International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 23s,2025
https://theaspd.com/index.php

Low Dose CT Versus Contrast-Enhanced CT In FDG PET/CT Protocols For Staging/Restaging Of Malignancy

Saied. M, Ahmed. S[1], Wagieh. S[2], Mohammed. Y[3], Omar. M[4]
[1,2,3,4]The department of nuclear medicine- Faculty of medicine- Cairo University.

Abstract
Objective: *Background: PET/CT combines functional and anatomical imaging, but the role of intravenous contrast-enhanced CT (ceCT) in integrated PET/CT protocols remains debated. While low-dose non-contrast CT is sufficient for attenuation correction and lesion localization, ceCT may improve staging accuracy, particularly in solid tumors.*
Aim: *To compare between non-contrast CT and ceCT in integrated PET/CT protocols in staging/restaging of malignant diseases to determine the added diagnostic value of IV contrast in tumor staging and restaging of malignant lesions.*
Patients and methods: *This was prospective research done from September 2021 to January 2023 in the Nuclear Medicine Unit (NEMROCK Center), Kasr Alainy Hospital, Cairo University, and a private facility collected data.*
Results: *Among 96 patients with solid tumors, PET/ceCT resulted in T stage upstaging in 23 (23.9%), N stage in 18 (18.7%), and M stage in 9 (9.5%), all statistically significant. Overall, PET/ceCT altered final staging in 31 patients (25.8%), predominantly intra-abdominal malignancies. In 24 lymphoma patients, only one case was upstaged.*
Conclusion: *PET/contrast-enhanced CT significantly improves staging accuracy in solid tumors, particularly intra-abdominal cancers, but provides minimal additional value in lymphoma. Routine CECT integration is recommended for solid tumors to guide management.*
Keywords: *PET/CT, Contrast-Enhanced CT, Tumor Staging, Malignancy*

INTRODUCTION

Dual-modality PET/CT imaging devices enable the combined acquisition of functional and morphological datasets in a single examination. The benefits of PET over standard contrast-enhanced CT stem from the additional functional information it provides. The additional availability of CT data provides nuclear medicine physicians with accurate anatomical background information. The essential inquiry for both the radiologic and nuclear medicine communities is what volume of CT will be necessitated in PET/CT imaging? Is the administration of intravenous CT contrast agents necessary?

Intravenous iodinated contrast agents are widely utilized for CT imaging but are utilized with reluctance for FDG PET/CT in limited oncological indications **[1].** If knowledge about vascular structures or tumor invasion into adjacent structures is required, a ceCT should be incorporated into the combined PET/CT examination. Nonetheless, for certain indications such as lymphoma, contrast appears to be unnecessary **[2].** Consequently, imaging protocols utilizing IV contrast for PET/CT must be adapted to each specific FDG-PET/CT indication to diminish unnecessary radiation exposure to the case **[3].**
Characteristics of lesion enhancement as well as delineation of vascular structures are the primary advantages for the application of iodinated intravenous contrast agents in ceCT **[4]**. The application of intravenous contrast agent is contraindicated in cases having renal insufficiency, allergy to iodine-containing contrast agents, in addition to hyperthyroidism **[5]**. In the absence of contrast enhancement, CT images are regarded as only partially diagnostic since important information is missing for a thorough diagnosis **[6]**. Nevertheless, with PET/CT especially, the unmodified utilization of high-density intravenous contrast agent was shown to yield artifacts on attenuation-corrected PET images, & consequently intravenous contrast was applied only reluctantly in numerous PET/CT centers **[7]**.
Our study aimed to compare contrast-enhanced CT and non-contrast CT in integrated PET/CT protocols in staging/restaging of malignant diseases to determine the added diagnostic value of IV contrast in tumor staging and re-staging using FDG PET/CT against non-contrast CT integrated PET/CT in evaluation of the primary malignant lesion, lymph nodal involvement, and distant metastatic lesions.

PATIENTS AND METHODS

This was prospective research done from September 2021 to January 2023 in the Nuclear Medicine Unit (NEMROCK center), Kasr Alainy Hospital, Cairo University, and a private facility collected data. The selection process involved recognizing those cases that fulfilled the criteria given below and that were permitted by the ethical committee.

Inclusion criteria: cases with histologically proved malignant neoplasm presented for FDG PET/CT either for initial staging or post-therapeutic restaging.

Exclusion Criteria: Patients having any contraindication of contrast administration or refusing to be injected with IV contrast.

Methods: All patients underwent clinical assessment, including full history taking, together with data from the initial histopathology report.

Protocol

Cases have been instructed to fast for minimum six hours and were asked to avoid strenuous exercise for the preceding twenty-four hours. Blood glucose levels were assessed in all cases prior to the injection of FDG. Serum blood glucose concentrations have been assessed using finger stick measurement prior to the injection of the radiotracer to confirm a serum glucose concentration under 200 milligrams per deciliter. All cases have been maintained in a warm and calm environment and were administered approximately 5.2 MBq of 18F-FDG per kilogram of body weight intravenously.

After 45–60 min, an initially low-dose CT has been conducted at 120 kilovolts and 80 milliamperes and a slice thickness of 3.75 millimeters. PET was then conducted immediately following the non-enhanced CT, with 6 to 7 beds with a two-minute acquisition per bed position in 3-D acquisition mode. PET scanning has been carried out routinely from the base of the skull through the mid-thigh whereas the cases were supine with arms above the head, when tolerated. For cases with head and neck tumors, the arms were by the sides, and scanning started from the skull vertex. Imaging has been conducted utilizing a PET/CT scanner (Biograph Vision PET/CT), 3.2 x 3.2-millimeter lutetium oxyorthosilicate (LSO) crystals, 48 mm^3 volumetric, and 214-picosecond time-of-flight performance. Finally, diagnostic contrast-enhanced full-dose CT has been conducted at 120 kV and 300 mA, and 140 milliliters of an iodinated contrast agent were first administered intravenously at three milliliters per second utilizing an automated injector.

Image interpretation: This study utilized PET/non-contrast CT & PET/contrast-enhanced CT for diagnostic imaging. Two nuclear medicine consultants independently interpreted both low-dose and full-dose investigations. Abnormal focal FDG uptake on PET images, correlating with CT lesions, was visually and semi-quantitatively assessed to identify primary or metastatic lesions. Increased FDG uptake in lymph nodes indicated metastatic spread, irrespective of their short-axis diameter. For neoplasms with poor FDG uptake, detection relied on CT abnormalities combined with clinical history, including primary site, pathology, and inflammatory history. Central unenhanced regions on CT scans, indicating necrosis, were considered indicative of cancer. TNM classification (8th edition, AJCC, effective January 2017) was applied twice for each patient: once with PET/non-enhanced CT and once with PET/contrast-enhanced CT. The Lugano staging classification was used for lymphoma. The TNM system classifies cancer based on tumor extent (T), regional lymph node metastasis (N), in addition to distant metastasis (M). Higher stage numbers denote more advanced cancer, determined by combining T, N, and M scores through stage grouping. The T, N, and M phases and final stage were compared between the two imaging groups for each patient.

Statistical analysis

Information was statistically described using mean ± SD, range, median, or frequencies (number of cases) and percentages as applicable. P-values under 0.05 have been considered statistically significant. All statistical analyses have been performed applying the IBM SPSS software platform 22.0.

RESULTS

Table 1 shows that the study included 120 patients [58 males (48.5%) & 62 females (51.5%)] with a mean age of 54.7 ± 25.9 years.

Table 2 illustrates that the 120 patients were proved to have malignant neoplasm pathologically. In our

study, the most prevalent tumor was breast cancer (27 cases, 22% of total cases), followed by lymphoma (24 cases, 20% of total cases). While the least prevalent neoplasm was the cutaneous cancer (1 case, 1% of total cases). Within 120 patients known to have primary FDG PET/CT scans, 51 cases (42.5% of total patients) were presented for initial staging. 69 patients (57.5% of total patients) were presented for re-staging after either surgical intervention, chemotherapy, hormonal therapy, or radiation therapy.

Table 3 shows that regarding the final stage, for PET/non-contrast CT studies, there were 39 cases with stage 0, 10 cases with stage I, 19 cases with stage II, 9 cases with stage III, and 19 cases with stage IV. While for PET/contrast-enhanced CT, there were 23 patients with stage 0, 11 cases with stage I, 14 cases with stage II, 20 patients with stage III, and 28 patients with stage IV.

Table 4 shows that regarding staging of cases with lymphoma presented for initial assessment, for PET/non-contrast CT studies there were 3 cases with stage I, 2 patients with stage II, 4 patients with stage III, and 4 cases with stage IV. While for PET/contrast-enhanced CT, there were 3 patients with stage I, 1 case with stage II, 5 patients with stage III, and 4 cases with stage IV. Regarding patients with lymphoma presented for re-staging, both PET/non-contrast CT studies and PET/contrast-enhanced CT show 1 case with Deauville score 1, 5 cases with Deauville score 2, no cases with Deauville score 3, 3 cases with Deauville score 4, and 2 cases with Deauville score 5.

Table 5 shows that for the 96 patients with solid neoplasm, PET/contrast-enhanced CT changed the T stage with upstaging of 23 patients (23.9%) as follows: 2 patients with breast tumor, 2 patients with endometrial cancer, 2 cases with renal neoplasm, one patient with lung cancer, 4 patients with hepatic neoplasm, 9 cases with pancreatic neoplasm, one patient had gastric neoplasm, one patient with urinary bladder neoplasm, and one patient with soft tissue sarcoma. It appeared statistically significant with a P value of 0.03.

Table 6 shows that for the 96 patients with solid neoplasm, PET/contrast-enhanced CT changed the N stage with upstaging 18 patients (18.7%) as follows: three patients with colon cancer, 2 cases with endometrial cancer, one patient with renal neoplasm, one case with head and neck neoplasm, one patient with hepatic neoplasm, 4 patients with pancreatic neoplasm, 4 patients with gastric neoplasm, and 2 cases with lung cancer. It appeared statistically significant with a P value of 0.01.

Table 7 shows that within 96 cases with solid neoplasm, PET/contrast-enhanced CT changed the M stage of 9 patients (10.4%) as follows: 3 patients with breast cancer, one patient with endometrial cancer, one patient with ovarian tumor, one patient with colon neoplasm, one patient with stomach neoplasm, and 2 patients with pancreatic neoplasm. It appeared statistically significant with a P value of 0.02.

Table 8 shows that regarding the final design for the whole sample size of 120 patients (96 patients with solid neoplasm and 24 patient with lymphoma), PET/contrast-enhanced CT changed the final staging for 31 patients (25.8 %) as follows, one patient with lymphoma, 4 cases with breast cancer, 3 cases with colon cancer, 4 cases with endometrial cancer, one patient with ovarian neoplasm, 3 cases with renal neoplasm, , one patient with lung neoplasm, 3 cases with hepatic neoplasm, 6 cases with pancreatic neoplasm, 4 patients with gastric neoplasm and 1 patients with urinary bladder neoplasm. It appeared statistically significant with P value 0.01.

Table 1: age and sex distribution in 120 patients of the study population

Gender			Age	
	Number	Percentage	Range	Mean ± SD
Male	58	48.5 %	19 - 84	52.4 ± 22.7
Female	62	51.5 %	18 - 90	55.9 ± 27.3
Total	120	100 %	18 - 90	54.7 ± 25.9

Table 2: primary neoplasm distribution within 120 patients of the study population

Site of the Primary	Number of patients	Initial	Re-staging
Lymphoma	24	13	11
Breast	27	8	19

Colon	11	2	9
Endometrium	5	1	4
Ovaries	5	3	2
Head and Neck	8	6	2
Kidney	6	1	5
Lungs	2	1	1
Liver	7	2	5
Pancreas	13	7	6
Stomach	5	2	3
Testes	2	1	1
Urinary bladder	2	1	1
Soft tissue sarcoma	2	2	0
Skin	1	1	0
Total	120	51	69

Table 3: Final tumor stage within 96 patients of solid neoplasm

Solid neoplasm		Final tumor stage					Total
		Stage 0	Stage I	Stage II	Stage III	Stage IV	
PET/non-contrast CT	Initial	0	8	15	8	7	38
	Re-stage	39	2	4	1	12	58
	Total	39	10	19	9	19	96
PET/contrast-enhanced CT	Initial	0	6	8	14	10	38
	Re-stage	23	5	7	5	18	58
	Total	23	11	15	19	28	96

Table 4: Stages within 24 patients with lymphoma

Lymphoma initial staging	Lugano Classification					Total
	Stage I	Stage II	Stage III	Stage IV		
PET/non-contrast CT	3	2	4	4		13
PET/contrast-enhanced CT	3	1	5	4		
Lymphoma assessment of response	Deauville score					
	Score 1	Score 2	Score 3	Score 4	Score 5	
PET/non-contrast CT	1	5	0	3	2	11
PET/contrast-enhanced CT	1	5	0	3	2	

Table 5: T stage upstaging within 96 patients of the study population

Primary	Number of patients	Number of patients with same stage	Number of upstaged patients	Percentage	P-value
Breast	27	25	2	7 %	P value = 0.03
Colon	11	11	0	0 %	
Endometrium	5	3	2	40%	

Ovaries	5	5	0	0 %	
Head and Neck	8	8	0	0 %	
Kidney	6	4	2	33%	
Lungs	2	1	1	50%	
Liver	7	3	4	57%	
Pancreas	13	4	9	70%	
Stomach	5	4	1	20%	
Testes	2	2	0	0 %	
Urinary bladder	2	1	1	50%	
Soft tissue sarcoma	2	1	1	50%	
Skin	1	1	0	0 %	
Total	96	73	23	23.9 %	

Table 6: N-stage upstaging within 96 patients of the study population

Primary	Number of patients	Number of patients with same stage	Number of upstaged patients	Percentage	P-value
Breast	27	27	0	0 %	P value = 0.01
Colon	11	8	3	27%	
Endometrium	5	3	2	40%	
Ovaries	5	5	0	0 %	
Head and Neck	8	7	1	12.5%	
Kidney	6	5	1	16.6%	
Lungs	2	0	2	100%	
Liver	7	6	1	14%	
Pancreas	13	9	4	30.7 %	
Stomach	5	1	4	80%	
Testes	2	2	0	0 %	
Urinary bladder	2	2	0	0 %	
Soft tissue sarcoma	2	2	0	0 %	
Skin	1	1	0	0 %	
Total	96	78	18	18.7 %	

Table 7: M stage upstaging within 96 patients of the study population

Primary	Number of patients	Number of patients with same stage	Number of upstaged patients	Percentage	P-value
Breast	27	24	3	11%	P value = 0.02
Colon	11	10	1	9 %	
Endometrium	5	4	1	20%	

Ovaries	5	4	1	20%	
Head and Neck	8	8	0	0%	
Kidney	6	6	0	0%	
Lungs	2	2	0	0%	
Liver	7	7	0	0%	
Pancreas	13	11	2	15%	
Stomach	5	4	1	20%	
Testes	2	2	0	0%	
Urinary bladder	2	2	0	0%	
Soft tissue sarcoma	2	2	0	0%	
Skin	1	1	0	0%	
Total	96	87	9	9.5 %	

Table 8: final upstaging within 120 patients of the study population

Primary	Number of patients	Number of patients with same stage	Number of upstaged patients	Percentage	P-value
Lymphoma	24	23	1	4%	
Breast	27	23	4	14%	P value = 0.01
Colon	11	8	3	27%	
Endometrium	5	1	4	80%	
Ovaries	5	4	1	20%	
Head and Neck	8	8	0	0%	
Kidney	6	3	3	50%	
Lungs	2	1	1	50%	
Liver	7	4	3	42%	
Pancreas	13	7	6	46%	
Stomach	5	1	4	80%	
Testes	2	2	0	0%	
Urinary bladder	2	1	1	50%	
Soft tissue sarcoma	2	2	0	0%	
Skin	1	1	0	0%	
Total	120	89	31	25.8 %	

Case Presentation

Case 1 Fig 1 and 2		
History	57-year-old male patient proved pathologically to have pancreatic adenocarcinoma presented for initial staging	
	Staging in non-contrast study	**Staging in contrast study**
TNM	**T3N0M1**	**T4N0M1**
Stage	**Stage IV**	**Stage IV**
Cause of change in T stage		**Vascular invasion**
Cause of change in final stage		**None**

FDG PET/CT without contrast

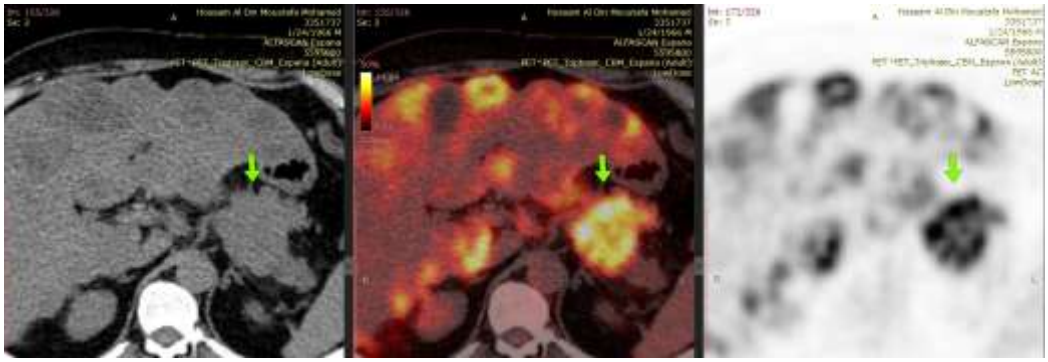

Fig 1: Non-contrast low dose CT, fused images and PET axial cuts demonstrates FDG-avid irregular exophytic pancreatic body mass

FDG PET/CT with contrast

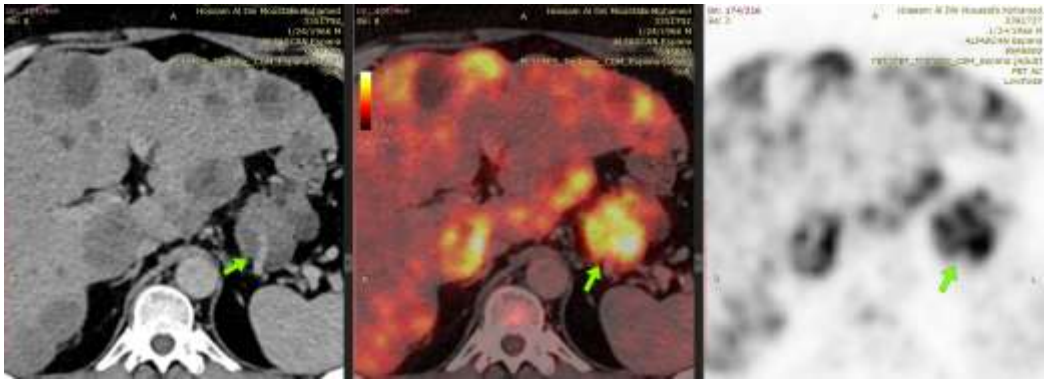

Fig 2: CT with contrast, fused images and PET axial cuts demonstrates FDG-avid irregular exophytic pancreatic body mass. The mass invades the adjacent splenic artery

DISCUSSION

Scialpi et al [8], looked after articles from January 2010 to July 2021 about the related role of PET/CT studies with contrast medium in the staging of different neoplastic lesions. They concluded that in the initial staging and monitoring of cancer cases, combined PET/ceCT allows accurate diagnostic information through providing both morphological and functional information derived from PET/ceCT imaging. They emphasized that both studies must be expressed in a single report, maintaining the specificities of each discipline to maximize the advantage in cancer cases.

Rodríguez-Vigil et al. [9] examined the agreement among contrast-enhanced PET/ceCT and unenhanced low-dose PET/CT in the identification of lesions and initial staging of NHL and HD. The research comprised forty-seven consecutive cases with biopsy-confirmed lymphoma (sixteen with HD and thirty-one with non-Hodgkin lymphoma), presenting for first staging. All cases had a PET/CT

examination comprising unenhanced low-dose CT for PET attenuation correction, the PET scan, and contrast-enhanced full-dose CT. There was complete consistency among low-dose PET/CT and PET/ceCT for the cervical nodal area. In only two cases, low-dose PET/CT revealed indeterminate outcomes for the abdominal and thoracic lymph nodes due to limited uptake in the infraclavicular and splenic hilar lymph nodes, correspondingly, which were difficult to identify on low-dose PET/CT nevertheless have been distinctly detected on full-dose PET/CT. Consequently, contrast-enhanced PET/ceCT revealed no indeterminate findings in these nodal areas. A statistically insignificant variance has been observed in the detection of extra-nodal sites between enhanced PET/ceCT and unenhanced low-dose PET/CT; nevertheless, enhanced PET/ceCT identified more sites in four out of forty-seven cases (P: 0.063). The four cases had gastric, renal, colonic, or pancreatic lymphomatous illness, identifiable as an elevated mass or region inside the viscera on enhanced PET/ceCT, but not detectable on unenhanced low-dose PET/CT. They determined that, whereas contrast-enhanced PET/ceCT identified a greater number of extra-nodal locations affected by lymphoma compared to unenhanced low-dose PET/CT, this distinction didn't achieve statistical significance. In total, the diagnostic enhanced-CT component of the PET/ceCT trial yielded additional data in only eight cases (seventeen cases), comprising two nodal lesions, four extra-nodal lesions, and two incidental results. Moreover, these additional results resulted in an alteration in stage for only one case (upstaged by full-dose PET/CT). They asserted that although the distinction in additive value of full-dose PET/CT is statistically minor, it seems to enhance the radiologist's confidence in lesion identification.

An investigation conducted by **Nakamoto et al. in [10]** indicated that PET/ceCT is beneficial in specific clinical situations, providing enhanced diagnostic accuracy; however, patients when an appropriate diagnosis has been achieved only with PET/ceCT were rare. For follow-up therapy, they indicated that the diagnostic performance of both approaches, utilizing either PET/ceCT or low-dose PET/CT, was similar. The authors determined that intravenous contrast isn't always required for post-therapeutic monitoring of malignant lymphoma when PET/CT is accessible and must be utilized only in specific undetermined patients.

One hundred and twenty cases (age range: thirty-eight to eighty-seven; mean: fifty-nine) with previously treated, histopathologically confirmed ovarian tumors had PET/CT tests with intravenous contrast agent at the PET Center for potential recurrence, as reported in a 2008 study by **Kitajima, K., et al.[11]** Pathological analysis and a clinical monitoring investigation of an imaging modality showed that 46 of the 120 cases had a recurrence or distant metastases. PET/CECT properly identified four individuals whose results were ambiguous on NC PET/CT. Both PET/CECT and NC PET/CT had four false-negative patients. A patient-based study revealed that PET/CECT had a sensitivity of 86.9% (40/46), specificity of 95.9% (71/74), and accuracy of 92.5% (111/120), whereas NC PET/CT had a sensitivity of 78.3 percent (36/46), specificity of 95.0 percent (70/74), and accuracy of 88.3% (106/120). There were statistically significant differences between PET/CECT and NC PET/CT in terms of sensitivity (p-value equal 0.0005), specificity (p-value equal to 0.023), and accuracy (p = 0.0001). It was determined that integrated PET/CECT is a more accurate imaging modality with better confidence for evaluating recurrence of ovarian cancer compared to an NC PET/CT scan, and that it also minimizes the incidence of ambiguous interpretations reported on NC PET/CT scans. When evaluating cases had ovarian cancer, PET/CECT has the potential to be a "one-stop-shopping" scan.

Morbelli et al. [12] found that the value of PET/ceCT over low-dose PET/CT is mainly for intraabdominal malignancy and head and neck tumors. For the former, they reported a sensitivity and specificity of PET/ceCT for GIT tumors of 95% and a specificity of 89.5% versus 71.25% and 84.25%, respectively, for low-dose PET/CT. This elevated sensitivity and specificity denote the ability of PET/ceCT to significantly reduce the false positive and false negative outcomes detected by low-dose PET/CT in abdominal lesions. These results reinforced our results about the significantly exaggerated upstaging value of PET/CE CT in intraabdominal lesions, where they show the highest change in T, N, M, and the final TNM upstaging. This information strongly underlines the importance of strictly selecting cases for the PET/ceCT.

CONCLUSION

Contrast-enhanced PET/CT (cePET/CT) offers little additional benefit for staging lymphoma compared to low-dose PET/CT, as it doesn't change the disease stage in over 95% of cases. However, for solid tumors, CePET/CT is highly valuable. It leads to upstaging of the final TNM stage in approximately one-third of patients. This effect is most significant in intra-abdominal cancers, where over 80% are upstaged. The technique is equally effective for both initial restaging and staging. Therefore, routine use of PET/CT is recommended for solid tumors to ensure accurate staging and guide precise treatment strategies.

RECOMMENDATIONS: Further research is recommended to evaluate the added value and diagnostic performance of contrast-enhanced PET/CT over low-dose PET/CT. Studies should focus on specific tumor types, especially head and neck cancers, and confirm findings with pathology or follow-up to clarify the technique's true benefit in different malignancies.

LIMITATION: The main limitation in our research is the relatively reduced number of cases with certain neoplasms. The inclusion of different neoplasms with different histopathologies and variable biological behavior.

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