Overview on Gastric Cancer

Chapter 3

Role of Nuclear Medicine in Gastric Malignancies

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1. Gastric Cancer

1.1 Diagnosis and Staging

The initial evaluation of patients suspected of harboring gastric malignancy involves an upper gastrointestinal endoscopy, which provides information about the disease's anatomical site and helps obtain tissue samples for definitive histological diagnosis [1]. After that, the accurate determination of the stage of the disease is essential to develop appropriate treatment strategies. The tumor, node, and metastasis (TNM) staging system of the eighth edition of the American Joint Committee on Cancer (AJCC) manual is currently the globally accepted standard for gastric cancer staging [2]. Conventional diagnostic modalities, viz. endoscopic ultrasonography (EUS) and computed tomography (CT), though widely used, have shown marked variability in the accuracy of gastric cancer staging [3]. At the same time, EUSperforms well in assessing the degree of tumor invasion, its operator-dependent accuracy, and suboptimal evaluation of distant lymph nodal involvement.

Similarly, although CT helps identify the extent of invasion in T4 lesions and enlarged regional and distant lymph nodes, its accuracy is limited for the less invasive T1-T3 lesions and normal-sized nodes [4]. Molecular imaging with 2-deoxy-2-[18F] fluoro-D-glucose-positron emission tomography/CT (18F-FDG-PET/CT) scan, thus, have an incremental role in the primary staging of gastric cancer. 18F-FDG is a radiolabelled glucose analog that accumulates in the malignant cells through the GLUT-1 transporter [5]. The utility of 18F-FDG-PET/CT

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in the staging of gastric cancer lies particularly in its ability to detect distant nodal, peritoneal, and organ metastases, which would alter the treatment decisions [3]. 18F-FDG-PET/CT is considered to be the most sensitive modality for this indication and can detect metastatic involvement in small, equivocal lesions, which could, otherwise, have been missed on CT alone. The National Comprehensive Cancer Network (NCCN) guidelines, thus, recommend 18F-FDG-PET/CT in the initial work-up of patients with gastric cancer, if clinically indicated and if metastatic disease is not evident [6]. Nevertheless, the inability to assess the degree of tumor invasion and poor spatial resolution limit its role in T and N staging, respectively [4]. Furthermore, the sensitivity of diagnosing diffuse- and mucinous-type gastric tumors is low due to poor FDG uptake in such malignancies owing to low cellularity and reduced GLUT1 expression (**Table 1**) [7].

1.2. Response Assessment

18F-FDG-PET/CT can be used for the evaluation of response following primary treatment of gastric cancer. The modality is particularly helpful when diagnostic contrast-enhanced CT (CECT) cannot be performed for response evaluation in patients with renal insufficiency or allergy to contrast agents [8]. The PET Response Criteria in Solid Tumors (PERCIST) has largely standardized the assessment of metabolic response using 18F-FDG-PET/CT (**Table 2**) [9]. The response categories observed as per PERCIST have been shown to significantly predict the progression-free survival in patients with advanced gastric cancers [10]. The criteria also hold promise for evaluating early treatment response in terms of reduction in metabolic burden before reducing tumor size [11]. Nevertheless, 18F-FDG-PET/CT cannot be reliably used for response assessment in tumors with baseline low FDG uptake (mucinous and signet ring adenocarcinomas) [7]. 18F-fluorothymidine (18F-FLT) is another PET tracer that has shown significant uptake in such tumors. Being a biomarker of cellular proliferation, 18F-FLT-PET could reliably identify early response at two weeks in locally advanced gastric cancer treated with neoadjuvant chemotherapy [12].

1.3. Surveillance:

18F-FDG-PET/CT can be considered for surveillance in patients with stage ≥II gastric cancers [13]. 18F-FDG-PET/CT can prove superior to CT alone in differentiating local recurrences (focal, intense FDG uptake) from treatment-related changes (diffuse, mild FDG uptake) as well as in detecting recurrent distant metastatic disease (Figure 1) [14]. In a retrospective study, Lee et al. showed a sensitivity of 84% and specificity of 88% with 18F-FDG-PET/CT in detecting recurrent disease on postoperative surveillance of patients with gastric cancer [15].

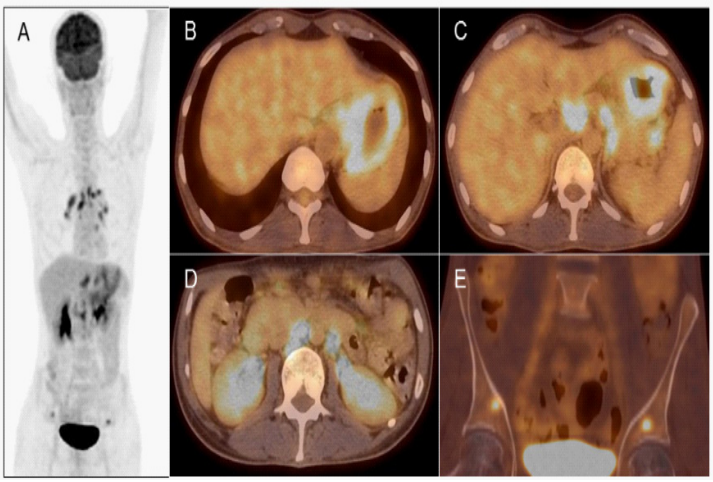

Figure 1: 43-years old male gastric adenocarcinoma, post-chemotherapy status. Patient underwent 18F-FDG-PET/CT for evaluation of suspected recurrent disease. 18F-FDG-PET/CT showed metabolically active circumferential thickening of the stomach wall (A,B), subcentrimetric and enlarged gastrohepatic, peripancreatic, gastrosplenic (C), paraaortic, and aortocaval lymph nodes (D), and bilateral iliac bone lesions (A,E) suggestive of recurrent disease.

Table 1: Strengths and pitfalls of 18F-FDG PET/CT in gastric adenocarcinoma.

Strengths
• Detects distant metastatic disease • Can differentiate local recurrences (focal, intense FDG uptake) from treatment-related changes (diffuse, mild FDG uptake) • Useful in cases where CECT is contraindicated (e.g. renal insufficiency, contrast allergy) • Role in prognosis
Pitfalls
• Low FDG uptake in diffuse- and mucinous-type tumors • False-positive in cases of infection and/or inflammation (e.g. mediastinal lymph nodes)

Table 2: PET Response Criteria in Solid Tumors (PERCIST) [9].

Complete Metabolic Response (CMR)	• Complete resolution of FDG uptake within measurable target lesion (<mean liver activity and indistinguishable from surrounding background) • Disappearance of all other lesions to background blood-pool levels • No new FDG-avid lesion
Partial Metabolic Response (PMR)	• Decrease in SULpeakof ≥30% and ≥0.8 SUL units between the most intense evaluable lesion at baseline and the most intense lesion at follow-up (not necessarily the same lesion) • Decrease in SULpeak of ≥0.8 SUL units in the target lesion • No increase in size >30% in the target lesion • No increase in SULpeak or size >30% in a nontarget lesion • No new FDG-avid lesions
Progressive Metabolic Disease (PMD)	• Increase in SULpeakof ≥30% and ≥0.8 SUL units in a target lesion • Increase in size ≥30% in target lesions, or unequivocal progression in nontarget lesion • ≥1 new lesion
Stable Metabolic Disease (SMD)	Not CMR, PMR or PMD

1.4. Prognostic and Predictive Role

18F-FDG-PET/CT parameters, viz. maximum and mean standardized uptake values (SUVmax and SUVmean), metabolic tumor volume (MTV), and tumor lesion glycolysis (TLG), have been identified as significant predictors of response and survival outcomes in FDG-avid gastric cancer patients [16,17]. Higher values denote an aggressive disease with an inherently worse prognosis. Few studies have also shown a positive correlation between FDG uptake and HER2 expression in gastric cancer patients [18,19].

1.5. Radiotherapy Planning

18F-FDG-PET/CT can be used for accurate target volume delineation before radiotherapy and helps in dose escalation to the tumor while reducing toxicity to the surrounding tissues [20]. However, its role in radiotherapy planning for locoregional gastric cancers is limited by the low-grade FDG uptake in certain histological types [7]. Nevertheless, 18F-FDG-PET/CT is effective in detecting liver metastasis from gastric cancer and hence, utilized for enhanced target delineation in stereotactic body radiotherapy to the liver disease [21].

1.6. Theranostics:

The field of "Theranostics" involves the combined approach of using the same or similar radiopharmaceuticals for diagnostic and therapeutic purposes (Table 3). In recent times, targeting the fibroblast-activation protein (FAP) expressed on the cancer-associated fibroblasts (CAFs) in the tumor stroma has garnered much interest. PET/CT with the radiolabelled FAP inhibitors (FAPI), 68Ga-FAPI-04 has not only outperformed 18F-FDG-PET/CT in the detection of primary and metastatic gastric cancers but also demonstrated tracer uptake in non-FDG-avid histological subtypes [22-25]. Targeted radionuclide therapy, with 90Y or 177Lu, labeled FAPI, holds considerable promise in treating advanced, refractory/relapsed metastatic gastric cancers.

Table 3: Theranostics in Gastric Malignancies

Approved applications		
Diagnostic modality	Therapeutic modality	Indication
^{68}Ga-DOTA-TATE/NOC	^{177}Lu-DOTATATE	SSTR-positive gastric NETs
^{111}In-Ibritumomab tiuxetan	^{90}Y-Ibritumomab tiuxetan	CD20-positive relapsed/refractory primary gastric lymphomas
Novel applications		
^{68}Ga-DOTA-TATE/NOC	^{225}Ac-DOTATATE	SSTR-positive gastric NETs, refractory to ^{177}Lu-DOTATATE
^{68}Ga-FAPI-04	^{177}Lu-FAPI-04/ ^{177}Lu-FAPI-46/ ^{177}Lu-FAP-2286/ ^{177}Lu-DOTAGA-SA-FAPI	Gastric malignancies with fibroblast-activation protein expression

2. Gastric Stromal Tumor

2.1. Diagnosis and Staging

CECT remains the modality of choice for the initial staging of gastric gastrointestinal stromal tumors (GISTs) [26]. The eighth edition of the AJCC staging manual incorporates both the TNM staging system and the mitotic rate of the tumor in the overall staging of GISTs [2]. 18F-FDG-PET/CT is increasingly used in the initial staging of GISTs. The modality may be particularly helpful in detecting an unknown primary GIST as well as small metastatic sites. 18F-FDG-PET/CT may also be beneficial for staging patients with renal dysfunction or intravenous contrast allergy [8]. The NCCN guidelines, while stating that 18F-FDG-PETis not a substitute for CECT, suggest the use of 18F-FDG-PET/CT in ambiguous findings seen on CECT alone and to assess complex metastatic disease in patients being considered for surgery [27]. Furthermore, a baseline 18F-FDG-PET/CT should be obtained in patients, where it is being considered for the assessment of treatment response [27].

2.2. Response Assessment

Tyrosine kinase inhibitors (TKIs), viz. imatinib, with or without surgical resection, remain the mainstay of treatment for GISTs [27]. Response assessment to TKIs is usually done every 8-12 weeks with abdominal CECT using the Choi criteria [28]. However, 18F-FDG-PET/CT can be used for early response assessment after 2-4 weeks of TKI (Fig.2). The TKIs are cytostatic, wherein changes in metabolic activity on 18F-FDG-PET/CT can precede the anatomical changes on CT alone. The European Organization for Research and Treatment of Cancer (EORTC) response criteria have been used to assess imatinib response on 18F-FDG-PET/CT [29].

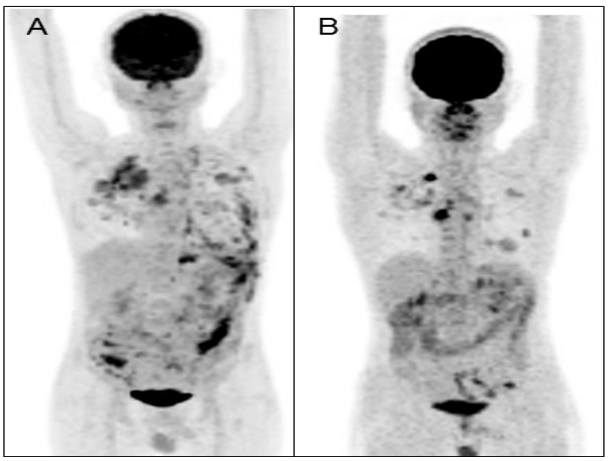

Figure 2: 43-years old male gastric GIST, post surgical resection for the primary, underwent 18F-FDG-PET/CT for recurrence evaluation. 18F-FDG-PET/CT showed metabolically active pleural and peritoneal deposists, suggestive of metastatic disease (A). The patients was started on imatinib. Follow-up 18F-FDG-PET/CT after 4 weeks showed significant reduction in the extent and avidity of the lesions, suggestive of partial response (B).

2.3. Surveillance:

Abdominal CECT, performed every 3-6 months, is recommended for surveillance in GISTs following treatment. 18F-FDG-PET/CT, while not routinely recommended, can be considered for clarifying ambiguous CT findings [27]. 18F-FDG-PET/CT is particularly helpful in differentiating recurrent and active disease from necrotic or inactive scar tissue and other benign changes [30]. Adverse effects to TKI therapy, viz. colitis, pancreatitis, hepatitis, and thyroiditis, can also be identified on surveillance 18F-FDG-PET/CT scans [31].

2.4 Prognostic and Predictive Role:

18F-FDG-PET/CT can be used to identify patients with primary and secondary resistance to imatinib. Lack of metabolic response on 18F-FDG-PET/CT performed during the first month of treatment with imatinib is predictive of primary resistance and should be followed with dose escalation. A continued lack of metabolic response on subsequent scans should prompt a switch to the second-line TKI sunitinib. Following treatment, the reappearance of FDG uptake in a previously non-avid lesion suggests secondary resistance [32].

3. Gastric lymphoma

3.1. Diagnosis and Staging:

Primary gastric lymphomas(PGLs) include either the mucosa-associated lymphoid tissue (MALT) lymphoma or the diffuse large B-cell lymphoma (DLBCL). 18F-FDG-PET/CT has high sensitivity (97-100%) for the detection of gastric DLBCL and hence, is beneficial over CT in its initial staging(Fig.3) [33]. The Lugano staging system used for this purpose defines stage I disease as confined to the stomach; stage II as an abdominal nodal spread or adjacent organ involvement (IIE); and stage IV as a disseminated extranodal spread supradiaphragmatic nodal disease [34]. 18F-FDG-PET/CT is particularly useful in detecting distant nodal and extranodal involvement with resultant upstaging of disease in 22% and downstaging in 14% of the cases [33]. MALT lymphomas have been reported to have variable FDG avidity, and the role of 18F-FDG-PET/CT in their initial staging remains controversial [35,36].

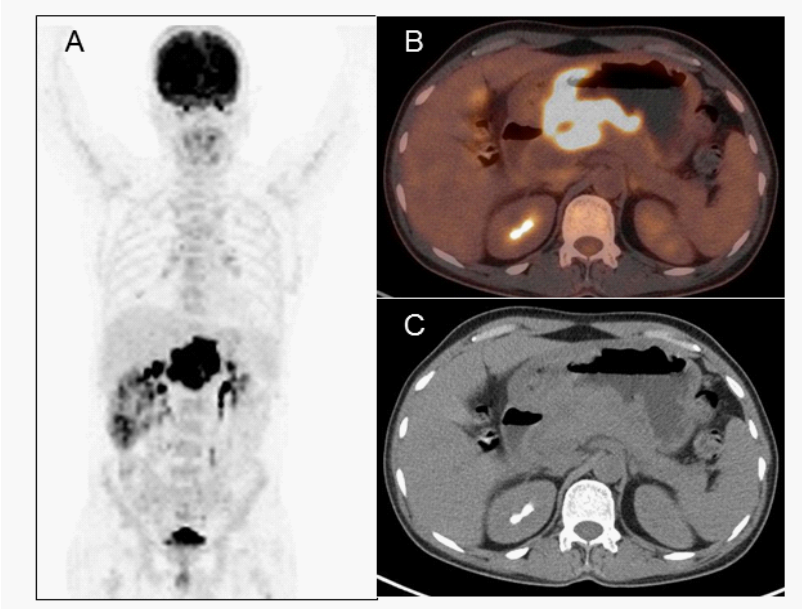

Figure 3: 40-years old male was diagnosed with gastric DLBCL, and underwent staging 18F-FDG-PET/CT. Maxi-mum intensity projection image showed metabolically active lesion in the middle in the abdomen (A), which corre-sponded to a lobulated mass in the antropyloric region of the stomach on the axial fused PET/CT (B) and CT im-ages (C). No perigastric lymph nodes were noted. Faintly FDG avid subcentimetric mediastinal lymph nodes, and consolidation in the right lung lower lobe were also noted (A), suggestive of secondary infective etiology. The pa-tient, thus, had stage I disease as per the Lugano staging system.

3.2. Response Assessment:

18F-FDG-PET/CT is useful in evaluating response post-treatment of PGLs. In one of the earliest studies, Kumar et al. demonstrated that a positive 18F-FDG-PET scan post-chemotherapy in patients of lymphomas with GI involvement was a strong predictor of disease relapse [37]. Over the years, PET/CT-based response evaluation in FDG-avid lymphomas has become standardized with the development of the Deauville 5-point scoring system and the Response Evaluation Criteria in Lymphoma (RECIL) [38,39].

3.3 Surveillance:

18F-FDG-PET/CT is useful in the detection of relapse in PGL patients following treatment. Sharma et al. evaluated 39 previously treated PGL patients who underwent 18F-FDG-PET/CT for suspected relapse or routine follow-up. 18F-FDG-PET/CT was reported to be highly accurate in the detection of disease relapse with sensitivity, specificity, and accuracy of 96%, 91%, and 93%, respectively [40].

3.4. Prognostic and Predictive Role:

A higher SUVmax on the baseline 18F-FDG-PET/CT has been shown to predict poorer survival outcomes in patients with PGL [41]. Additional parameters, viz. MTV and TLG have also been reported to predict response and survival outcomes in patients of primary gastric DLBCL [42].

3.5. Radioimmunotherapy:

90Y-Ibritumomab tiuxetan is a radiolabelled monoclonal antibody targeting the CD20 receptor and is approved for the treatment of relapsed/refractory, CD-20 positive, B-cell follicular non-Hodgkin lymphoma [43]. Few studies have also evaluated its role in the setting of extranodal indolent lymphomas. In a prospective phase II trial, 13 patients with relapsed/refractory PGL were administered 0.4 mCi/kg of 90Y-Ibritumomab tiuxetan, and complete remission was observed in 10/13 patients.Five of these patients, further, had a long-term response with response durations ranging from 31-50 months after radioimmunotherapy [44]. In another study, six patients with relapsed/refractory MALT lymphoma (two with gastric lymphoma) were treated with 90Y-Ibritumomab tiuxetan, of which four patients achieved completeremission [45]. Treatment-related adverse events were largely limited to manageable hematological toxicities [44].

4. Gastric Neuroendocrine Tumor

4.1 Diagnosis and Staging:

The 2019 World Health Organization (WHO) classifies the gastroenteropancreatic NENs (GEP-NENs) into a) the well-differentiated neuroendocrine tumors (NETs), and b) the poorly differentiated neuroendocrine carcinomas (NECs). The well-differentiated GEP-NETs are further divided into three grades: grade 1 - <2 mitoses/10 high-power field (HPF) or Ki67 index <3%; grade 2 – 2-20 mitoses/10 HPF or Ki67 index3-20%; and grade 3 - >20 mitoses/10 HPF or Ki67 index >20%. Further, all poorly differentiated NECs are considered as grade 3 [46]. Somatostatin receptors (SSTRs) are G-protein-coupled receptors overexpressed on the tumor cells in well-differentiated NETs. Radiolabelled somatostatin analogs used in PET, viz. 68Ga-DOTANOC, 68Ga-DOTATATE and 68Ga-DOTATOC,64Cu-DOTATATE, target these SSTRs and have high sensitivity and specificity for the detection of well-differentiated NETs [47,48]. SSTR PET/CT is, therefore, indicated for the localization of unknown primary in patients with known metastatic NET or high clinical/biochemical suspicion. SSTR PET/CT has also been shown to be superior to conventional imaging as well as SSTR scintigraphy (111In-pentreotide) in the initial staging of NETs. On the contrary, 18F-FDG-PET/CT has low sensitivity for well-differentiated NETs; however, it remains the imaging modality of choice for NECs [49].

4.2 Response Assessment:

The use of SSTR PET/CT for response assessment in NETs is controversial since a reduction in the SSTR expression could signify either a decrease in the tumor burden or dedifferentiation. Few studies have shown the utility of modified PERCIST using SSTR PET/CT for response assessment in NETs. However, this needs validation in prospective studies

[50,51]. Nevertheless, the use of SSTR PET/CT is appropriate in cases of discordance between clinical/biochemical and CT outcomes and to clarify ambiguous CT findings.SSTR PET/CT also proves beneficial for follow-up non-measurable CT lesions, e.g., skeletal metastases [49]. 18F-FDG-PET/CT can be used for response assessment following cytotoxic chemotherapy in NECs.

4.3. Peptide Receptor Radionuclide Therapy:

Peptide receptor radionuclide therapy (PRRT) has emerged as a mainstay of treatment for advanced, inoperable/metastatic, well-differentiated SSTR-positive NETs over the past few decades (Table 3). Both 90Y and 177Lu labeled somatostatin analogs have been successfully tried in NETs following progression with cold somatostatin analogs. Of these,177Lu-DOTATATE was accorded Food and Drug Administration (FDA) approval following the landmark NETTER-1 trial, which showed significant improvement in the progression-free survival in the 177Lu-DOTATATE arm [52]. Subsequently,studies have also shown benefits with 177Lu-DOTATATE in the first-line setting [53,54]. Patient selection is based on a baseline SSTR PET/CT, and those were having lesions with SSTR expression more than that of the liver are considered eligible for therapy (Table 4) [53-55]. 177Lu-DOTATATE is typically administered at an activity of 7.4 GBq per cycle, up to four cycles, at 8-12 weeks intervals, with several studies reporting objective radiological response rates of 30-40% and disease control rates of 80-85%. An infusion of basic amino acids, comprising lysine and arginine, is concurrently administered as a prophylactic measure against nephrotoxicity, and adverse events, if any, are largely transient and of grades 1-2 [52-56]. Recently, targeted alpha therapy with 225Ac-DOTATATEhas proven beneficial in patients, refractory to 177Lu-DOTATATE [57].

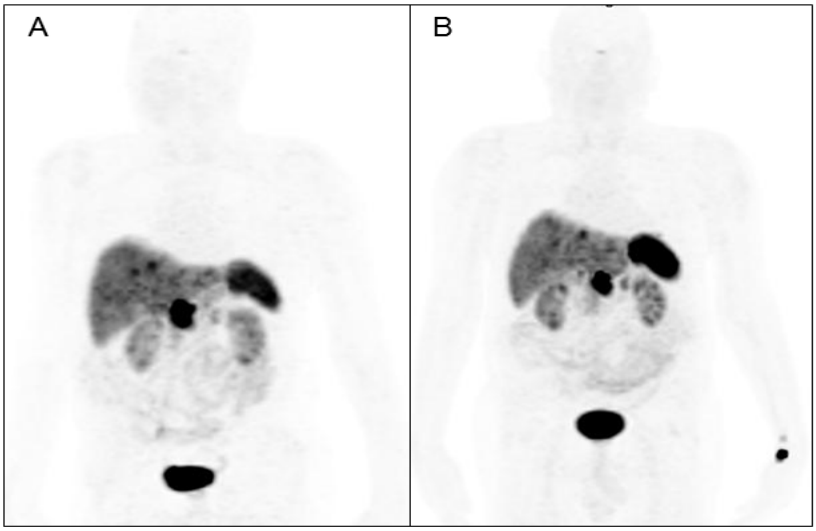

Figure 4: 45-years old male was grade 2 gastric NET, post surgical resection for the primary and 18 months of octreotide LAR. Baseline 68Ga-DONANOC PET/CT showed SSTR expressing enlarged abdominal lymph node and liver lesions (A). Patient, then, underwent four cycles of 177Lu-DOTATATE. Eight weeks after tha last cycle, repeat 68 Ga-DONANOC PET/CT was suggestive of stable disease (B).

Table 4: Eligibility criteria for Peptide Receptor Radionuclide Therapy.

•	Histologically confirmed well-differentiated NETs
•	Inoperable/metastatic disease
•	Lesions showing SSTR expression more than that of liver
•	No discordant (FDG-positive, SSTR-negative) lesion
•	Stablehematological parameters: hemoglobin ≥8 g/dL; total leukocytecounts ≥3000/μL; neutrophils ≥1500/μL; platelets ≥75000/μL
•	Estimated Glomerular Filtration Rate (eGFR) ≥50 mL/min
•	Total bilirubin ≤ 3 x upper limit of normal
•	Serum albumin ≥3 g/dL

4.4. Prognostic and Predictive Role:

Dual SSTR and 18F-FDG-PET/CT have prognostic significance in the setting of metastatic NETs, with SSTR expression showing inverse correlation with the tumor grade and increased FDG avidity signifying higher tumor grade or dedifferentiation. Dual tracer PET/CT allows for the whole-body lesion characterization and hence, helps assess tumor heterogeneity, which can be missed on single-site biopsies [58]. This is essential for the selection of the appropriate treatment strategy from the choices of somatostatin analogs, PRRT, and chemotherapy. Patients with low-grade NETs, usually SSTR-positive and FDG-negative, benefit from somatostatin analogs/PRRT. On the contrary, those with high-grade tumors, usually FDG-positive and SSTR-negative, will require the institution of cytotoxic chemotherapy. Patients with lesions showing both SSTR and FDG positivity may benefit from a combination approach using PRRT plus chemotherapy [59].

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