Review

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False Positive Findings of ^{68}Ga-DOTATOC PET/CT: A Systematic Review

^{68}Ga-DOTATOC PET/BT'nin Yanlış Pozitif Bulguları: Sistematik Derleme

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Abstract

This systematic review aimed to explore the currently reported false positive findings of Gallium-68 (^{68}Ga)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid Tyr3-octreotide (^{68}Ga-DOTATOC). PubMed, Web of Science, and Scopus databases were used to conduct a systematic search and were updated until March 4, 2024. Three authors independently screened the titles and abstracts of the retrieved articles and selected the articles based on the inclusion and exclusion criteria. In a qualitative analysis of 42 included research articles involving 601 patients, 219 false positive findings were identified and categorized. Non-oncologic etiologies predominated, constituting 50.2% of pitfalls, followed by benign oncologic (27.4%) and malignant neoplasms (22.4%). Anatomically, the abdomen was the most common site for pitfalls (30.6%), followed by the musculoskeletal (22.4%), head and neck (20.5%), and pelvic (14.6%) regions. Chest region findings were least frequent, accounting for only 11.9%. This study elucidates potential false positive findings, predominantly occurring in the abdominal and head-neck regions—primary sites for meningiomas and neuroendocrine tumors (NETs). Understanding these false-positive findings is crucial for accurate diagnosis. Furthermore, recognizing these pitfalls may lead to novel applications of ^{68}Ga-DOTATOC beyond its conventional use in evaluating NETs and meningiomas, potentially expanding its current utility.

Keywords: ^{68}Ga-DOTATOC, SSTR, PET/CT, false positive findings, false positive uptake, diagnostic pitfalls, pitfalls, systematic review

Öz

Bu sistematik derlemenin amacı, Galyum-68 (^{68}Ga)-1, 4, 7, 10-tetraazasilododeskan-1, 4, 7, 10-tetraasetik asit Tyr3-oktreotid (^{68}Ga-DOTATOC) ile bildirilen yanlış pozitif bulguları incelemektir. Sistematik tarama için PubMed, Web of Science ve Scopus veritabanları kullanıldı ve aramalar 4 Mart 2024 tarihine kadar güncellendi. Üç yazar, elde edilen makalelerin başlık ve özetlerini bağımsız olarak tarayarak dahil etme ve dışlama kriterlerine göre seçim yaptı. Altı yüz bir hastayı kapsayan 42 araştırma makalesinin nitel analizinde 219 yanlış pozitif bulgu saptandı ve kategorize edildi.

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Onkolojik olmayan etiyolojiler baskındı ve hataların %50,2'sini oluşturdu; bunu iyi huylu onkolojik (%27,4) ve kötü huylu neoplazmlar (%22,4) izledi. Anatomik olarak en sık hatalar karın bölgesinde (%30,6) görüldü; bunu kas-iskelet sistemi (%22,4), baş-boyun (%20,5) ve pelvik (%14,6) bölgeler takip etti. Göğüs bölgesi bulguları en az sıklıkla görüldü ve yalnızca %11,9 oranında raporlandı. Bu çalışma, yanlış pozitif bulguların çoğunlukla karın ve baş-boyun bölgelerinde ortaya çıktığını ve bunların menenjiyomlar ile nöroendokrin tümörlerin (NET'ler) primer bölgeleri olduğunu göstermektedir. Bu yanlış pozitif bulguların anlaşılması, doğru tanı için kritik öneme sahiptir. Ayrıca bu hataların tanınması, ^{68}Ga-DOTATOC'un NET'ler ve menenjiyomların değerlendirilmesindeki geleneksel kullanımının ötesinde, potansiyel olarak yeni uygulama alanlarına genişletilmesine katkı sağlayabilir.

Anahtar kelimeler: ^{68}Ga-DOTATOC, SSTR, PET/BT, yanlış pozitif bulgular, yanlış pozitif tutulum, tanısal tuzaklar, tuzaklar, sistematik derleme

Introduction

Gallium-68 (^{68}Ga)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid Tyr3-octreotide (^{68}Ga-DOTATOC) is a positron emission tomography (PET) imaging agent that is expressed primarily in neuroendocrine tumor pathologies and meningiomas and contains abundant somatostatin receptor (SSTR) type 2 (1). In 2001, the first study on this promising PET tracer targeting SSTRs was published, introducing DOTATOC labeled with ^{68}Ga (2). Multiple comparative studies have been subsequently conducted to benchmark its reliability against the traditionally used ^{111}In-octreotide single photon emission computed tomography (CT) ovel SSTR imaging agent in different neuroendocrine tumor subtypes (3,4,5). ^{68}Ga-DOTATOC has generally demonstrated superiority to ^{111}In-octreotide regarding detection rate, sensitivity, and image resolution (3,4,5).

^{68}Ga-DOTATOC is utilized not only for imaging purposes but also for a theranostic approach, a concept that has become increasingly relevant in recent years (6). Radiotheranostics, involving the use of ^{68}Ga-DOTATOC for quantitative imaging of tumor-related biomarkers, is considered the pinnacle of personalized nuclear medicine (6). Initial evaluation with ^{68}Ga-DOTATOC aids in identifying individuals suitable for SSTR-based peptide radionuclide receptor therapy (PRRT) (7). Patients who demonstrate positive accumulation of the radiolabeled molecule in tumor lesions are deemed eligible for PRRT, which involves intravenous administration of a SSTR targeting molecule labeled with a therapeutic radionuclide such as lutetium-177-DOTA peptides (7). The increasing use of radiotheranostics in nuclear medicine is currently widely recognized (6).

Although the sensitivity of ^{68}Ga-DOTATOC PET/CT compared to that of other imaging modalities has been well studied, the cancer specificity and positive predictive value of ^{68}Ga-DOTATOC-avid PET/CT findings are currently understudied. Pitfalls have been observed to affect various anatomic sites and are linked to various disease entities, potentially limiting optimal diagnostic accuracy (8). With the increasing number of SSTR PET imaging studies performed worldwide, there are consequently many reported cases of false-positive ^{68}Ga-DOTATOC-avid findings, but most of these findings have been published as case reports.

The objective of this systematic review was to explore the currently reported false positive findings of ^{68}Ga-DOTATOC and study their relative prevalence, aiming to provide an up-to-date overview relevant for the interpretation of clinical ^{68}Ga-DOTATOC PET/CT findings.

Materials and Methods

Search Strategy

This systematic review adapted its methodology from the guidelines of the preferred reporting items for systematic reviews and meta-analyses (9). The study has not been registered in PROSPERO or any other registration domains. Three authors—DAA, ASA, and AA-I—conducted a systematic search of PubMed, Web of Science, and Scopus-indexed articles to identify research publications exploring SSTR-positive findings beyond physiologic distribution, NETs and meningiomas using ^{68}Ga-DOTATOC as the primary radiotracer.

The search algorithm combined key terms of interest and their related Medical Subject Headings terms (10). No language or date filters were applied during the data retrieval. The systematic literature search and extraction methods were updated until March 4, 2024. Studies were included if they clearly specified false positive findings and provided patient demographics for individuals with the pitfall of interest. All research papers, except meeting abstracts, were considered eligible for inclusion. Preclinical, simulation, and animal studies were excluded from the analysis.

The same three authors reviewed the titles and abstracts of the retrieved articles using the aforementioned search algorithm. They applied the previously mentioned inclusion and exclusion criteria, eliminating articles that were clearly ineligible.

Data Extraction

This systematic review extracted comprehensive datasets from the included studies. General extracted information

encompassed the primary author's name, publication year, total study sample size, study language, patient characteristics (such as gender and age), journal name, and article subtype. Additionally, specific qualitative data related to false positive findings were collected, including the name of each diagnostic pitfall, its anatomical site, and its etiology. Microsoft Excel Version 2016 was utilized for data organization and collection.

Assessment of Methodological Quality and Risk of Bias

The methodological quality of the original articles included in this systematic review, which examine the diagnostic utilities of ^{68}Ga-DOTATOC PET/CT, was independently evaluated utilizing the standardized Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) protocol (11). QUADAS-2 scores were analyzed to ascertain the risk of bias and the methodological applicability of the studies (11).

For single reported instances, we employed an adapted version of the CAse REport (CARE) scoring system to evaluate the credibility of the presented data. This methodology utilizes a comprehensive set of 13 parameters outlined in the CARE checklist (12). Adapted CARE quality assessment framework categorizes manuscripts based on criteria adherence: high-quality papers meet at least 10 criteria, intermediate-quality 5-9, and low-quality no more than 4 (13).

Results

Study Inclusion

Overall, 42 research articles met the eligibility criteria for the systematic review (Figure 1A) (4,5,6,7,8,14,15,16,17,18, 19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35, 36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52, 53). These studies included a total of 601 patients, with a slight male predominance, constituting approximately 54% of the total patient population. Nearly two third of the included studies were published in journals specializing in nuclear medicine (4,8,14,15,16,17,21,24,25,27,28, 29,31,32,33,34,35,37,38,39,43,45,46,49). The majority of the studies were conducted in European countries, which accounted for the correspondence in 34 studies, representing 81% of the total. Most of the research articles were case reports or interesting images, comprising 60% of the total publications (8,14,16,18,21,23,25,26, 29,31,32,33,34,35,37,39,40,42,43,44,46,48-50,52,53). Original research studies followed in frequency, making up one-third of the total publications and were mostly retrospective in nature (4,15,17,19,20,22,24,27,28,30, 36,38,41,45,51).

Finally, a single review article was identified that showcased a diagnostic pitfall in single reported case (Table 1) (47).

Methodological Quality

The QUADAS-2 qualitative assessment of original studies (Figure 1B), revealed a high risk of bias and high applicability concerns in the patient selection domain for four studies, primarily due to small sample sizes and suboptimal recruitment strategies (17,19,20,38). An additional study exhibited high patient selection bias risk owing to its limited sample size (30). Two studies demonstrated unclear biases and applicability concerns stemming from retrospective recruitment (27,51). One prospective study showed unclear patient selection applicability due to its limited sample size, potentially affecting generalizability (45). A single study presented unclear applicability concerns due to ambiguous blinding of readers to clinical information (38). Furthermore, one study displayed unclear applicability in reference standards, which were absent for a subset of included patients (19).

Regarding case reports, two-thirds of the reported cases demonstrated high quality according to adapted CARE criteria, while the remaining one-third was of intermediate quality (Figure 1C). Notably, no low-quality case reports were observed. A more comprehensive qualitative assessment is provided in the Supplementary Tables 1 and 2.

Overview of False Positive Findings

A total of 219 false positive findings were detected, with the most commonly encountered finding being uptake in the pancreatic uncinate process (23.7%), followed by uptake in the vertebral hemangioma (15.9%), uptake in the head and neck squamous cell carcinoma (HNSCC) (14.1%), and non-specific uptake in the prostate (11.4%). All other pitfalls were reported less frequently. All false positive findings were subsequently classified based on their anatomic location and etiology (Table 2).

Head and Neck Region

The head and neck region ranked third in terms of frequency of false positive findings. HNSCC with avidity for ^{68}Ga-DOTATOC was the predominant finding in this region. It is noteworthy that malignant causes were more common in this region, with only a small percentage of benign oncologic conditions identified and no non-oncologic causes noted (Table 3).

Chest Region

The chest region exhibited the lowest frequency of false positive findings. Notably, subacute myocardial infarction was the most commonly observed condition in this area. Subsequently, there were five instances of immunotherapy-

Table 1. General characteristics of included studies

First author, year	Country	Study	Total sample (Gender)	Age	Journal
Al-Ibraheem, 2022 (16)	Jordan	CR	1 (1M)	64	Nuclear Medicine and Molecular Imaging
Al-Ibraheem, 2016 (14)	Jordan	CR	1 (1M)	49	Nuklearmedizin
Al-Ibraheem, 2011 (15)	Jordan	OR	43 (13M, 30F)	64	European Journal of Nuclear Medicine and Molecular Imaging
Bashir, 2021 (8)	Denmark	CR	15 (3M, 12F)	67	European Journal of Nuclear Medicine and Molecular Imaging
Höög, 2018 (26)	Sweden	CR	2 (2M)	71	Clinical Genitourinary Cancer
Khalaf, 2020 (29)	Jordan	CR	1 (1M)	13	Nuclear Medicine and Molecular Imaging
Johnbeck, 2017 (28)	Denmark	OP	59 (35M, 24F)	61	Journal of Nuclear Medicine
Lapa, 2015 (30)	Germany	OP	12 (7M, 5F)	52	International Journal of Cardiology
Richard, 2023 (42)	France	CR	1 (1F)	73	Clinical Nuclear Medicine
Werner, 2016 (53)	Germany	CR	5 (3M, 2F)	61	Journal of Medical Imaging and Radiation Oncology
Putzer, 2009 (41)	Austria	OR	51 (29M, 22F)	60	Journal of Nuclear Medicine
Bollano, 2022 (18)	Sweden	CR	1 (1M)	20	European Heart Journal
Trevisi, 2022 (50)	Italy	CR	1 (1F)	82	Journal of Cancer Research and Therapeutics
Vandekerckhove, 2021 (52)	Belgium	CR	1 (1M)	66	Acta Clinica Belgica
Ceccato, 2020 (20)	Italy	OR	16 (7M, 9F)	66	Endocrine Connections
Gossili, 2020 (24)	Denmark	OR	8 (8M)	67	Hellenic Journal of Nuclear Medicine
Lococo, 2017 (33)	Italy	CR	1 (1M)	77	Clinical Nuclear Medicine
Lococo, 2021 (34)	Italy	CR	5 (1M, 4F)	67	Clinical Nuclear Medicine
Pinot, 2021 (40)	France	CR	1 (1M)	67	Clinical Nuclear Medicine
Umana, 2022 (51)	Italy	OR	67 (33M, 34F)	69	Anticancer Research
Treglia, 2014 (49)	Switzerland	CR	1 (1F)	48	Nuclear Medicine and Molecular Imaging
Ryoo, 2020 (43)	Korea	CR	1 (1F)	55	Nuclear Medicine and Molecular Imaging
Jacobsson, 2012 (27)	Sweden	OR	50 (26M, 24F)	59	Clinical Nuclear Medicine
Binse, 2016 (17)	Germany	OR	15 (8M, 7F)	59	Journal of Nuclear Medicine
Gilardi, 2017 (23)	Italy	CR	1 (1F)	68	Endocrine
Peter, 2014 (39)	Germany	CR	1 (1M)	77	Clinical Nuclear Medicine
Gabriel, 2007 (4)	Austria	OP	84 (48M, 36F)	58	Journal of Nuclear Medicine
Gauthé, 2018 (22)	Spain	OR	79 (40M, 39F)	65	European Radiology
Lorusso, 2021 (35)	Italy	CR	1 (1M)	58	Clinical Nuclear Medicine
Fabritius, 2021 (21)	Germany	CR	1 (1F)	74	Clinical Nuclear Medicine
Paquet, 2018 (38)	France	OR	15 (10M, 5F)	53	European Journal of Nuclear Medicine and Molecular Imaging
Schmidt, 2019 (46)	USA	CR	1 (1M)	60	World Journal of Nuclear Medicine
Takesh, 2011 (48)	Germany	CR	1 (1F)	59	Radiology Case Reports
Guglielmo, 2022 (25)	Italy	CR	1 (1M)	81	Clinical Nuclear Medicine
Sharma, 2013 (47)	India	RA	7 (2M, 5F)	38	American Journal of Roentgenology
Boughdad, 2021 (19)	Switzerland	OR	11 (10M, 1F)	71	Journal for ImmunoTherapy of Cancer
Mahajan, 2019 (37)	USA	CR	1 (1M)	70	Clinical Nuclear Medicine
Saeed, 2022 (44)	Germany	CR	1 (1M)	73	RöFo

Table 1. Continued					
First Author, Year	**Country**	**Study**	**Total sample (Gender)**	**Age**	**Journal**
Laurens, 2018 (31)	Netherlands	CR	1 (1M)	56	Clinical Nuclear Medicine
Schartinger, 2013 (45)	Austria	OP	15 (13M, 2F)	55	European Journal of Nuclear Medicine and Molecular Imaging
Liberini, 2019 (32)	Italy	CR	1 (1M)	42	Clinical Nuclear Medicine
Luboldt, 2010 (36)	Germany	OR	20 (20M)	67	Molecular Imaging and Biology
CR: Case reports, F: Female, M: Male, OP: Original prospective studies, OR: Original retrospective studies, RA: Review article					

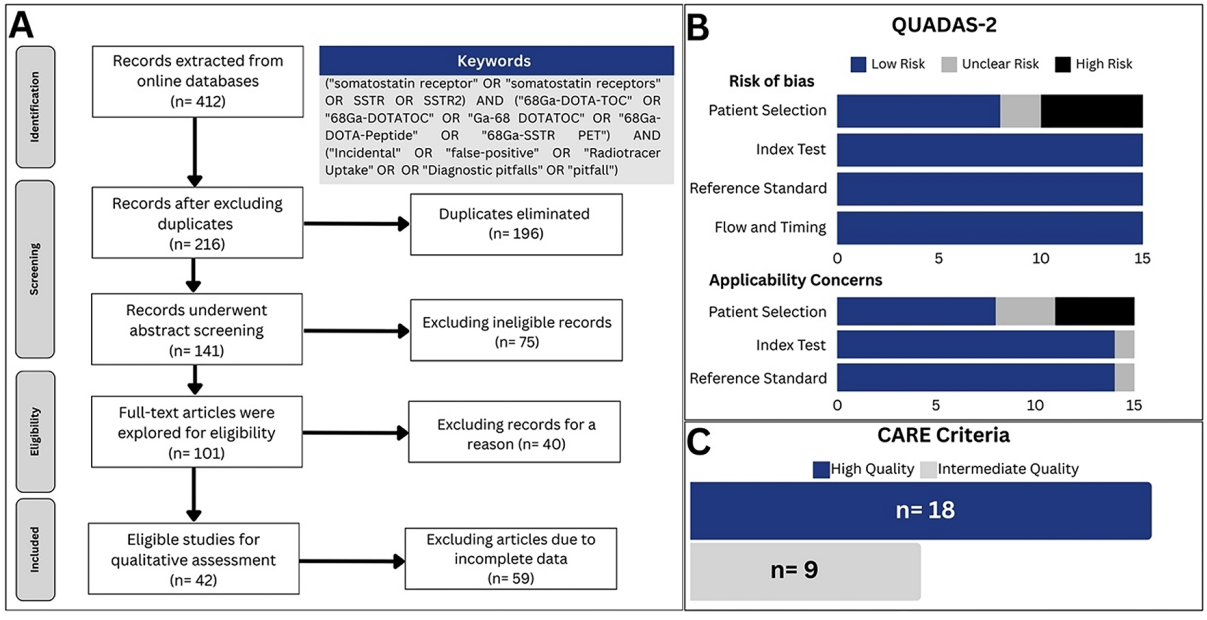

Figure 1. (A) A flowchart demonstrating the process of data acquisition, duplicate removal, screening, and final inclusion. (B) Results from standardized Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) protocol assessment. (C) Results from the adapted CAse REport (CARE) scoring system, OR: Original retrospective studies, SSTR: Somatostatin receptor, 68GA: Gallium-68 PET: Positron emission tomography

induced myocarditis (Figure 2), and five instances of a pleural solitary fibrous tumor. Furthermore, several diagnostic challenges were recorded and categorized (Table 4).

Abdomen and Pelvis

The abdomen and pelvis are areas in which false positive findings commonly occur. Together, these regions account for approximately 45% of all false positive findings. Pitfalls in the abdomen are more prevalent, representing 30.6%, while pelvic pitfalls make up 14.6% (Figure 3). Within the abdomen, uptake in the pancreatic uncinate process is the most frequently encountered pitfall (23.7%). Whereas, pelvic pitfalls were mostly due to non-specific uptake in the prostate. Additional findings are detailed in Table 5.

Table 2. Classification of false positive findings based on anatomical location and underlying cause		
Region-based analysis		
Anatomic site	**Number of observations**	**Percentage**
Head and neck	45	20.5%
Chest	26	11.9%
Abdomen	67	30.6%
Pelvis	32	14.6%
Musculoskeletal	49	22.4%
Etiology-based analysis		
Etiology	**Number of observations**	**Percentage**
Non-oncologic etiology	110	50.2%
Benign oncologic etiology	60	27.4%
Malignant oncologic etiology	49	22.4%

Musculoskeletal Region

The musculoskeletal region is the anatomic site where benign oncologic findings are commonly found. Among these findings, vertebral hemangioma was the most frequently observed entity compared to other conditions (Table 6).

Etiology-based Analysis

Etiology-based analysis revealed that non-oncologic etiologies predominated, constituting 50.2% of pitfalls, followed by benign oncologic etiologies (27.4%) and malignant neoplasms (22.4%). Non-specific ^{68}Ga-DOTATOC uptake within the pancreatic uncinate process or prostate was the most common cause of non-oncologic findings. Benign oncologic findings were primarily due to vascular tumors (n=38; 63.3% of all benign oncologic findings). HNSCC was the most prevalent malignant oncologic finding (n=31; 63.4% of observed malignancies). A detailed etiology-based analysis is summarized in Supplementary Table 3.

Table 3. False positive findings in head and neck region

Etiology	Finding	Number	Percentage
Malignant oncologic (n=38; 84.5%)	HNSCC	31	68.8%
	Poorly differentiated thyroid cancer	4	9%
	Papillary thyroid cancer	1	2.22%
	CNS lymphoma	1	2.22%
	Intracranial metastasis from breast cancer	1	2.22%
Benign oncologic (n=7; 15.5%)	Vestibular schwannoma	3	6.7%
	Pituitary adenoma	1	2.2%
	Parotid basal cell adenoma	1	2.2%
	Parotid pleomorphic adenoma	1	2.2%
	Intracranial hemangioblastoma	1	2.2%

CNS: Central nervous system, HNSCC: Head and neck squamous cell carcinoma

Discussion

A full systematic review of literature exploring false positive findings in ^{68}Ga-DOTATOC PET/CT imaging is highly relevant, especially given the increased demand and investment following its Food and Drug Administration approval in 2019 (54,55). Understanding the pitfalls, common findings, and physiological uptake of ^{68}Ga-DOTATOC is essential for accurate interpretation of imaging results, yet these topics have not been adequately studied. This is evident from the fact that the majority of current literature consists merely of case reports shared in isolated instances (8,14,16,18,21,23,25,26,29,31,32,33,34,35,37,39,40,42,43,44,46,48,49,50,52,53). There is also a lack of prospective original studies primarily aimed at identifying false-positive findings (4,30,45).

Overall, 219 false positive findings were observed, with the abdomen being the most frequent site for pitfall occurrence. For instance, pancreatic uncinate process uptake was the most prevalent finding in this systematic

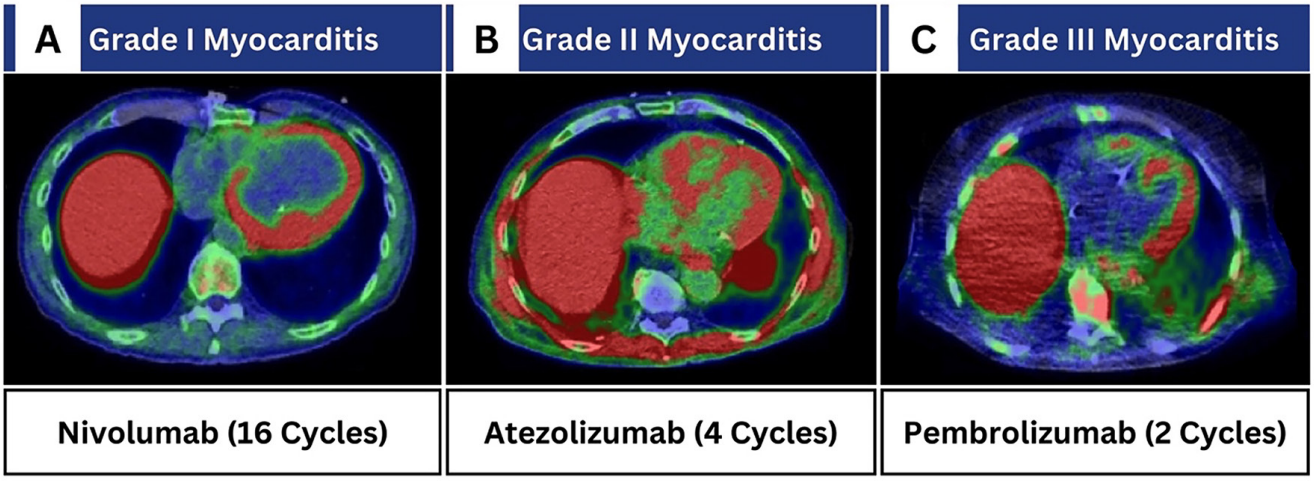

Figure 2. (A-C) Fused Gallium-68 (^{68}Ga)-1,4,7,10-tetraazacyclododecane-1, 4,7,10-tetraacetic acid Tyr3-octreotide (^{68}Ga-DOTATOC) positron emission tomography/computed tomography (PET/CT) images were performed for three cancer patients treated with immune checkpoint inhibitors. The fused axial cardiac PET/CT views reveal (A) diffuse ventricular wall ^{68}Ga-DOTATOC expression, or (B, C) patchy ventricular wall ^{68}Ga-DOTATOC expression correlating with clinically confirmed immunotherapy-induced myocarditis. All figure subpanels were reproduced from Figure 1 of previous original research by Boughdad under the Creative Commons license (CC BY 4.0) (19)

review, highlighting significant challenges in evaluating primary and locoregional gastroenteropancreatic neuroendocrine tumors. Historically, pancreatic uncinate process uptake in SSTR imaging was initially thought to be solely part of physiological distribution (56).

Table 4. False positive findings in the chest region

Etiology	Finding	Number	Percentage
Non-oncologic (n=21; 80.8%)	Subacute myocardial infarction	6	23%
	Immunotherapy-induced myocarditis	5	19.2%
	Acute myocarditis	3	11.5%
	Cardiac sarcoidosis	2	7.6%
	Acute pericarditis	1	3.9%
	Myocarditis post COVID-19 vaccination	1	3.9%
	Radiotracer embolus	1	3.9%
	Mediastinal lymphadenitis	1	3.9%
	Post-surgical chest wall inflammation	1	3.9%
Benign oncologic (n=5; 19.2%)	Pleural solitary fibrous tumor	5	19.2%

COVID-19: Coronavirus disease 2019

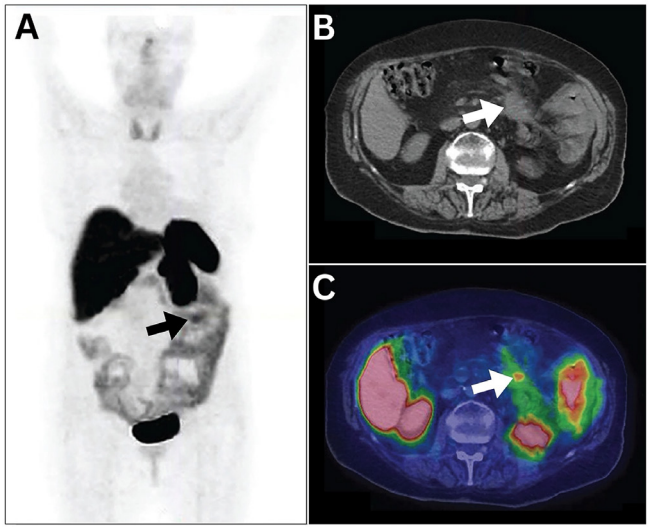

Figure 3. (A-C) Maximum intensity projection, axial computed tomography (CT), and fused Gallium-68 (^{68}Ga)-DOTATOC positron emission tomography (PET)/CT images performed in an 82-year-old woman with history of resected pancreatic neuroendocrine tumor. A mildly ^{68}Ga-DOTATOC-avid focus in the proximal jejunum was detected, ultimately diagnosed as mesenteric fibromatosis on histopathology. The figure was reproduced from Figure 1 primary supplied by Trevisi et al. (50) under a Creative Commons license (CC BY-NC-SA 3.0)

However, further research has linked its occurrence to various entities such as pancreatic head polypeptide hyperplasia, insulin resistance, and diabetes (57,58). Current European association of nuclear medicine guidelines advise a thorough assessment of ^{68}Ga-DOTATOC uptake in the uncinate pancreatic process, emphasizing the importance of comparing PET/CT findings with diagnostic CT images to exclude the presence of any visually identifiable lesions that may necessitate further examination (59). The evaluation of conventional imaging holds significant importance during the reporting process, and it is crucial to consider clinical correlation with underlying chronic conditions to recognize relevant contributing factors. Abdominal splenule also presents a significant diagnostic challenge and is often misattributed to lymph node metastasis or pancreatic neoplasm (43,44,48,49,52,53). Recent reports have marked the successful definitive diagnosis of splenosis through the utilization of technetium-99m-macroaggregated albumin-red blood cell or abdominal magnetic resonance imaging (43,44).

The second most common site for false positive findings was the musculoskeletal system, where vascular tumors, mostly vertebral hemangiomas, predominate and can mimic skeletal metastatic lesions, necessitating imaging correlation for optimal diagnosis (22,23). Third, pitfalls were found in the head and neck regions, mostly due to tumorous etiologies. With the low physiological ^{68}Ga-DOTATOC uptake in the brain, ^{68}Ga-DOTATOC might help evaluate various neuro-oncological conditions beyond meningiomas (60). While Schartinger et al. (45) found ^{68}Ga-DOTATOC expression in therapy-naive HNSCC patients, their uptake was variable, limiting accurate evaluation. However, this study highlighted that more than 93% of studied HNSCC patients had positive SSTR2 expressions on immunohistochemistry (45). Therefore, detection of ^{68}Ga-DOTATOC-avid focus within the head and neck region should not be automatically attributed to NETs, as many other etiologies can overlap when assessing this challenging region (61).

Another area of potential interest is the thoracic cavity, where myocardial uptake has been predominantly linked to myocardial infarction, inflammation, and immunotherapy adverse effects (18,19,30). Such findings have stimulated many physicians to explore the potential utility of ^{68}Ga-DOTATOC in these vital conditions, with several clinical trials ongoing to investigate its potential in infective endocarditis (NCT05432427), acute myocarditis (NCT03347760), and cardiac sarcoidosis (NCT04206163).

Table 5. False positive findings in the abdomen and pelvis			
Abdomen (n=67; 30.6%)			
Etiology	**Finding**	**Number**	**Percentage**
Non-oncologic (n=62; 92.5%)	Pancreatic uncinate process	52	77.6%
	Abdominal splenule	6	8.9%
	Mesenteric lymphadenitis	2	3%
	Acute gastritis	1	1.5%
	Chronic pancreatitis	1	1.5%
Malignant oncologic (n=4; 6%)	Metastatic pancreatic lesion from RCC	2	3.0%
	Primary left RCC	1	1.5%
	Abdominal leiomyosarcoma	1	1.5%
Benign oncologic (n=1; 1.5%)	Mesenteric fibromatosis (desmoid tumor)	1	1.5%
Pelvis (n=32; 14.6%)			
Non-oncologic (n=25; 78.1%)	Non-specific prostatic uptake	25	78.1%
Malignant oncologic (n=7; 21.9%)	Primary advanced prostate cancer	7	21.9%
RCC: Renal cell carcinoma			

Table 6. False positive findings in the musculoskeletal system			
Musculoskeletal system (n=49; 22.4%)			
Etiology	**Finding**	**Number**	**Percentage**
Benign oncologic (n=47; 95.9%)	Vertebral hemangioma	35	71.4%
	Tumor-induced osteomalacia	6	12.2%
	Solitary fibrous tumor	2	4.1%
	Capillary angioma	1	2.05%
	Non-ossifying fibroma	1	2.05%
	Tibial enchondroma	1	2.05%
	Spinal hemangioblastoma	1	2.05%
Non-oncologic (n=2; 4.1%)	Vertebral osteophyte	1	2.05%
	Periarticular vertebral inflammation	1	2.05%

Within the pelvic region, non-specific prostatic uptake was remarkably prevalent. Gossili et al. (24) reported that 4.5% of men exhibited incidental prostate ^{68}Ga-DOTATOC uptake during the examination of 178 male patients who underwent 193 ^{68}Ga-DOTATOC PET/CT studies. After confirming that no malignancy was found in the examined prostate in this population, the authors hypothesized that such incidental ^{68}Ga-DOTATOC findings are best labeled as non-specific (24). However, this evidence is singular and requires further investigation to explore various factors that may affect such observations. In such circumstances, biochemical correlation can help exclude prostatic malignancies, which can also present as false-positive findings (36).

This study has several limitations, primarily due to the sole reliance on qualitative assessment, while many other important factors such as lesion uptake kinetics and lesion-to-background ratios were not recorded and analyzed. Such datasets were not evenly reported or addressed in the included publications, which were mostly case reports.

Conclusion

This systematic review explores the potential false positive findings that may arise during ^{68}Ga-DOTATOC PET imaging. These false positive findings are often seen in the abdominal and head-neck regions, which are common locations for primary meningiomas and neuroendocrine tumor occurrences. Acknowledging these findings serves multiple purposes. Firstly, it raises awareness about possible locations and causes of diagnostic errors in order to prevent misinterpretation and improve reporting. Secondly, identifying these pitfalls may open up new possibilities for the use of ^{68}Ga-DOTATOC beyond its traditional role in treating NETs and meningiomas, potentially broadening its current applications.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.A-A., A.S.A., S.T.L., N.O., H.A., A.K., M.H.S., A.AI., Concept: D.A-A.,, A.S.A., S.T.L., A.AI., Design: D.A-A., A.S.A., N.O., A.K., M.H.S., Data Collection or Processing: D.A-A., A.S.A., S.T.L., A.AI., Analysis or Interpretation: D.A-A., S.T.L., N.O., A.AI., Literature Search: D.A-A., A.S.A., H.A., Writing: D.A-A., A.S.A., N.O., A.AI.

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Supplementary Tables 1-3

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