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Pioneering Personalized Precision Medicine: Direct-to-Tumor Interventional Radiology at Envita Medical Centers

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Abstract

This study highlights the noteworthy response of a 67-year-old male patient presenting with Stage 4 Metastatic high-grade poorly differentiated small cell type neuroendocrine carcinoma who was treated at Envita Medical Centers using their proprietary treatment technology. Treatment of neuroendocrine neoplasms (NENs) is challenging due to the heterogeneous nature of these tumors, their variable therapeutic response, generally poor prognosis, and the need for a multidisciplinary care team. Envita has pioneered a minimally invasive novel technology known as the Chemo Immuno Precision Injection (CIPI™) within their Interventional Radiology Oncology Department (EnvitaIR™). CIPI™, an innovative and advanced variation of transarterial chemoembolization (TACE), is a unique, proprietary, image-guided, direct-to-tumor drug delivery platform designed for genetically targeted, precise, personalized chemo- and immuno-therapy. CIPI™ also incorporates chemo-adjunctive agents to enhance treatment effectiveness, facilitating precise tumor targeting while simultaneously activating systemic immunotherapy to combat any distant metastases and circulating tumor cells. In contrast to systemic drug delivery where only a minuscule fraction of the drug reaches the tumor site, CIPI™ directs 95% - 100% of the targeted medication into the tumor. Envita's use of interventional radiology represents a leap forward in cancer treatment, specifically drug targeting and delivery, offering patients a highly personalized, minimally invasive alternative to traditional surgery and radiotherapy, especially in inoperable regions and in cases where patients have failed the

standard NCCN (National Comprehensive Cancer Network) guideline recommendations, an area not unfamiliar to interventional radiology. Innovative personalized medication combinations, image-guided technology, as well as drug targeting using personalized medicine offered at Envita Medical Centers with techniques such as CIPI™, have resulted in proven, exceptional results for many challenging cases with improved patient outcomes. The results achieved for this patient clearly demonstrate the effectiveness of personalized targeted drug delivery within interventional oncology. Envita's overall response rate, based on measuring patient response outcomes as well as leading disease indicators including circulating tumor cells and mutant allele frequency, was 72% based on an analysis of 199 late-stage cancer patients treated at Envita Medical Centers over a two-year period. This rate was only 0% - 2% for patients undergoing standard of care because there were no surviving patients in most cases, resulting in a 35-fold improvement in overall response rate for Envita patients compared to those undergoing standard of care [1]. These results are especially significant because approximately 95% of patients coming to Envita present with Stage 3 or Stage 4 cancer; most have previously failed standard of care and hence represent the most challenging cohort to treat [1]. Patient outcomes at Envita highlight the key attributes of personalized precision therapy leading to an enhanced quality of life and longevity: targeting the tumor's genetic and molecular profile, direct-to-tumor drug delivery capability, as well as rigorous evaluation and prompt, adaptable care.

Keywords

Neuroendocrine Neoplasm (NEN), Neuroendocrine Carcinoma (NEC), Interventional Radiology (IR), Interventional Oncology (IO), Chemo Immuno Precision Injection (CIPI™), Chemoembolization, Somatostatin Analogs (SSAs)

1. Introduction

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of malignancies that can emanate from neuroendocrine cells in a number of different organs throughout the body; these are most common in the gastrointestinal tract and bronchopulmonary system but can also originate in the pancreas, urinary bladder, ovaries, prostate, thyroid, and adrenal glands [2]-[7]. The global annual incidence and prevalence of NENs are approximately 6/100,000 and 35/100,000, respectively, with numbers rising incessantly [8]. This rare group of tumors presents with non-specific and heterogeneous clinical symptoms, often leading to distant metastasis and inoperable disease by the time a diagnosis is confirmed [9]-[11]. Functionally, NENs are classified into two groups based on histology, proliferation rate, and clinical behavior: 1) neuroendocrine tumors (NETs) or carcinoids, which are well-differentiated and low-proliferating NENs, and 2) small or large cell neuroendocrine carcinomas (NECs), which represent 10% - 20% of

total NENs, are poorly differentiated and highly proliferating NENs [7] [12]-[15]. NETs usually present with well-developed organoid or neuroendocrine shapes, whereas NECs appear as solid sheet-like proliferations with irregular nuclei [7]. NETs produce plenty of secretory granules with high expression of neuroendocrine markers such as chromogranin and synaptophysin; NECs produce few secretory granules with low expression of neuroendocrine markers [7]. Although there is no uniform nomenclature for NENs, NETs, and NECs due to the different historic terminologies used to define them, these tumors are lumped together as a homogeneous group based on the expression of neuroendocrine markers [6] [7]. Based on whether NETs secrete biologically active hormones or not, these are classified as functional or nonfunctional NETs, respectively [9].

NEN diagnosis is often delayed because of their non-specific presentation, generally resulting in distant metastasis and inoperable disease [10] [11]. A NET patient survey reported a mean delay of 52 months between symptom onset and diagnosis for 1928 patients; patients also described limited NET-specific treatment options, poor accessibility to NET specialists, and lack of a knowledgeable and aligned healthcare team [9] [11]. Advanced diagnostic techniques, streamlined precision care, aggressive treatment strategies, and prompt follow-up are therefore required for favorable NEN patient outcomes.

NET treatment generally involves multiple specialties and is tailored based on proliferation rate, site, stage, grade, degree of differentiation, functionality, extent of disease, as well as patient factors such as age and comorbidities [5] [9]. The current treatment for NETs is not standardized, but some therapeutic guidelines exist based on patient characteristics [16]. Surgery, focused on margin-negative resection and lymphadenectomy, is recommended for localized disease with curative intent [5] [9] [17]. Although adjuvant therapy has not been shown to enhance cure rates following surgery, consensus guidelines recommend platinum-based chemotherapy for patients with fully resected, poorly differentiated cancers [9] [18]. In patients with low volume, non-functional asymptomatic metastatic disease, imaging and expectant management of disease is the general course of action [9]. Well-differentiated neuroendocrine neoplasms typically express somatostatin receptors; these are utilized for imaging analysis (^{68}Ga-Dotatate) as well as for therapeutic purposes (octreotide acetate and ^{177}Lu-Dotatate) [19]. Somatostatin analogs (SSAs), octreotide long-acting repeatable (LAR) and lanreotide, are the first-line treatment for NETs; these can control hormonal production and tumor growth, although systemic therapy has not demonstrated a significant improvement in overall survival [9] [17]. Cytoreductive surgery with resection of the primary tumor may be recommended for metastatic disease and difficult-to-control secretory symptoms [9].

The National Comprehensive Cancer Network (NCCN) provides treatment guidelines for different types of locoregionally advanced and/or distant metastatic disease; however, there are insufficient data to support a specific sequential therapeutic strategy for an optimum NEN response. The NCCN provides guidelines

for the evaluation, treatment, and follow-up of well and poorly differentiated NENs based on the primary organ that is impacted and for unknown primaries. The initial workup incorporates a complete patient evaluation using computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor (SSTR) agonist-based Positron Emission Tomography (PET)-CT, and biochemical assessment; treatment generally incorporates tumor resection where possible and/or systemic therapy with or without radiation, and follow-up surveillance. Systemic therapy includes treatment using chemotherapy, somatostatin analogs, targeted therapy, immunotherapy, and/or PRRT. Although a number of systemic therapies exist for NENs, these guidelines are very general and no specific treatment regimens currently exist for a particular NEN.

In contrast to the standard therapy and guidelines for NEN treatment, Envita Medical Centers is focused on delivering personalized, precision-targeted therapy intratumorally without significant surgical mediation. Envita employs their proprietary Interventional Radiology (IR) technology, a targeted, minimally invasive, image-guided, direct-to-tumor approach for intratumoral drug delivery. Interventional oncology (IO), the fastest-growing subspecialty of interventional radiology, is now recognized as the fourth pillar of cancer care. It integrates diagnosis, therapy, and symptom management to offer cancer patients minimally invasive, highly precise tumor targeting along with lower-risk alternatives to conventional surgery [20]-[22]. IO also addresses some of the limitations of surgery, radiation dosages, and toxicity associated with systemic chemotherapy. Image-guided, percutaneous, minimally invasive biopsies to obtain tissue for cytologic and histologic examination are increasingly being performed for most organ systems with high accuracy and fewer complications using interventional radiology [23] [24]. Imaging modalities such as ultrasound, computed tomography (CT), fluoroscopy, magnetic resonance imaging (MRI), Positron Emission Tomography/Computed Tomography (PET/CT) scans, and nuclear medicine imaging allow real-time imaging for monitoring the needle trajectory to the desired lesion, providing greater therapeutic accuracy and shorter surgery time [23] [25]-[27]. Proper imaging of the tumor-feeding arteries, arteriography, vascular anatomy, drug delivery, and embolization using advanced imaging techniques such as computed tomography angiography (CTA), cone-beam CT, ultrasound, X-ray fluoroscopy, or MRI is a prerequisite for successful IO [20] [28] [29].

Interventional radiology techniques are also used to facilitate vascular access for drug delivery [23]. Image-guided therapeutic intratumoral delivery can be achieved using catheter-based approaches or direct intratumoral injections [20]. One such procedure, transarterial chemoembolization (TACE), is commonly used for hepatic tumors as well as other malignancies. It involves delivering chemotherapy directly into the tumor-feeding artery through a microcatheter (approximately the size of a hair follicle), followed by embolization of the same artery. This dual approach enables efficient, tumor-targeted drug delivery while simultaneously inducing ischemic necrosis of the tumor [30]. Embolization cuts off the

blood supply to the tumor, causing cancer cell ablation and more effective drug penetration [22]. Chemoembolization improved the survival of patients with unresectable hepatocellular carcinoma compared to controls who were administered symptomatic treatment [31]. IO offers significant advantages compared to resective surgery and systemic therapy, including precision targeting, diminished systemic toxicity, enhanced efficacy, real-time disease and treatment monitoring, far fewer side effects, better quality of life, and faster recovery. These are discussed below in more detail.

Precision Targeting and Reduced Systemic Toxicity: IO leverages minimally invasive techniques to deliver treatments directly to the tumor site, thereby enhancing efficacy and minimizing systemic side effects. This precision targeting reduces the impact on healthy tissues and maximizes the therapeutic effect on cancerous cells. Locoregional chemo- and immunotherapy drug delivery provides increased patient tolerability and is associated with a better quality of life without the typical side effects of traditional chemotherapy or systemic immunotherapy, such as tissue loss, cardiomyopathy, sinusoidal injury, hair loss, etc. [22] [32] [33]. Image-guided injections ensure that treatments, such as immunotherapeutic agents, are delivered intratumorally at enhanced drug concentrations with minimal systemic exposure. These locoregional therapies not only ablate cancer cells and modulate the tumor immune microenvironment but also stimulate a systemic adaptive immune response [34]. In the case of systemic drug delivery, a minuscule fraction of the total dose reaches the tumor site, with the remaining dose being distributed to other healthy organs and tissues [35]. Although limited quantitative data exist for the biodistribution of chemotherapeutic drugs in various organs and the tumor site, recent data for the intravenous injection of radio-cisplatin in mice bearing subcutaneous lung tumors indicated that the peak drug uptake in the tumor was only 4.7% injected dose/g of tissue 15 minutes after injection [36]. Cisplatin uptake was high in the blood, lungs, and kidneys after injection [36]. This is in stark contrast to intratumoral CIPI™, where 100% of the drug is directed into the tumor. In rats bearing subcutaneously transplanted Dunning AT1 prostate carcinoma tumors, intratumoral injection of polymeric drug carrier N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers not only caused maximum accumulation in the tumor but also decreased localization to healthy tissues; intravenous injection caused the highest accumulation in the spleen, followed by the lungs and tumor [37]. Intratumoral injections of the HPMA copolymers enhanced the tumor-to-organ localization ratios by 2000% compared to intravenous injections [37]. In another study, the median intra- and extratumoral drug concentration ratio in patients with unresectable liver metastasis of colorectal cancer or unresectable intrahepatic cholangiocarcinoma treated with oxaliplatin-eluting microspheres (OEM-TACE) or conventional oxaliplatin-containing systemic therapy was 18.53 and 1.10, respectively, indicating that the OEM-TACE procedure delivered the drugs more effectively into the tumor tissue compared to the normal hepatic parenchyma [38].

Enhanced Efficacy: Direct drug delivery to the tumor site has the potential to enhance treatment efficacy due to higher therapeutic bioavailability, particularly for immunotherapies that activate the immune system locally within the tumor environment [39]. This localized activation can help overcome the immunosuppressive microenvironment of tumors and facilitate better treatment outcomes with limited off-target effects and systemic toxicity [39]. For instance, local treatment in the tumor area of tumor-bearing mice using a cytotoxic T-lymphocyte associated protein 4 (CTLA-4) blocking antibody caused effective tumor eradication with enhanced systemic tumor-specific $CD8^+$ T-cell response and decreased treatment-induced toxicity [40].

Combination Therapies: IR techniques can be used in combination with systemic therapies to enhance overall treatment efficacy. For example, local tumor ablation can be followed by systemic immunotherapy to address both local and distant disease. In a study that evaluated the effect of TACE, molecularly targeted agents (T), and immune checkpoint inhibitors (I) in hepatocellular cancer (HCC) patients, the TACE + T + I group (42 patients) exhibited significantly longer median overall survival and median progression-free survival (24 and 9.70 months, respectively) compared to the control TACE + T group (45 patients, 21.40 and 7.00 months, respectively) [41]. Patients in the TACE + T + I group exhibited a higher objective response rate (52.4%) compared to the TACE + T group (17.8%); the molecularly targeted agents and immune checkpoint inhibitors were administered orally or intravenously [41].

Real-time Monitoring: Interventional oncology is a valuable image-guided theranostic tool because it can couple diagnostics and therapy in real-time to determine biodistribution, predict optimal drug dosage, as well as real-time treatment response [32] [42]. The use of imaging technology in IO not only guides effective treatment delivery but also allows treatment response monitoring in real-time. This enables prompt treatment modifications, allowing for personalized therapy [32] [43].

Less Invasive with Faster Recovery: As a minimally invasive, image-guided approach, IR generally involves smaller incisions, less pain, and shorter recovery times compared to traditional surgery. This can lead to shorter and more affordable hospital stays, quicker return to normal activities, and fewer complications for patients, resulting in a better quality of life [44] [45]. Cancer is one of the leading causes of morbidity and mortality globally; cancer patients endure significant adversity and deteriorated quality of life due to their symptom burden as well as the impact of cytotoxic and immunotherapy drugs [46] [47]. In a study of 768 cancer patients with 40% enduring head and neck cancer, 82% of the patients had low quality of life scores; quality of life analysis incorporated several domains such as general, physical, psychological, and economic well-being, familial relationships, sexual and personal ability, patient-physician relationship, etc. [46]. Another multi-area cross-sectional study that involved 800 patients undergoing chemotherapy utilized the EQ-5D-5L Quality of Life Questionnaire, the Karnofsky

Performance Status, the center's own symptom checklist, and the Edmonton Symptom Assessment and Visual Analogue Scale, and concluded that the negative quality of life in cancer patients was attributed to the disease and its phase, its duration, treatment, and number of chemotherapy cycles involved; regular assessment and intervention were essential for improving quality of life and patient outcomes [47]. In contrast to most oncology clinics that report unfavorable quality of life scores in cancer patients, 88% of Envita patients experienced an overall symptom improvement and enhanced quality of life [1] [48] [49]. Patients treated at Envita, 95% of whom presented with Stage 3 or Stage 4 cancer, experienced 43 times greater improvement in quality of life compared to late-stage cancer patients undergoing palliative chemotherapy; these significant results were attributed to Envita's personalized therapeutic algorithms incorporating personalized medicine and direct-to-tumor precision therapy [1].

Potential for Repeat Treatments: IR procedures can be spaced out and repeated at the same location, if necessary, which is particularly useful in managing cancers that are resistant to initial treatments or in cases where the disease recurs [22]. Local tumor control with repeat intervention for new or recurrent disease is particularly valuable for patients with advanced cancer because they may have multiple metastatic events [50].

Precision, Innovation, and Advances in Personalized Medicine: The field of interventional radiology is rapidly evolving with the integration of artificial intelligence (AI), advanced imaging techniques, enhanced lesion detection, and targeted personalized medicine [51] [52]. Innovations in fusion imaging techniques, robotics, and catheter technology continue to enhance the precision and effectiveness of IR treatments, thereby improving patient prognosis and longevity [42] [52] [53].

Accessibility and Cost-Effectiveness: IR procedures can be performed on an outpatient basis in many cases, which is more cost-effective due to reduced hospital stays compared to inpatient surgical treatments [44]. Outpatient accessibility also means that treatments can potentially be made available to a wider range of patients.

The current study delves into the case of a 67-year-old male patient who presented at Envita Medical Centers with Stage 4 Metastatic high-grade poorly differentiated small cell type neuroendocrine carcinoma. With over 24 years of experience in treating patients with advanced cancer, Envita's personalized treatment strategy was driven by the Chemo Immuno Precision Injection (CIPI™), an image-guided, minimally invasive interventional radiology technology to provide direct-to-tumor, targeted, personalized chemotherapy and immunotherapy based on the patient's tumor genetic and transcriptional profile, which is the real future of precision oncology. CIPI™ delivers a micro-dosed combination of chemo- and immuno-therapy drugs in combination with adjuvant agents to enhance drug effectiveness and minimize side effects. This article clearly articulates the process, benefits, and outcomes of Envita's interventional radiology procedures, making it

suitable for both medical professionals and educated patients, with an emphasis on the precision as well as the minimal invasiveness of the techniques, supported by visual evidence from this particular case. Detailed images from the IR procedure and a gallery of anonymized patient images showcase the treatment stages and results.

2. Patient Consent

Written informed consent for the publication of this case study has been obtained from the patient by Envita Medical Centers.

3. Case History

A 67-year-old male patient presented with high-grade poorly differentiated small cell type neuroendocrine carcinoma. Approximately two months prior to starting treatment at Envita, the patient had developed ongoing pain in his mid-back and right side. Subsequent bloodwork showed elevated liver enzymes; a CT scan revealed a large 17.7 × 11.4 × 13.3 cm hypodense mass in the right hepatic lobe, a 6.4 × 5.6 × 7.4 cm retroperitoneal mass in the left adrenal gland, a left periaortic node (13 mm in short axis), and multiple masses in the left retroperitoneal space measuring up to 2 cm. The primary source of the tumor was not identified, but given significant adrenal involvement, this was most likely the primary. An ultrasound-guided needle core biopsy of the liver mass confirmed high-grade poorly differentiated small cell type neuroendocrine carcinoma based on the morphologic features (small blue cells with sparse cytoplasm), presence of necrosis, strong reactivity to keratin markers, neuroendocrine expression, and enhanced proliferation (Ki-67) of up to 98% (**Figure 1**).

The patient experienced significant weight loss, poor appetite, and gradually increasing intermittent abdominal pain but refused standard chemotherapy, which predicted a prognosis of one year and a 5% response rate. The patient's oncology surgeon recommended surgery to remove his liver tumor, left adrenal gland, kidney, as well as lymph nodes. The patient, who denied invasive care, did not receive any standard oncology treatment prior to receiving care at Envita Medical Centers. His total treatment duration at Envita was 128 days and the patient continues to be monitored by the physicians at Envita Medical Centers.

An initial CT scan, PET/CT scan, and ultrasound-guided needle biopsy of the liver confirmed Stage 4 metastatic high-grade poorly differentiated neuroendocrine carcinoma. A follow-up PET CT scan using 18-fluorodeoxyglucose (FDG) indicated that the right hepatic lobe was replaced by a centrally necrotic hypermetabolic mass measuring 18.7 × 15.7 × 14.0 cm (SUV max 15.0). The images also displayed a 7.1 × 6.4 × 8.0 cm hypermetabolic mass associated with the left adrenal gland (SUV max 12.2), a 4.3 × 3.9 cm hypermetabolic para-aortic node (SUV max 11.9), as well as several additional masses in the left pararenal fat and adjacent para-aortic retroperitoneum.

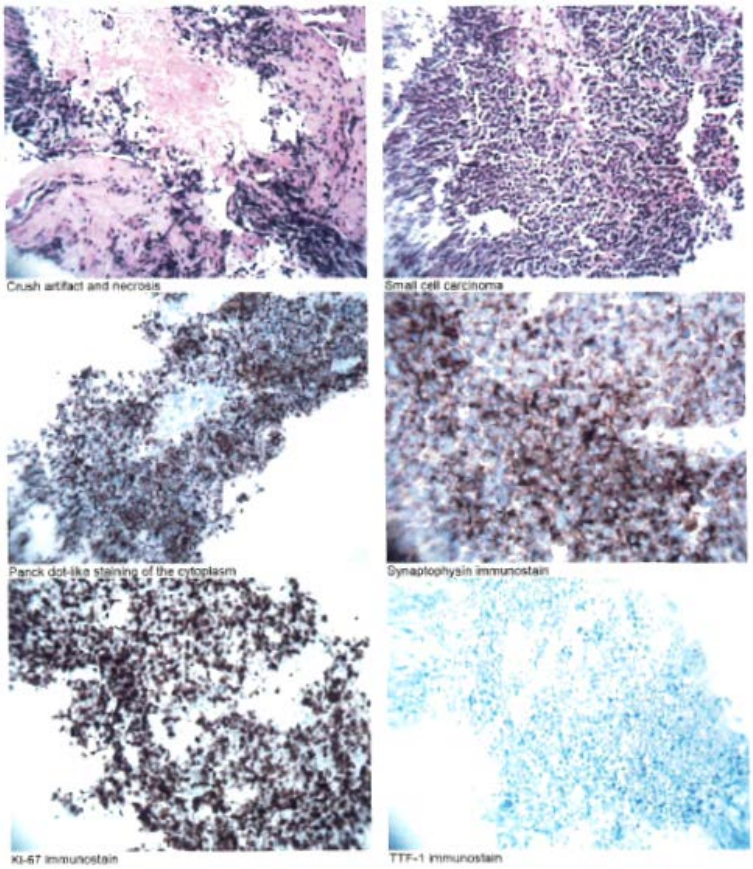

Figure 1. Immunohistochemical staining for slides obtained from an ultrasound-guided biopsy of a liver mass demonstrated the presence of necrosis, dot-like strong reactivity for cytokeratin (CK) AE1/AE3, high synaptophysin expression, and Ki-67 proliferation > 90%. TTF-1 immunostaining was negative in tumor cells. Analysis was performed by LabCorp (Laboratory Corporation of America).

4. Case Management and Protocols

The patient's treatment regimen at Envita comprised an amalgamation of integrative and personalized therapy consisting of direct-to-tumor targeted CIPI™, Genetically Targeted Fractionated Chemotherapy (GTFC™), immunotherapy, and oxidative as well as nutrient support. Instead of undergoing significant surgical resection, the standard of care for NEN treatment, the patient was treated with Envita's proprietary direct-to-tumor targeted precision chemotherapy and immunotherapy interventional radiology regimen called CIPI™. Envita's proprietary CIPI™ approach is novel compared to the standard TACE or intratumoral injection because it utilizes genetically targeted precision oncology to not only specifically target a patient's tumor but also activate their immune system intratumorally and systemically to destroy any metastatic disease and circulating tumor cells. The patient-specific precision CIPI™ medication can be injected or infused multiple times directly into the tumor site using one or both of the following approaches, depending on the tumor site, size, and accessibility. The first method includes directly injecting the drugs percutaneously into the tumor using CT or ultrasound

guidance. The second method is intravascular and involves inserting a catheter into a groin or arm artery and advancing the catheter to the feeding arteries of the tumor using fluoroscopy. The intravascular procedure can also be performed using drug-eluting bead transarterial chemoembolization (DEB-TACE); these microscopic beads comprise an effective embolization system that can deliver controlled, high doses of chemotherapeutic drugs locally. The CIPI™ procedure is generally well tolerated.

IR procedures at Envita Interventional Radiology (EnvitaIR™) are meticulously planned and executed using the latest imaging technologies. The EnvitaIR™ CIPI™ procedure consists of the following steps:

4.1. Pre-Procedure Preparation

1) Patient Evaluation

Prior to the CIPI™ procedure, Envita IR specialists undergo a complete patient evaluation, which comprises a thorough physical examination, review of symptoms, medical history, previous treatments, surgical history, family history, social history, allergies, and medications that the patient may be taking. Cell-free DNA extracted from the patient's liquid biopsy sample is also analyzed using a 523 next-generation sequencing gene panel to determine potentially actionable mutations for targeted drug delivery.

2) Imaging Studies

The interventional radiologist reviews the patient's pertinent and most recent CT or PET scans to map the precise tumor location and extent; these imaging scans are used to formulate an effective preliminary plan to treat the patient's cancer using interventional radiology. A consultation between the treating physician and interventional radiologist usually follows, and a treatment strategy is agreed upon.

3) Informed Consent

The physician communicates the treatment plan to the patient. The interventional radiologist educates the patient regarding the CIPI™ procedure and imaging modalities, techniques used, associated risks, benefits, and appropriate alternatives. Often there are no other good options for treatment. Although, in some cases, alternatives may include systemic chemotherapy alone, surgery, and/or radiation as second- or third-line treatments. Some risks associated with the CIPI™ procedure include bleeding, allergic reaction, infection, sedation complication, hyper immune response, sequela, and poor treatment response. The CIPI™ procedure is scheduled and completed only after the patient's consent.

4.2. Procedure Execution

1) Image Guidance

Envita interventional radiologists utilize specialized instruments such as CT to visualize and assess the tumor site in real-time. For this patient, initial unenhanced CT images of the abdomen were obtained with the patient in a prone po-

sition, and the entire CIPI™ procedure was performed using CT imaging in real-time.

2) Direct Treatment Application

Treatment comprising targeted chemotherapy, immunotherapy, and adjuvant agents is administered intratumorally, ensuring targeted delivery to the tumor with minimal impact on the surrounding healthy tissues.

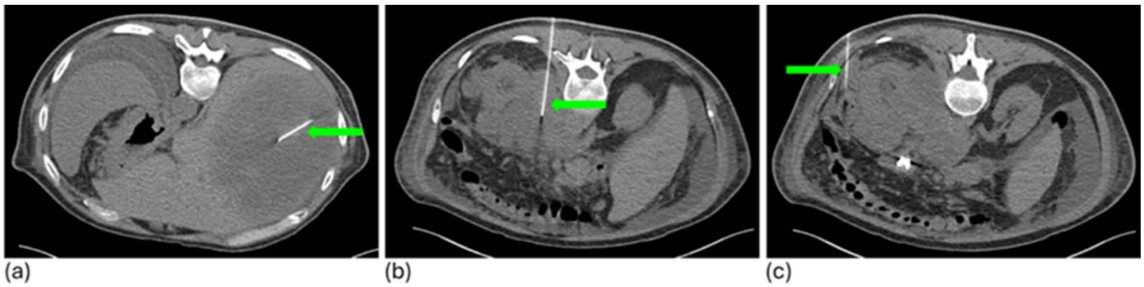

Figure 2. The first CT-guided percutaneous CIPI™ procedure shows intratumoral drug delivery into the (a) right liver mass, (b) left adrenal gland mass, and (c) left pararenal metastatic lesions, using a 22-gauge spinal needle (shown with a green arrow).

CT-guided percutaneous CIPI™ was delivered intratumorally into the patient's right liver mass, left adrenal gland mass, and left pararenal metastatic lesions; this procedure was scheduled thrice during the course of his treatment (**Figure 2** and **Figure 3**). The patient's left flank and abdomen were prepped in a sterile fashion, and he was sedated for the procedure. Drugs were delivered percutaneously with CT guidance intratumorally using a 22-gauge spinal needle that was inserted into various areas of the large mass in the right lobe of the liver, left adrenal gland mass, and the left pararenal area. The procedure was performed with maximum barrier sterile technique that included sterile gloves and gown, a surgical hat, and mask.

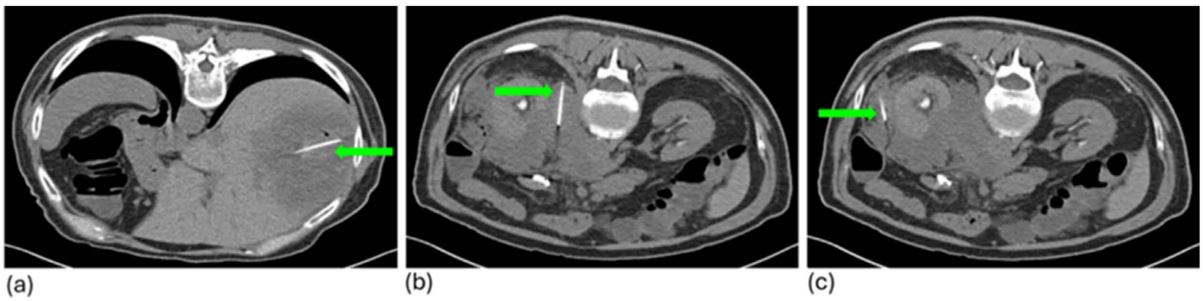

Figure 3. A repeat CT-guided percutaneous CIPI™ procedure shows intratumoral drug delivery into the (a) right liver mass, (b) left adrenal gland mass, and (c) left pararenal metastatic lesions, using a 22-gauge spinal needle (shown with a green arrow).

4.3. Post-Procedure Monitoring

1) Immediate Assessment

The tumor site is immediately evaluated following the procedure to assess drug delivery accuracy and identify any immediate complications. The patient is kept

under observation for 1.5 hours in the recovery area and discharged if stable.

2) Post-Treatment Assessment

Following the CIPI™ procedure, Envita IR specialists undergo a complete patient evaluation, which comprises a thorough physical examination, review of symptoms, list of medications, as well as the required bloodwork.

3) Follow-Up Care

The patient is regularly monitored through imaging, clinical evaluation, and laboratory tests to gauge treatment response and manage any complications. The CIPI™ procedure can be repeated at the same or different locations in the case of disease metastasis or recurrence.

The treatment protocol at Envita Medical Centers employs an amalgamation of personalized, precision integrative oncology including CIPI™, GTFC™ and immunotherapy, with continuous disease monitoring using tumor markers, circulating tumor cells, and follow-up imaging. GTFC™ is Envita's proprietary, personalized, fractionated low-dose chemotherapy-driven treatment tailored specifically to the patient's tumor genetic and molecular profile. GTFC™ delivers metronomic chemotherapy doses compared to traditional regimens and precisely targets the patient's tumor cells with minimal impact on healthy cells. Unlike traditional chemotherapy, GTFC™ is designed to target 7 - 10 tumor genetic biomarkers; the resulting customizable drugs are formulated in Envita's in-house Vertisis Custom Pharmacy.

4.4. Results and Patient Response to Treatment

In this study, the patient declined conventional oncology treatment before initiating care at Envita. Envita's unique treatment strategy was guided by monitoring Patient-Reported Outcome (PRO) scores, leading indicators of disease such as circulating tumor cells (CTCs), Tumor Methylation Score, Variant Allele Frequency (VAF), as well as imaging at the initiation and toward the end of treatment. The patient's vital signs, physical state, vision changes, neurological state, heart function, gastrointestinal function, cognitive function, sexual function, and mental issues were assessed regularly during treatment. Additionally, the patient's blood samples were regularly analyzed for complete blood counts, hormones, metabolic panels, as well as cancer markers to evaluate therapeutic response and toxicity effects as well as to modify treatment strategies.

PRO scores. The patient reported an overall PRO symptom score of 35 at treatment initiation; each symptom was scored between 0 - 10, with a higher score indicating lower quality of life. Envita's PRO score questionnaire, which utilizes a 10-point Likert scale, includes an evaluation of symptoms commonly observed in cancer patients, such as physical assessment (fatigue, stamina, weight changes), neuropathies (pain, weakness, numbness), vision changes, neurological assessment (memory, dizziness, speech), gastrointestinal problems, cognitive function, sexual function, and mental issues (anxiety, depression). The questionnaire is scored by the patient and is evaluated regularly during treatment, thereby empow-

ering the patient to directly contribute to their health assessment and quality of life as well as offering a comprehensive assessment of treatment effectiveness [54]. The PRO score system also enables Envita's specialized oncology medical staff to effectively evaluate and modify treatment strategies promptly as needed.

The final PRO score reported by the patient at the end of treatment was 17, implying a significant improvement in quality of life (**Figure 4(a)**).

Tumor markers. An initial assessment of circulating tumor cells (CTCs) detected 40 CTCs per 7.5 mL of whole blood (Menarini Silicon Biosystems). CTCs are biomarkers of cancer progression; these are tumor cells that have separated from the primary tumor or metastatic site [55] [56]. CTC detection and enumeration allow for early detection, metastasis, and prognosis of cancer; a CTC count of ≥ 5 CTC/7.5 mL of blood generally indicates metastatic disease [56].

The patient's initial baseline Tumor Methylation Score, calculated as the normalized sum of methylated circulating-tumor DNA (ctDNA) molecules at more than 500 loci that are hypermethylated in cancer compared to normal tissue, was 25,000 (Northstar Response). Differences in methylated ctDNA represent a change in the tumor fraction [57]. Additionally, a 523-gene liquid biopsy panel (Tempus) using peripheral blood was used to determine potentially actionable and biologically relevant genomic variants for targeted therapy as well as the median variant allele fraction (VAF). The median VAF at treatment initiation was 39.1%.

CTC analysis at the end of treatment resulted in 0 CTC/7.5 mL of whole blood (Menarini Silicon Biosystems), a momentous improvement compared to CTC levels at treatment initiation (**Figure 4(b)**). At this time, the patient's Tumor Methylation Score was 1900 (Northstar Response), corresponding to an approximately 92% decrease compared to the original score (**Figure 4(c)**). These results were based on a decrease in methylated ctDNA molecules, indicating a decrease in tumor fraction; methylated ctDNA was quantified at greater than 500 loci known to be hypermethylated in tumors [57] [58]. The patient's median VAF at the end of treatment decreased to 6.8% (Tempus), representing an 83% reduction compared to the median VAF at treatment initiation (**Figure 4(d)**).

Imaging. The patient's three main regions of disease involvement included the large right hepatic mass, the left retroperitoneal mass confluent with the pancreatic tail and the left adrenal gland, and the multifocal left perirenal soft tissue deposits (**Figure 5**). The patient demonstrated significant recovery after approximately 3 months of treatment. A PET/CT scan following treatment using Gallium-68 Dotatate, a newer radiotracer specific for neuroendocrine cancers and a more sensitive method for the diagnosis and staging of NETs, indicated significant tumor regression [5]. The PET/CT scan demonstrated decreased size of soft tissue lesions and photopenia within all three regions of disease involvement. The right hepatic lobe mass following treatment measured 9.5 × 7 cm; this was significantly smaller compared to the 17 × 13 cm mass observed before treatment (**Figure 5**). No new hepatic lesions were observed. The left retroperitoneum confluent mass inseparable from the left adrenal gland, pancreatic tail, and left upper kidney decreased in size from the prior 7.5 × 7 cm to 5 × 4 cm with very mild uptake (**Figure**

5). The left para-aortic region was also significantly improved, measuring 3 × 2 cm following treatment compared to the 4 × 3.5 cm mass before treatment.

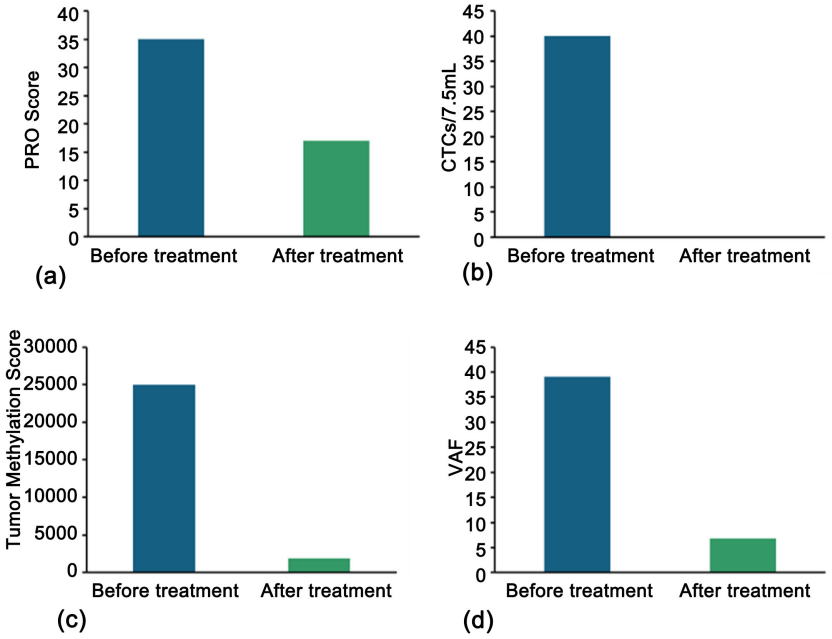

Figure 4. The patient's treatment response was evaluated using Patient Reported Outcome (PRO) scores, as well as tumor markers, Circulating Tumor Cells, CTCs (b), Tumor Methylation Score (c), and Variant Allele Fraction, VAF (d), before and after treatment.

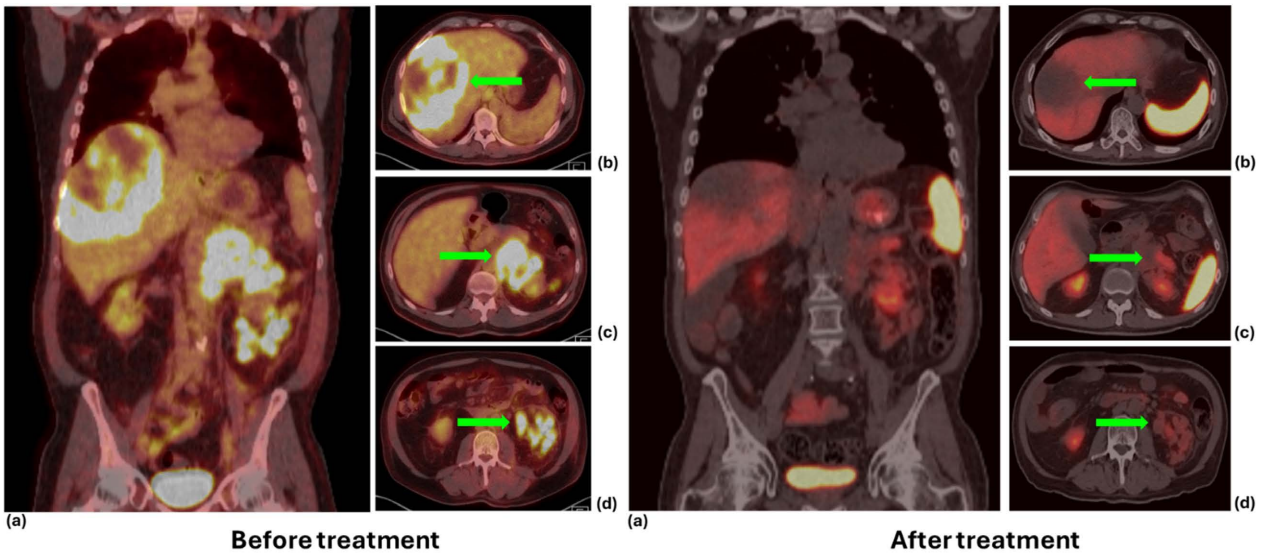

Figure 5. Coronal (a) and axial images ((b), (c), and (d)) at approximately the same location for the patient before (left) and 3 months after treatment at Envita Medical Centers (right). Intense FDG uptake on the FDG-PET/CT scan (left, indicated by green arrows) was seen before treatment in the large liver mass (b), left adrenal gland mass, the probable origin of the neuroendocrine carcinoma (c), and metastatic satellite lesions extending into the left pararenal region (d). There is none or very little dotatate uptake in the corresponding Gallium-68 Dotatate PET/CT images following treatment (indicated by green arrows), representing tumor regression. Physiologic dotatate uptake following treatment can be seen in the spleen and urinary bladder after treatment (right).

These results corroborate the superior level of quality precision care delivered to Envita patients and the significance of personalized precision treatment utilizing advanced genomics, transcriptomics, tailored immunotherapy, in combination with innovative drug delivery strategies such as CIPI™ for improved treatment outcomes in patients battling advanced cancer.

5. Discussion

NENs represent varying degrees of aggressiveness and hence are challenging to treat, often requiring a multidisciplinary approach [59]. Prognosis depends on the stage, primary tumor site, histological grade, sex, race, age, and year of diagnosis in patients [6]. Data from 35,618 patients with NETs identified from the Surveillance, Epidemiology, and End Results (SEER) program suggested that the median survival duration in patients with G1 (well differentiated) and G2 (moderately differentiated) NETs was 124 and 64 months, respectively, whereas the survival duration for patients with G3 (poorly differentiated) and G4 (undifferentiated) NETs was only 10 months [6]. Data compiled using another SEER program between 1973 and 2012 for 162,983 patients suggested that the mean overall survival for patients with NEC (extrapulmonary, gastrointestinal, unknown primary, and other sites) was only 7.7 months; localized, regional, and distant disease had a median survival of 20.7, 13.6, and 5.8 months, respectively [60]. Aggressive precision-targeted therapies, prompt evaluation, and a well-aligned multidisciplinary care team are therefore critically needed for effective NEN treatment to improve patient outcomes and enhance longevity.

NECs are highly proliferative, and demonstration of general neuroendocrine marker positivity is considered mandatory, especially in cases where liver metastasis is suspected [19] [61]. Ki-67 is a clinically established prominent proliferation marker used for grading multiple types of human cancer [62] [63]. Poorly differentiated NECs present with abundant necrosis and greater than 55% Ki-67 [64]. The AE1/AE3 cytokeratin (CK) expression, including dot-like keratin-positivity, is observed in neuroendocrine carcinomas [19] [64] [65]. Synaptophysin is a sensitive neuroendocrine marker, and Ki-67 is a proliferative NET marker that is highly reproducible when used to grade tumors as per the European Neuroendocrine Tumor Society (ENETS) and World Health Organization (WHO) classification [19] [66]. The thyroid transcription factor-1 (TTF-1) enables identification of metastatic NETs of pulmonary origin; its expression was negative in NETs of other origins (pancreas, skin, ovary, and thymus) [67].

First-line NET treatment typically involves SSAs, whereas second-line NET treatment is patient-specific, but lacks any standard treatment regimen and is not based on the patient's tumor genetic or molecular profile. This study provides a glimpse into the future of oncology, where precision care and patient comfort are of paramount importance. As we look to the future, the benefits of interventional radiology in oncology are becoming increasingly apparent. Envita's proprietary CIPI™ technology is a non-surgical, minimally invasive, precision-targeted ther-

apy that utilizes tumor mutation-specific drug algorithms to deliver a combination of targeted chemotherapy, immunotherapy, and chemo-adjunctive agents directly to the tumor site; CIPI™ may be administered with or without chemoembolization. The CIPI™ agents are a combination of chemotherapy drugs that are commonly used in conventional chemotherapy, immunologic agents to stimulate the patient's immune system against their cancer, as well as chemo-adjunctive agents. This combination is the key to successful treatment and calls out the "P" (precision) in CIPI™. The oncology team at Envita Medical Centers customizes the chemotherapy/immunologic combination to treat the patient's cancer. Unlike the common practice in conventional oncology, which is based on NCCN's standard treatment protocols, the patient's tumor profile is thoroughly evaluated using genetics and biomarkers to individualize their treatment at Envita. Chemotherapy continues to be the most common cancer treatment strategy; chemotherapy regimens are dictated by the NCCN Clinical Practice Guidelines [68]. However, this standard chemotherapy approach has resulted in drug resistance and toxicity [69] [70]. Systemic chemotherapy is generally dosed in higher concentrations in order to properly treat multiple metastatic lesions, leading to significant toxicity and deterioration in the patient's quality of life. Targeting the tumor by direct injection allows for less toxic doses of systemic chemotherapy.

Cutting-edge techniques employed by Envita's Interventional Radiology team showcase the impact of precision-targeted, minimally invasive, image-guided surgical procedures for direct tumor ablation. As discussed in this study, a detailed CIPI™ procedure, supplemented by visual aids from the actual case study, including CT imaging during the procedure and pre- vs post-treatment images, illustrates Envita's innovative technology for effective patient response. Standard of care chemotherapy predicted a prognosis of one year and a 5% response rate for this patient which was significantly improved following care at Envita Medical Centers. A case study documenting the response outcomes of 199 late-stage cancer patients treated at Envita Medical Centers over a two-year period demonstrated a 35-fold improvement in overall response rates [1]. Envita's treatment strategy was guided by longitudinal testing, monitoring patient-reported outcomes, and leading indicators of disease, including CTCs and mutant allele frequency (MAF), and individualized precise interventions; these strategies contributed to an overall patient response rate of 72% [1]. Furthermore, 88% of these patients experienced a 43-fold improvement in quality of life compared to patients undergoing standard-of-care chemotherapy and palliative care [1]. These results corroborate Envita's commitment to patient care, which is driven by their innovative personalized precision therapeutic algorithms incorporating genomic and molecular targeting of the tumors, as well as precisely delivering these mutation-matched agents directly to the tumor site [1]. Results from this study illustrate the role of interventional oncology in the delivery of personalized precision medicine targeting the patient's tumor and tumor microenvironment utilizing advanced genomics, transcriptomics, and immunotherapy for a noteworthy disease outcome.

6. Conclusions

This study demonstrates the effectiveness of personalized precision therapy using Envita's proprietary interventional radiology technology known as Chemo Immuno Precision Injection™ (CIPI™) for treating advanced cancers. CIPI™ was developed as a minimally invasive, image-guided platform to deliver personalized, metronomic doses of chemotherapy, immunotherapy, as well as chemo-adjuvant agents directly to the tumor site. This study examines the case of a 67-year-old patient who presented at Envita Medical Centers with Stage 4 Metastatic high-grade poorly differentiated small cell type NEC. The original CT and FDG PET/CT scans indicated that the three main regions of disease involvement included a large right hepatic mass, left retroperitoneal mass confluent with the pancreatic tail and the left adrenal gland, and multifocal left perirenal soft tissue deposits. The patient was treated over a duration of 128 days using Envita's personalized therapeutic algorithms incorporating interventional radiology, GTFC™, immunotherapy, and integrative care. Treatment using the interventional oncology protocols employed by Envita completely eliminated the need for major resective surgery and/or radiation and demonstrated a leap forward in modern oncology, offering patients a highly effective, less invasive, and less complicated alternative to traditional cancer care.

The patient's PRO score, CTC levels, Tumor Methylation Score, and VAF were improved following treatment. Specifically, the patient's PRO score was reduced from 35 to 17, CTC levels decreased from 40 to 0 CTCs/7.5 mL of whole blood, Tumor Methylation Score dropped from 25,000 to 1900, and VAF diminished from 39.1% to 6.8% from treatment initiation to the end of treatment. A follow-up Gallium-68 Dotatate PET/CT scan towards the end of treatment indicated significant tumor regression within all three regions of disease involvement. The personalized treatment regimen at Envita not only enhanced the patient's quality of life but also optimized patient care to achieve tumor regression and increase longevity. Following care at Envita Medical Centers, the patient continues to be actively monitored and currently has stable disease.

This study has clearly articulated the process, benefits, and outcomes of Envita's personalized interventional radiology (IR) procedures. Detailed images of the IR procedure, along with pre- and post-treatment scans, showcase the precision and minimal invasiveness of these techniques, emphasizing noteworthy clinical results. In addition to these findings, CIPI™ (Chemo Immuno Precision Injections) has been successfully utilized across a wide range of tumor types and anatomical locations. Based on this extensive clinical experience, CIPI™ has demonstrated efficacy even in patients who are refractory to conventional care.

Some limitations of interventional radiology include indirect physician visual and surgical access to the tumor and tumor microenvironment, which must be compensated for by advanced anatomical, pathological, and functional imaging, as well as pretherapeutic planning [22]. Interventional oncology at Envita aims to combat the disease with its focus on image analysis and precision medicine tai-

lored to each patient's cancer. As research progresses, the role of IR in delivering direct immunotherapy and other targeted treatments is expected to expand, offering new hope for cancer patients. The synergy linking imaging innovations, personalized medicine, robotics, and AI has the potential to revolutionize interventional oncology [51]. These advancements promise to refine the current treatment paradigms and provide patients with more precise, personalized, and less invasive treatment options in the fight against cancer.

Conflicts of Interest

In the interest of transparency regarding potential conflicts, Dino Prato, NMD, serving as the founder, researcher, and CEO of Envita Medical Centers, leads the initiative on personalized treatment modeling. All other authors are employees of Envita Medical Centers. Notably, all physicians at Envita contribute to algorithm design, a process that demands rigorous oversight and training to ensure impartiality and the highest standards of patient care.

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