstrating total cell necrosis following Y90 radioembolization. The excellent pathological response of Y90 radioembolization breaks ground on the potential value it offers as a curative treatment for advanced liver diseases.

The effectiveness of Y90 radioembolization on this grade 3 primary hepatic neuroendocrine tumor prompts discussion on curating treatment plans to provide direct-liver-therapies as an initial intervention in part of a multimodal treatment plan. Investigating Y90 radioembolization as an initial therapy is also supported with their benefits of preserving the quality of life in patients, possibly circumventing patients from the side effects or risks of systemic treatments. Restricting Y90 radioembolization to treat unresectable liver tumors limits its potential utilization in multimodal cancer treatment.

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