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P. Decazes, S. Thureau, R. Modzelewski, M. Damilleville-Martin, P. Bohn, et al.. Benefits of positron emission tomography scans for the evaluation of radiotherapy. *Cancer/Radiothérapie*, 2020, 24 (5), pp.388-397. 10.1016/j.canrad.2020.02.007 . hal-02922525

HAL Id: hal-02922525

<https://hal.science/hal-02922525>

Submitted on 18 Jul 2022

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Benefits of positron emission tomography scans for the evaluation of radiotherapy

Intérêt de la tomographie par émission de positrons pour l'évaluation de la radiothérapie

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Conflict of interest

None.

Summary

The assessment of tumour response during and after radiotherapy determines the subsequent management of patients (adaptation of treatment plan, monitoring, adjuvant treatment, rescue treatment or palliative care). In addition to its role in extension assessment and therapeutic planning, positron emission tomography combined with computed tomography provides useful functional information for the evaluation of tumour response. The objective of this article is to review published data on positron emission tomography combined with computed tomography as a tool for evaluating external radiotherapy for cancers. Data on positron emission tomography combined with computed tomography scans acquired at different times (during, after initial and after definitive [chemo-]radiotherapy, during post-treatment follow-up) in solid tumours (lung, head and neck, cervix, oesophagus, prostate and rectum) were collected and analysed. Recent recommendations of the National Comprehensive Cancer Network are also reported. Positron emission tomography combined with computed tomography with (¹⁸F)-labelled fluorodeoxyglucose has a well-established role in clinical routine after chemoradiotherapy for locally advanced head and neck cancers, particularly to limit the number of neck lymph node dissection. This imaging modality also has a place for the

evaluation of initial chemoradiotherapy of oesophageal cancer, including the detection of distant metastases, and for the post-therapeutic evaluation of cervical cancer. Several radiotracers for positron emission tomography combined with computed tomography, such as choline, are also recommended for patients with prostate cancer with biochemical failure. (¹⁸F)-fluorodeoxyglucose positron emission tomography combined with computed tomography is optional in many other circumstances and its clinical benefits, possibly in combination with MRI, to assess response to radiotherapy remain a very active area of research.

Keywords

Radiotherapy, positron emission tomography, monitoring, therapeutic response

Résumé

L'évaluation de la réponse tumorale pendant et après la radiothérapie détermine la suite de la prise en charge des patient (adaptation du plan de traitement, surveillance, traitement adjuvant, traitement de sauvetage ou soins palliatifs). En plus de son rôle dans le bilan d'extension et le planning thérapeutique, la tomographie par émission de positrons combinée à la tomodensitométrie fournit des informations fonctionnelles utiles pour l'évaluation de la réponse tumorale. L'objectif de cette revue est de compiler et résumer des données publiées sur la tomographie par émission de positrons combinée à la tomodensitométrie en tant qu'outil d'évaluation de la radiothérapie externe des cancers. Des données sur la tomographie par émission de positrons combinée à la tomodensitométrie acquise à différents moments (pendant, après les [chimio]radiothérapies initiale et définitive, et au cours du suivi post-traitement) dans les tumeurs solides (poumon, tête et cou, col de l'utérus, œsophage, prostate et rectum) ont été recueillies et examinées. Des recommandations récentes du National Comprehensive Cancer Network sont également rapportées. La tomographie par émission de positrons combinée à la tomodensitométrie au (¹⁸F)-fluorodésoxyglucose a un rôle bien établi en routine clinique après la chimioradiothérapie des cancers de la tête et du cou localement avancés, notamment pour limiter le nombre de curages ganglionnaires cervicaux. Cette modalité d'imagerie a également une place pour l'évaluation de la chimioradiothérapie initiale du cancer de l'œsophage, notamment pour détecter des métastases à distance, et pour l'évaluation post-thérapeutique des cancers du col de l'utérus. Plusieurs radiotraceurs utilisés pour la tomographie par émission de positrons combinée à la tomodensitométrie, comme ceux à la choline, sont également recommandés pour les patients atteints d'un cancer de la prostate présentant un échec biochimique. La tomographie par émission de positrons combinée à la tomodensitométrie au (¹⁸F)-fluorodésoxyglucose est facultative pour de nombreuses autres indications et la détermination des avantages cliniques de l'évaluation de la réponse tumorale par cette technique d'imagerie, éventuellement en association avec l'IRM, demeure un domaine de recherche très actif.

Mots clé

Radiothérapie, tomographie par émission de positons, suivi, réponse thérapeutique

1. Introduction

Radiotherapy is a major modality for the treatment of many cancers. One of the key points is the identification of the target volume(s) to be treated. Anatomical imaging, including computed tomography (CT) but also magnetic resonance imaging (MRI), has a fundamental role in locating the lesions to be treated and the organs to be preserved.

Functional positron emission tomography imaging combined with computed tomography (PET/CT), mainly with (^{18}F)-fluorodeoxyglucose (^{18}FDG), also has a well-established role before radiotherapy for initial extension assessment, particularly for lung and oesophageal cancers, and for radiotherapy planning, including non-small cell lung cancer, head and neck cancer, lymphoma and oesophageal cancer (1). PET/CT is also interesting for assessing tumour response, as the metabolic response may be earlier than the anatomical response, with the ^{18}FDG uptake decreasing earlier than the tumour volume (2). However, PET/CT performed during or after radiotherapy may also be affected by treatment-related changes, such as radiation-induced inflammation uptake, potentially compromising the analysis (3).

The tumour response evaluated during radiotherapy offers the opportunity to adapt the treatment planning to a reduced target volume, to determine sub-volumes possibly defined by biological properties (e. g. proliferation or hypoxia) and to spare more organs at risk (adaptive radiotherapy). The evaluation of the tumour response after radiotherapy also determines the subsequent steps of the patient's management (monitoring, adjuvant or salvage treatment, palliative care, etc.).

The goals of PET/CT differ according to the timing of the examination compared to the radiotherapy. These different times, illustrated in Figure 1, are:

- PET/CT during radiotherapy (interim evaluation): the objective is to modify the radiotherapy planning according to variations in volume or tumour metabolism. The time window is rather narrow, as too early PET/CT may not detect the tumour response, while too late examination may be altered by post-therapeutic inflammation while limiting the significance of a possible change in the radiotherapy plan.
- PET/CT after initial (chemo)radiotherapy to assess response and adapt subsequent treatment with, for example, the choice of a "watch and wait" policy rather than planned surgery in case of a complete response.

- PET/CT after exclusive (chemo)radiotherapy to assess response and detect early failure, at least 3 months after radiotherapy for most cancers.
- PET/CT during follow-up to detect and/or localize a relapse.

This review, updating a previous work (4), focuses on PET/CT when it is performed during radiotherapy, at the end of preoperative radiotherapy, after radiotherapy completion and during follow-up. As far as possible, recent recommendations from the National Comprehensive Cancer Network (NCCN) are reported for the various indications and are summarized in Table 1. We did not cover PET/CT after initial chemotherapy without radiotherapy, brain tumours, lymphomas and metastases.

2. PET/CT during radiotherapy (interim evaluation)

The evaluation of tumour response during (chemo)radiotherapy may pave the way for: 1/ reduction of target volumes in the event of tumour regression, 2/ reduction of the radiotherapy dose in sensitive tumours or 3/ increase in the intensity of treatment (total dose, acceleration of radiotherapy, salvage surgery...) in resistant tumours (5). In practice, the radiotherapy planning would be adapted ("adaptive radiotherapy") to the tumour response by redefining the target volume and increasing the total dose ("boost") or dose per fraction with a maintained constant treatment time ("accelerated boost"). These adaptations are possible thanks to *intensity-modulated radiotherapy*, where the doses delivered are of variable intensity. With this technique, complex and deliberately heterogeneous dose distributions can be obtained that target form and biological subvolume (precisely adapt to the biologic target volume). Ideally, information on tumour response is obtained early enough so that a significant part of the radiotherapy can be modified (6). We present the results obtained in lung, oesophageal and head and neck cancers.

2.1. Lung

Concomitant chemoradiotherapy remains the standard treatment for locally advanced non-operable non-small cell lung cancer, with overall survival remaining low (7,8). ¹⁸F¹⁸FDG PET/CT is commonly used for initial staging.

PET/CT can be performed during radiotherapy as confirmed by the analysis of 53 ¹⁸F¹⁸FDG serial PET/CT performed in ten patients with non-small cell lung cancer showing the absence of significant artefacts induced by radiotherapy (9). A systematic review of 21 series (627 patients) concluded that the tumour response to ¹⁸F¹⁸FDG PET/CT during radiotherapy ("interim PET/CT") could be used as a predictor of local control and survival in patients with non-small cell lung cancer (10). A decrease in the uptake of ¹⁸F¹⁸FDG in the primary tumour was associated with better local control and long-term survival. This was also demonstrated by our team, which prospectively included 52 patients in a multicentre, strictly quality-controlled study comparing ¹⁸F¹⁸FDG PET/CT before and during the fifth week of radiotherapy (2Gy per fraction, 10Gy per week). The maximum SUV (SUV_{max}) at 5 weeks

was the only predictor of death or tumour progression at 1 year (odds ratio [OR] of 1.97, 95% confidence interval [95% CI]: 1.25-3.09, $p = 0.003$) in multivariate analysis. A value of SUVmax at 5.3 has a sensitivity of 70% and specificity of 92% to predict tumour progression or death at one year (5). However, the systematic review mentioned above highlighted the great heterogeneity between studies, for example with regards to patient selection criteria, treatment modalities, PET/CT acquisitions, timing and predictive parameters studied (10).

However, adaptive radiotherapy guided by PET/CT is feasible and would allow for a significant reduction in doses to normal tissues compared to traditional planning techniques (11).

A study involving 102 patients with 30 patients who received a dose adjustment according to the mid-treatment PET showed that patients who received adaptive radiotherapy had a 5-year survival rate 19% better than standard radiotherapy (12). However, the interoperator reproducibility of pertherapeutic tumour segmentation may be limited, and this reproducibility may be improved by an easily applicable SUVmax-based segmentation method that can be used for replanning (13).

Other radiotracers have been studied in non-small cell lung cancer with a particular interest in tumour radiobiology. This is notably the case of ^{18}F -labelled misonidazole (^{18}F -miso) which is a tumour hypoxia tracer, strongly associated with in vitro radioresistance or ^{18}F -fluorothymidine (^{18}FLT) which indicates an active proliferation of tumour cells, potentially overcome by accelerated radiotherapy. A pilot study conducted in five patients with non-small cell lung cancer showed that PET/CT performed in series with ^{18}FDG , ^{18}F -miso and ^{18}FLT could be done almost simultaneously before and during radiotherapy (14). A larger prospective multicentric series (79 patients) confirmed the poor prognosis of hypoxic tumours defined by ^{18}F -miso. In this trial, there was a significant decrease in ^{18}FDG and ^{18}F -miso during treatment, and it was demonstrated that a selective increase in the radiotherapy dose targeted at ^{18}F -miso-avid subvolumes was possible without increasing toxicity [12, 13].

In summary, interim ^{18}FDG PET/CT is a predictor of local control and survival in patients with non-small cell lung cancer. This examination is not recommended as a routine clinical procedure but recent results, to be confirmed on larger cohorts, show the interest of adaptive radiotherapy based on the results of this PET scan.

2.2. Oesophagus

Oesophageal cancers have an overall poor prognosis. Most tumours are locally advanced (grade T3 or above) at the time of diagnosis. Preoperative treatment is indicated in operable patients with locally advanced oesophageal cancer (17,18), this treatment allowing a complete anatomopathological response on the surgical piece for approximately 40% of patients (19,20). These patients with complete anatomopathological response may thus not be treated surgically but monitored. Assessment

of tumour response during initial chemoradiotherapy would identify patients with insufficient response, candidates for early surgery, and those with significant response, in whom surgery could be delayed or even avoided. However, in a study of 37 patients, the ^{18}F FDG SUVmax variation at two weeks from the start of treatment was not sufficiently reliable to predict histopathological response (ROC accuracy: 67%), likely due to radiation-induced inflammation (20). Similarly, our team showed in 57 patients with squamous cell carcinoma that, although the uptake of ^{18}F FDG (SUVmax), metabolic tumour volume and total lesion glycolysis decreased at 21 days in PET/CT, the tumour response at 3 months and 1 year was more effectively predicted by the parameters measured on PET/CT performed before treatment (21). This is consistent with our observation that the high uptake areas of ^{18}F FDG in the pretreatment PET/CT indicate preferential relapse sites, these sub-volumes being a potential target for increased radiotherapy doses (22).

In a meta-analysis of four studies investigating the prediction of response by interim ^{18}F FDG PET, the overall sensitivity, specificity and odds ratio were 85% (95% CI: 76 – 91), 59% (95% CI: 48 – 69) and 6.82% (95% CI: 2.25 – 20.72), respectively (23). The authors concluded that interim PET/CT should not be routinely used to guide therapeutic strategy in patients with oesophageal cancer (23).

To date, possible therapeutic adjustments based on variations in the ^{18}F FDG uptake during radiotherapy have not been studied in randomized trials. PET/CT during initial chemoradiotherapy for oesophageal cancer is not recommended as a routine clinical procedure.

2.3. Head and neck

Controversial results have been reported for ^{18}F FDG PET/CT during chemoradiotherapy in patients with head and neck squamous cell carcinoma (24–27). For example, in a series of 26 patients, no significant correlation was observed between changes in ^{18}F FDG uptakes (primary tumour and lymph nodes) at 2 weeks and locoregional control, nor between the overall metabolic response and clinical outcomes (27). In 40 other patients, the sensitivity of PET/CT at 47 Gy (week 4) was low, with the absence of a significant correlation between metabolic response and overall survival attributed to radiation-induced inflammation (26). On the other hand, a reduction of more than 50% in SUVmax at weeks 1 or 2 (radiotherapy dose administered between 10 and 20 Gy) was reported as a potential prognostic marker in 37 patients (25). A systematic review (25 series) concluded that most studies were in favour of PET/CT to predict, during treatment, the response to chemo-radiotherapy, while highlighting its low predictive value (28).

Other radiotracers have been investigated in patients with squamous cell carcinoma of the head and neck. In a prospective study of 16 patients, three ^{18}F -miso PET/CT were performed at weeks 0, 2 and 5 to explore temporal changes in tumour hypoxia during chemoradiotherapy. The mean

SUVmax/SUVmean of background (TBRmax) decreased significantly from 1.94 to 1.57 (week 2) and 1.27 (week 5), with this decrease being associated with better clinical outcomes (29). Similar results have been reported with ¹⁸F-fluoroazomycin arabinoside (Faza), another tracer of hypoxia (30). In addition, changes in the uptake of ¹⁸F-FLT were reported in advance of the tumour's volume response (31,32), with increased ¹⁸F-FLT uptake after treatment associated with disease recurrence or persistence of residual tumour (32).

In summary, the early tumour response to chemoradiotherapy of head and neck squamous cell carcinomas can be assessed by ¹⁸FDG PET/CT at week 2 during treatment, with controversial results regarding its predictive/predictive value. It remains to be seen whether a change in therapeutic strategy based on tumour response would bring clinical benefit.

3. PET/CT after initial chemoradiotherapy

Initial chemoradiotherapy (neoadjuvant) is part of the standard management of locally advanced locally operable rectal and oesophageal cancers (18,33). Since a complete anatomopathological response is a possibility after this initial treatment, some patients may benefit from a "watch and wait" strategy rather than surgery if the tumour response is properly assessed. In addition, tumour assessment after initial chemoradiotherapy can also help to plan the surgical approach and detect a patient who has become inoperable, for example as a result of metastasis.

3.1. Rectum

For locally advanced rectal cancer, the standard approach is preoperative chemoradiotherapy followed by surgery. In the case of a complete clinical response after chemoradiotherapy, a "watch and wait" policy may be considered in patients at high risk of surgery (33). Initial chemoradiotherapy gives a complete anatomopathological response rate of 15 to 27% in patients with locally advanced rectal cancer (34,35). "Definitive" chemoradiotherapy has become an option in the event of complete clinical remission after initial chemoradiotherapy in high-risk surgical patients, but only if the response assessment is sufficiently accurate (33). A systematic review gathered current data on MRI with diffusion-weighted imaging (DWI) and ¹⁸FDG PET/CT. Both MRI and PET/CT had high negative predictive values to determine complete anatomopathological response, but did not have the specificity and positive predictive values necessary to safely select patients (35).

For MRI, a non-randomized study compared 129 patients followed after a complete clinical response with 228 patients who underwent surgery for an incomplete response. All patients had post-chemoradiotherapy MRI to confirm their clinical response. A local relapse occurred in 44 (34%) non-operated patients and 36 of the 41 relapses without distant disease were treated by salvage surgery. A paired analysis of surgical and non-surgical patients (109 patients in each group) reported an improvement in colostomy-free survival at 3 years in non-surgical patients (hazard ratio [HR] = 0.45,

95% CI: 0.31-0.63, $p < 0.0001$; absolute difference 26%, 95% CI: 13-39). Differences in overall three-year survival were not considered statistically significant (96%, 95% CI: 88-98 vs. 87%, 95% CI: 77-93) (36).

Regarding PET/CT, a systematic review found that SUVmax after chemoradiotherapy was significantly associated with histological response in 6 studies. The SUV variation (Δ SUVmax as a % of baseline SUVmax) was also significantly different between response groups in seven studies, showing that PET/CT could have a role in predicting outcome for locally advanced rectal cancers (37).

However, to date, according to the American recommendations of NCCN 2.2019, during the evaluation after neoadjuvant chemoradiotherapy, only the thoracic CT, abdominal CT or MRI and pelvic MRI are recommended (38), the possibility of improving results by combining PET/CT with 18 FDG, possibly in combination with MRI, has yet to be clinically demonstrated.

3.2. Oesophagus

Approximately 30% of patients with oesophageal cancer treated with neoadjuvant chemoradiotherapy do not have any residual tumours on the surgical tissue and could avoid surgery (17). Non-invasive tools (CT, ultrasound endoscopy) do not accurately assess tumour response (39). Endoscopy with or without biopsy also does not accurately predict the histological tumour response (40). 18 FDG PET/CT was studied to identify tumours that responded to chemoradiotherapy and those that did not respond sufficiently. A meta-analysis of 6 series (out of 26 series with a total of 1,544 patients) showed that a complete PET/CT response 3 weeks after chemoradiotherapy was associated with a significant increase in overall survival and disease-free survival (HR = 0.51, 95% CI: 0.40 - 0.64, $p < 0.00001$ and 0.47, 95% CI: 0.38 - 0.57, $p < 0.00001$, respectively)(41). A prospective cohort of 138 consecutive patients comparing PET/CT with endoscopy to predict complete histological response found low sensitivity (57% and 24%, respectively) and low positive predictive value (27% and 28%, respectively) (42).

In summary, 18 FDG PET/CT does not reliably identify tumours in complete response after chemoradiotherapy, but may be useful for re-evaluation after chemoradiotherapy, particularly to exclude lymphatic and blood metastases (43). According to NCCN 2.2019, it is recommended between 5 and 8 weeks after the end of preoperative treatment (38). In case of a complete response, also present on upper gastrointestinal endoscopy with biopsy, esophagectomy (preferred in case of adenocarcinoma) or monitoring (recommendation category 2B) are recommended, with a preferred esophagectomy for patients with persistent local disease (38).

4. PET/CT after exclusive chemoradiotherapy

The assessment of tumour response at the end of exclusive (chemo)radiotherapy is useful for discussing, in the event of persistent disease, possible salvage treatment or palliative treatment. The

morphological response (tumour size in CT) may be several weeks or months delayed compared to changes in tracer uptake, and ^{18}F FDG PET/CT could provide a more accurate quantification of therapeutic response than anatomical changes determined by CT (44,45). However, radiotherapy and chemotherapy can cause inflammatory changes and high diffuse accumulation of ^{18}F FDG in the healthy tissues surrounding the tumour, producing false positive results (46). This limitation of post-therapeutic PET/CT imaging has limited its clinical use (47). The ideal time for the first ^{18}F FDG PET/CT examination after radiation therapy may depend on the type of cancer. High rates of false positive and false negative results have been reported when PET/CT was acquired too soon after the end of radiotherapy (46,48). We present studies on lung, head and neck and cervical cancers.

4.1. Lung

^{18}F -FDG PET/CT performed at the end of chemo-radiotherapy has an important prognostic value. A prospective study evaluated its long-term prognostic value when performed 14 weeks after chemoradiotherapy in 173 patients with stage III non-small cell lung cancer. Higher tumour SUVs (SUV_{peak} or SUV_{max}) have been associated with poorer survival, although a cut-off value for clinical practice could not be established (49). A secondary analysis of SUV measured in regional lymph nodes revealed that high residual absorption after treatment was associated with a poorer local and regional response (50).

A meta-analysis (five studies) reported that a higher SUV_{max} on post-therapeutic ^{18}F FDG PET/CT was associated with lower overall survival (HR = 1.32, 95% CI: 1.15 - 1.51) and lower local control (HR = 2.01, 95% CI: 1.16 - 3.46). After stereotactic radiotherapy for most stage I primary tumours, the hazard ratio for local control was 2.19 (95% CI: 1.34 - 3.60). The threshold values for separating high and low SUV_{max} values differed from one study to another (51).

^{18}F FDG PET/CT at the end of treatment is not routinely recommended for non-small cell lung cancer according to NCCN recommendations 7.2019 (38). If performed, it should not be performed until at least 3 months after radiotherapy to avoid false positive results due to radiation-induced lung disease (52). Persistent uptakes associated with radiation-induced lung disease can sometimes last 15 months after the end of treatment and justify a biopsy. Sequential and semi-quantitative ^{18}F FDG PET/CT could be useful to distinguish radiation-induced inflammation from tumour recurrence (53). An example of the PET/CT post-therapeutic evaluation of non-small cell lung cancer treated with chemoradiotherapy is shown in Figure 2.

4.2. Head and neck

In recent decades, strategies for treating advanced head and neck squamous cell cancers have gradually shifted from surgery to radiotherapy, which is often associated with chemotherapy (54,55). In a systematic review of 51 studies (2335 patients) on ^{18}F FDG PET/CT use to assess post-treatment

response, sensitivity, specificity, positive predictive value and negative predictive value for the primary site were 79.9%, 87.5%, 58.6% and 95.1%, respectively (56). These estimations for the cervical lymph nodes were 72.7%, 87.6%, 52.1% and 94.5%, respectively. Tests performed more than 12 weeks after the end of final treatment had a moderately higher diagnostic accuracy (56).

A prospective, randomized and controlled trial analysed 564 patients with N2-N3 disease and treated with systematic neck dissection after initial chemoradiotherapy (282 patients) or neck dissection only in the event of an incomplete/equivocal response to the PET/CT performed 12 weeks after the end of chemoradiotherapy. Fewer neck dissections (54 versus 221) were performed in the PET/CT-guided surveillance group, with similar rates of surgical complications in both groups (42% and 38%, respectively). At a median follow-up of 36 months, the overall survival rate at 2 years was 85% (95% CI: 81 – 89) in the monitored group and 82% (95% CI: 77 – 86) in the planned surgery group (57). In a prospective multicentric study including 152 patients and using a standardized analysis of ¹⁸FDG PET/CT performed 12 weeks after chemoradiotherapy, the negative predictive value of PET/CT was 92% (95% CI: 87 – 95) to predict either a negative anatomopathological result on dissection or a control after more than 12 months of follow-up (58). Standardized reports reduced the number of equivocal reports (15 to 3%, $p=0.003$) (58).

From now on, and in particular according to the recommendations of the NCCN (3.2019), ¹⁸FDG PET/CT performed 12 weeks after chemoradiotherapy for advanced head and neck squamous cell carcinoma is recommended in order to reduce the number of neck dissection. (38,59).

4.3. Cervix

For cervical cancer, patients with initial locoregional therapeutic failure can be treated with curative intent, hence the importance of post-therapeutic ¹⁸FDG PET for early detection of failure (48).

In a cohort of 92 women treated with external radiation, brachytherapy and concomitant chemotherapy, 65 (70%) complete ¹⁸FDG PET/CT responses were reported in 65 patients (70%), compared to 15 (16%) partial responses and 12 (13%) disease progression. The progression-free survival rates at 3 years were 78%, 33% and 0% respectively ($p<0.001$) (60). In a larger series of 328 patients from the same group, of 40 patients (12%) with a partial ¹⁸FDG PET/CT response, 14 (35%) had no confirmed failure after a median follow-up of 35 months, 15 (38%) had an isolated local failure and 11 (28%) had a distant failure (61). In other words, salvage surgery, if indicated for patients with partial response, would have been unnecessary for 25 patients (63%). In addition, 40 of 173 patients

(23%) had tumour recurrence (34 remotely) after a complete PET/CT response and 24 of 25 patients (96%) with progressive PET/CT disease had a metastatic disease.

According to the American Society of Clinical Oncology, ¹⁸FDG PET/CT at 3 months after chemoradiotherapy remains an option for patients at high risk of locoregional failure (62). In version 3.2019 of the NCCN recommendations, cervical cancer monitoring depends on the stage of the disease (38). For patients with stage IB3 cancer according to the International Federation of Gynaecology and Obstetrics (FIGO) or patients who have required postoperative radiotherapy or chemotherapy due to high risk factors, PET/CT performed 3 to 6 months after the end of treatment is possible (38). For patients with FIGO stage II-IV cancer, PET/CT (preferably) or an injected abdominal-pelvic CT scan is recommended within 3 to 6 months of the end of treatment, with pelvic MRI being optional (38). The role of PET/MRI remains experimental.

5. PET/CT during follow-up

In many cancers, ¹⁸FDG PET/CT is considered superior or equivalent to conventional modalities for the detection of local or distant recurrences. (63,64). The three limitations illustrated in non-small cell lung cancer are valid for other cancers: 1) local inflammatory changes and fibrosis after treatment lead to false positive results and modify the specificity of the technique, 2) detection of brain metastases by PET/CT has the same limitations as in the pretherapeutic assessment, 3) additional radiation exposure and higher medical costs due to PET/CT should be taken into consideration (63).

On the other hand, the overall strength of ¹⁸FDG PET/CT for the follow-up appears to be its high sensitivity and high negative predictive value.

In the following paragraphs, we present the value of PET/CT for the follow-up of cancers treated conventionally by radiotherapy (lung, head and neck, oesophagus, cervix and prostate cancers) but the results of the meta-analyses presented may also include the follow-up of cancers treated by surgery and chemotherapy.

5.1. Lung

A meta-analysis of 13 studies (1035 patients) concluded that ¹⁸FDG PET/CT was superior to conventional imaging techniques (CT, bone scan, MRI) to detect lung cancer recurrence. Sensitivity and specificity were 90% and 90% for ¹⁸FDG PET/CT, compared to 78% and 80% for conventional imaging techniques (65). A document review revealed changes in the management of 30 to 88% of patients followed by ¹⁸FDG PET/CT, based on prior clinical suspicions of recurrence (66). In patients with suspected recurrence, ¹⁸FDG PET/CT ruled out recurrence or metastasis in about one-quarter of

cases (66). The absence or low ^{18}F FDG uptake is considered a definitive indicator that there is no recurrence of lung cancer (53).

^{18}F FDG PET/CT is not recommended according to NCCN 7.2019 for the follow-up of patients with non-small cell lung cancer (38). ^{18}F FDG PET/CT may, however, be useful to study benign CT abnormalities (such as atelectasis, condensation and radiofibrosis) to differentiate them from active neoplastic disease. After radiotherapy, it is recommended to confirm histologically the suspicion of recurrence on ^{18}F FDG PET/CT because previously irradiated areas may remain intense for up to 2 years after irradiation (38). In the case of stereotactic radiotherapy, the diagnosis of recurrence may be difficult because benign inflammatory/fibrotic changes may remain ^{18}F FDG-avid for 2 years or more after treatment, emphasizing the importance of follow-up by a team experienced in such post-therapeutic effects, especially since some patients with localized recurrences after stereotactic radiotherapy may benefit from a new stereotactic surgical or radiotherapeutic treatment (38).

5.2. Head and neck

^{18}F FDG PET/CT is interesting for detecting recurrences accessible for curative surgery in the event of local-regional recurrence, second primary cancer or oligometastatic disease (67).

The performance of ^{18}F FDG PET/CT in detecting early recurrence or second primary cancer was compared retrospectively to a neck CT and physical examination/endoscopy in 99 patients. Sensitivity, specificity, positive and negative predictive values for detection of local and regional recurrence, remote recurrence and a second primary cancer were 100%, 87%, 57% and 100%, respectively, for ^{18}F FDG PET/CT, compared to 62%, 95%, 67% and 94%, respectively, for neck CT and 23%, 99%, 75% and 89%, respectively, for physical examination/endoscopy (64). In 19 patients with positive ^{18}F FDG PET/CT results, a significant change in disease management occurred, resulting in either salvage or systemic treatment (64).

A meta-analysis of 23 studies (2247 PET/CT) reported overall sensitivity and specificity of 92% and 87% respectively for recurrence detection (68). It has been suggested to combine early (12 weeks after chemoradiotherapy) and late (at 1 year) PET/CT to improve detection of recurrences (58). However, if ^{18}F FDG PET/CT is recognized as potentially useful in the event of a suspicion this examination is not recommended for systematic monitoring (69).

5.3. Oesophagus

Survival after a recurrence of oesophageal cancer is low (70). In a meta-analysis of eight studies (486 patients), the combined sensitivity and specificity of ^{18}F FDG PET/CT for the diagnosis of recurrence were 96% and 78% respectively (71). The high false positive rate justifies histopathological confirmation of the suspected recurrence of ^{18}F FDG (71).

According to NCCN 2.2019 recommendations, for patients with T1b cancer treated with chemoradiotherapy, in addition to endoscopic follow-up, imaging follow-up (injected thoracoabdominal CT or ^{18}F FDG PET/CT) should be considered every 6 to 9 months for the first two years and annually for up to 5 years. PET/CT is not indicated in the follow-up of other patients (38).

5.4. Cervix

Many systematic reviews and meta-analyses have been published concerning the diagnostic value of ^{18}F FDG PET(/CT) to diagnose cervical cancer recurrence [73–77]. Good sensitivity and specificity have been reported for ^{18}F FDG PET with or without CT, as the accuracy of CT is limited to detect recurrent cervical cancer [77]. For example, the pooled sensitivity and specificity of ^{18}F FDG PET to detect locoregional recurrence were 82% and 98% respectively (73).

However, the addition of ^{18}F FDG PET/CT for routine surveillance (clinical examination, CT, MRI) has been evaluated as more costly with only a minimal increase in efficacy, including in women with persistent and recurrent cervical cancer. The use of ^{18}F FDG PET/CT for systematic surveillance has thus been criticized (72,74,77), and the use of imaging, including PET/CT, for surveillance is limited and reserved for exploration in the event of symptoms or abnormalities on clinical examination (78). NCCN (version 5.2019) recommends PET/CT to be performed if there is a suspicion of recurrence or metastasis and pelvic MRI also be considered in this case (38).

5.5. Prostate

^{18}F FDG PET/CT plays a very limited role in prostate cancer patients, including in the localization of the disease in patients with biochemical failure after treatment [80]. PET/CT with radiolabelled acetate and radiolabelled choline can explore prostate cancer, with the majority of studies using radiolabelled choline [81]. Choline can carry a radioelement ^{11}C (half-life 20 minutes) or ^{18}F (half-life 110 minutes). The physiological biodistributions of ^{11}C -choline and ^{18}F -fluorocholine are generally similar, with the exception of the lower excretion of the renal tracer of ^{11}C -choline (reduced accumulation in the bladder) [81].

A meta-analysis (19 studies, 1555 patients) of PET/CT with radiolabelled choline in patients with biochemical relapse reported overall sensitivity and specificity of 86% and 93% for all disease sites (prostatic bed, lymph nodes and bones), 75% and 82% for prostate recurrence, 100% and 82% for ganglion metastases [82].

The diagnostic performance of choline PET/CT depends on serum prostate specific antigen levels and kinetics. In a systematic review of 14 articles, the overall combined detection rate of choline PET/CT was 58%, increasing to 65% when the serum prostate specific antigen concentration doubling time was 6 months or less, to 71% when the serum prostate specific antigen concentration increase

kinetics was more than 1 ng/mL per year and 77% when it was more than 2 ng/mL per year [83]. Another radiotracer, ¹⁸F-fluciclovine, has results comparable to choline PET with an 85% match [84].

New tracers are under development, but they are not yet fully approved by the regulatory authorities (French or American), are not readily available and are considered experimental products at this time. For example, imaging of prostate specific membrane antigen using gallium-68 can provide better detection of recurrences at lower serum prostate specific antigen levels with comparable sensitivity and specificity and better detection rates (84,85).

According to the recommendations of NCCN 4.2019, the use of PET/CT or PET/MRI with choline or fluciclovine may be used in cases of biochemical recurrence to detect small volumes of the disease in soft tissue or bone, with histological confirmation recommended taking into account the risk of false positive [38]. Indeed, it has been demonstrated the value of localized treatment in case of oligoprogression.

6. Conclusion

We have seen in this review that, in many cancers, PET/CT is potentially useful for interim evaluation during radiotherapy, at the end of neo-adjuvant radiotherapy, at the end of final treatment or during follow-up. Table 1 is a summary table of the usefulness of the indications.

Despite this usefulness, cost-effectiveness must generally be taken into account before deciding to perform a PET/CT scan. In addition, greater standardization of evaluation parameters must be achieved. If combined PET/MRI has been evaluated only to a limited extent in this area, it is hoped that the two techniques will have a synergistic effect for a better therapeutic evaluation. Finally, the recommendations in this field evolve regularly and require regular updating.

Author contribution

PD: conceptualization, data curation, writing - original draft; ST: writing - review and editing; RM, PB: resources; MDM: data curation, visualization; PV: conceptualization, supervision, writing - review and editing.

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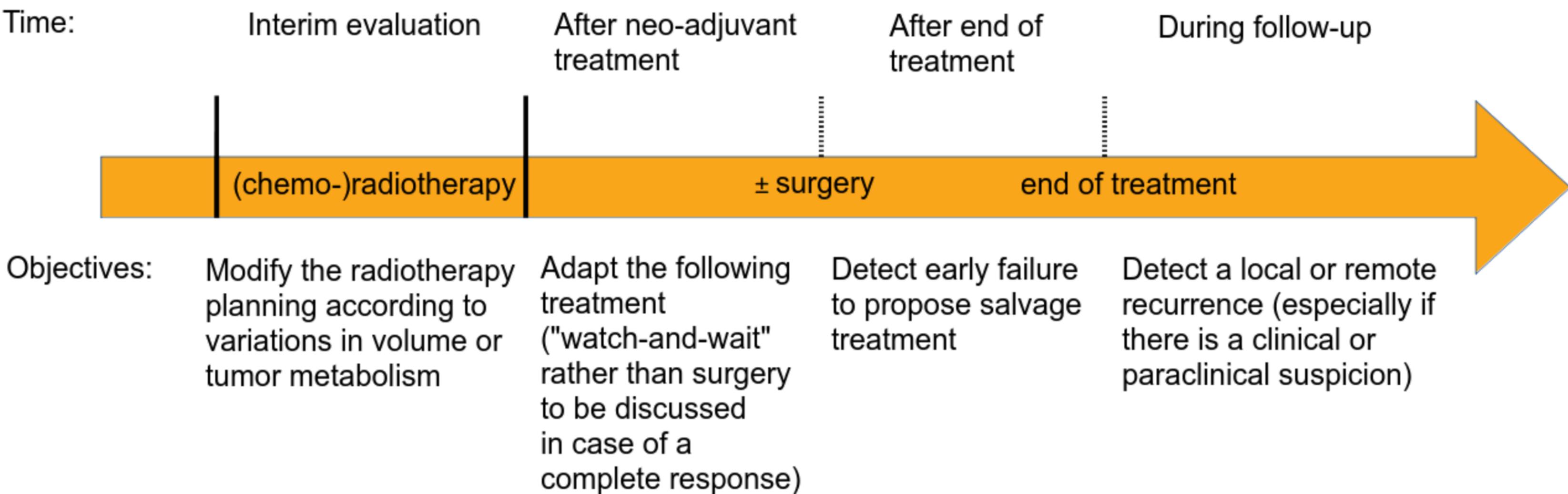
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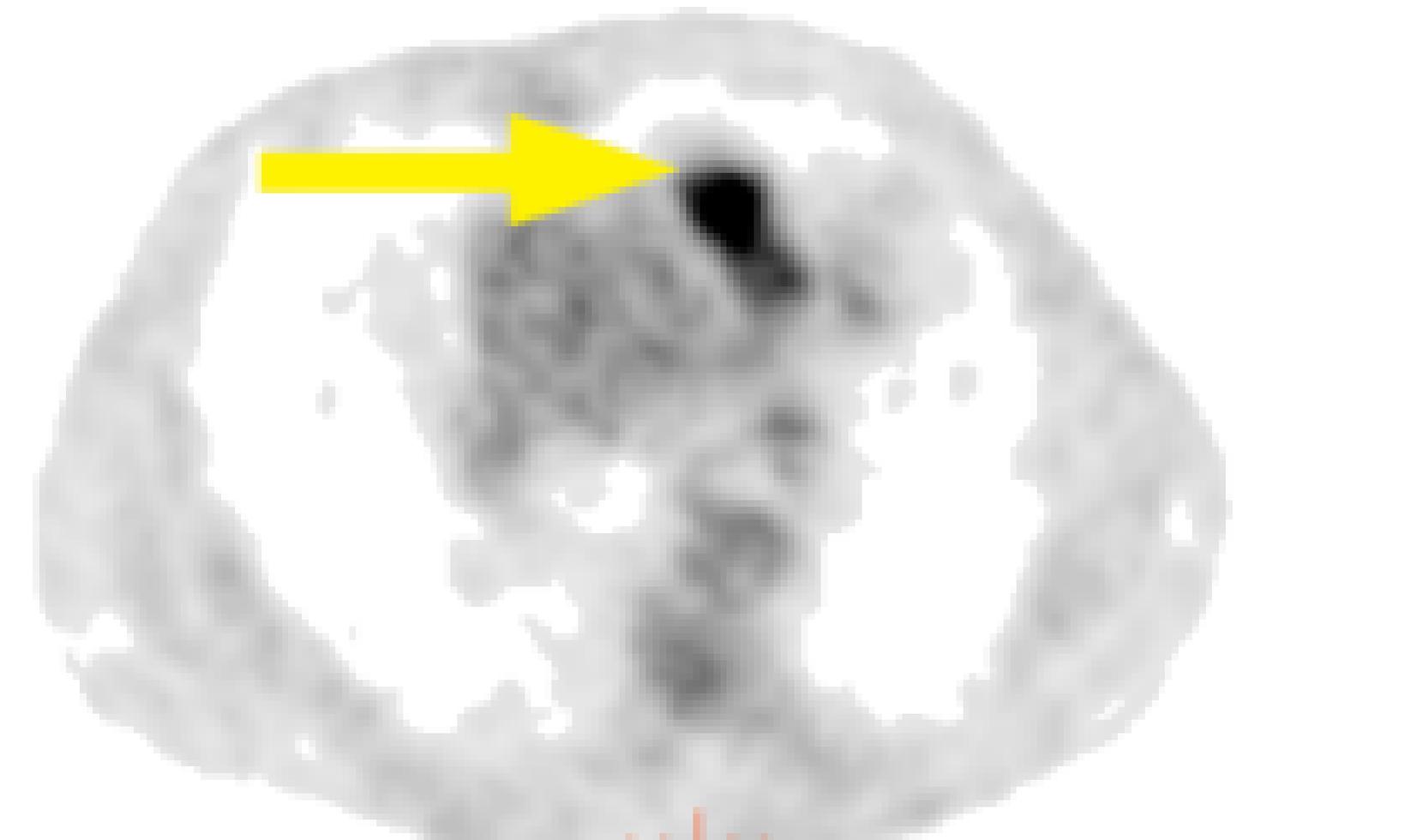
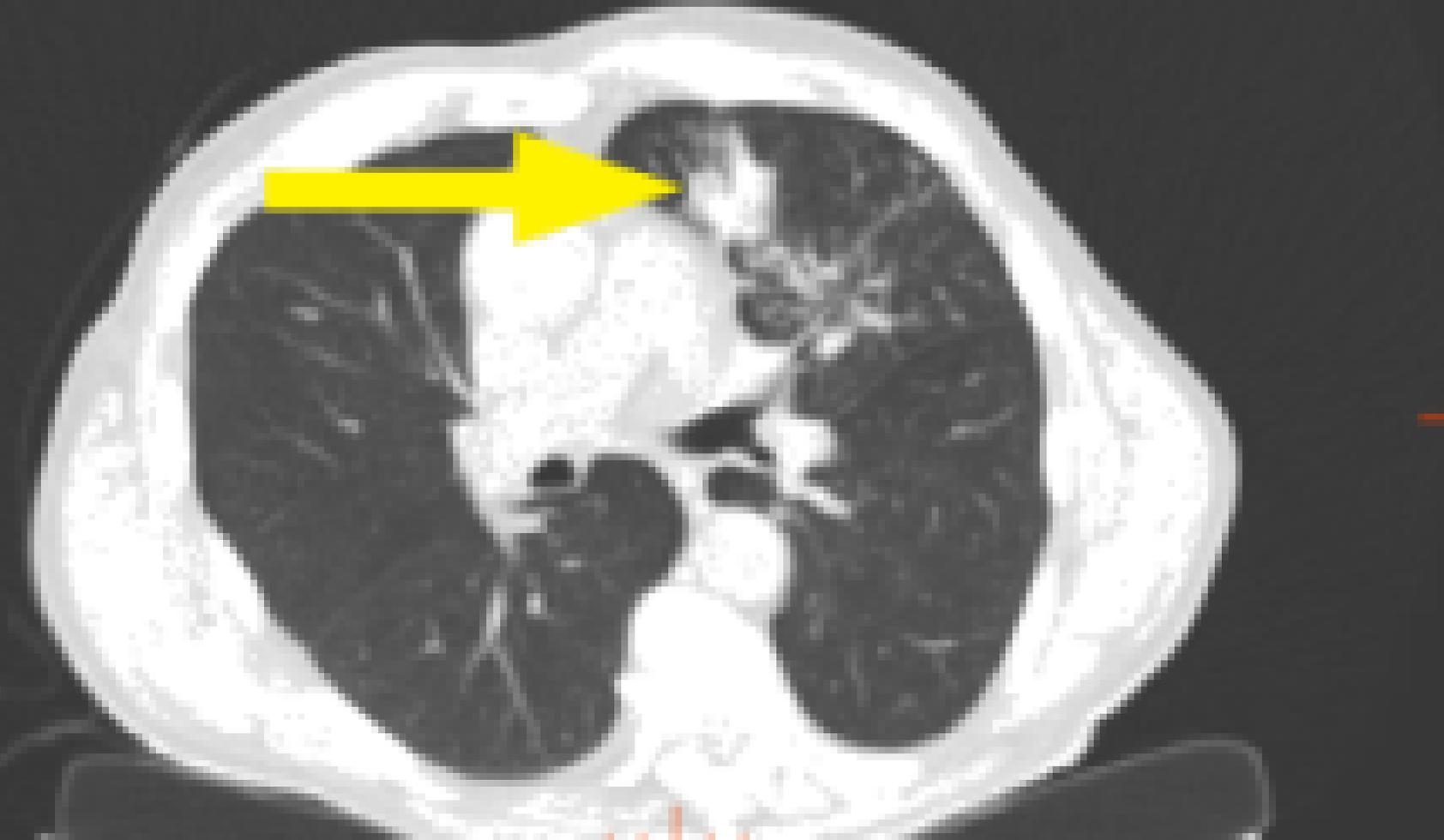
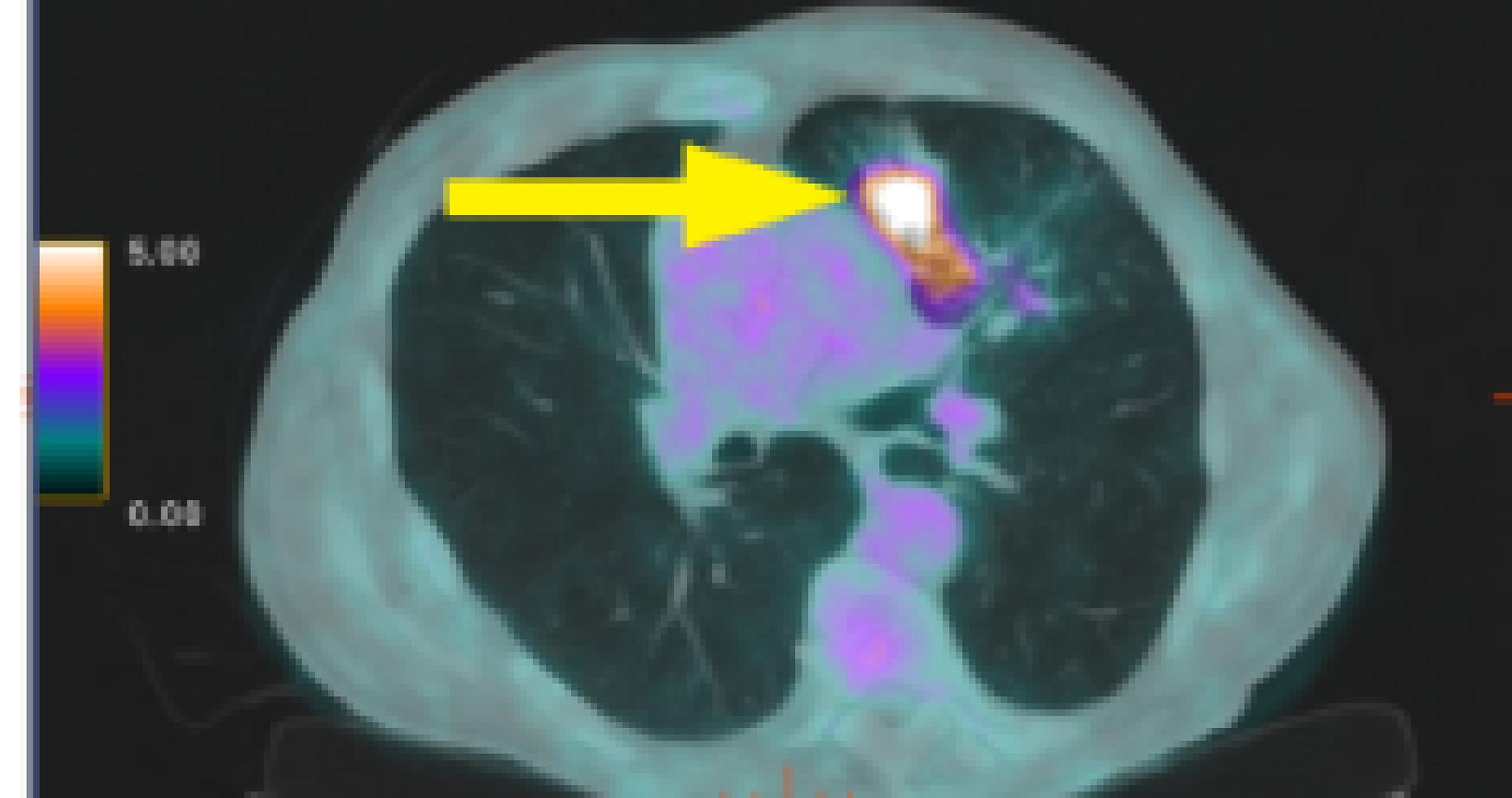
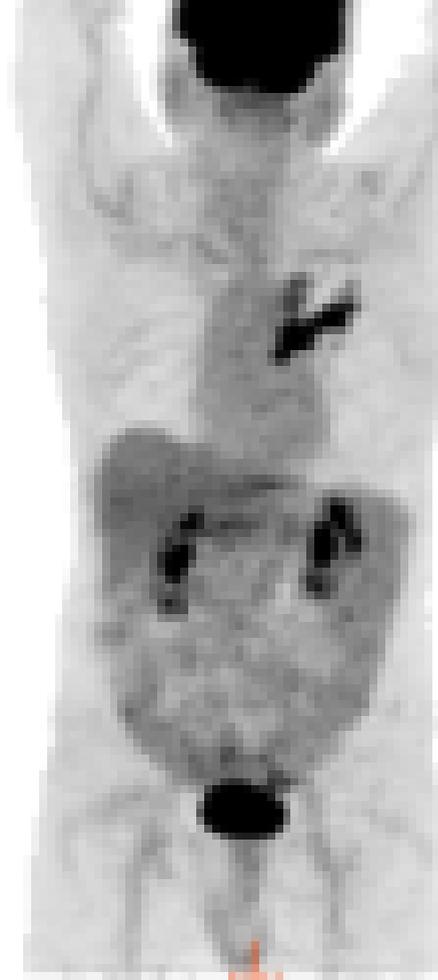
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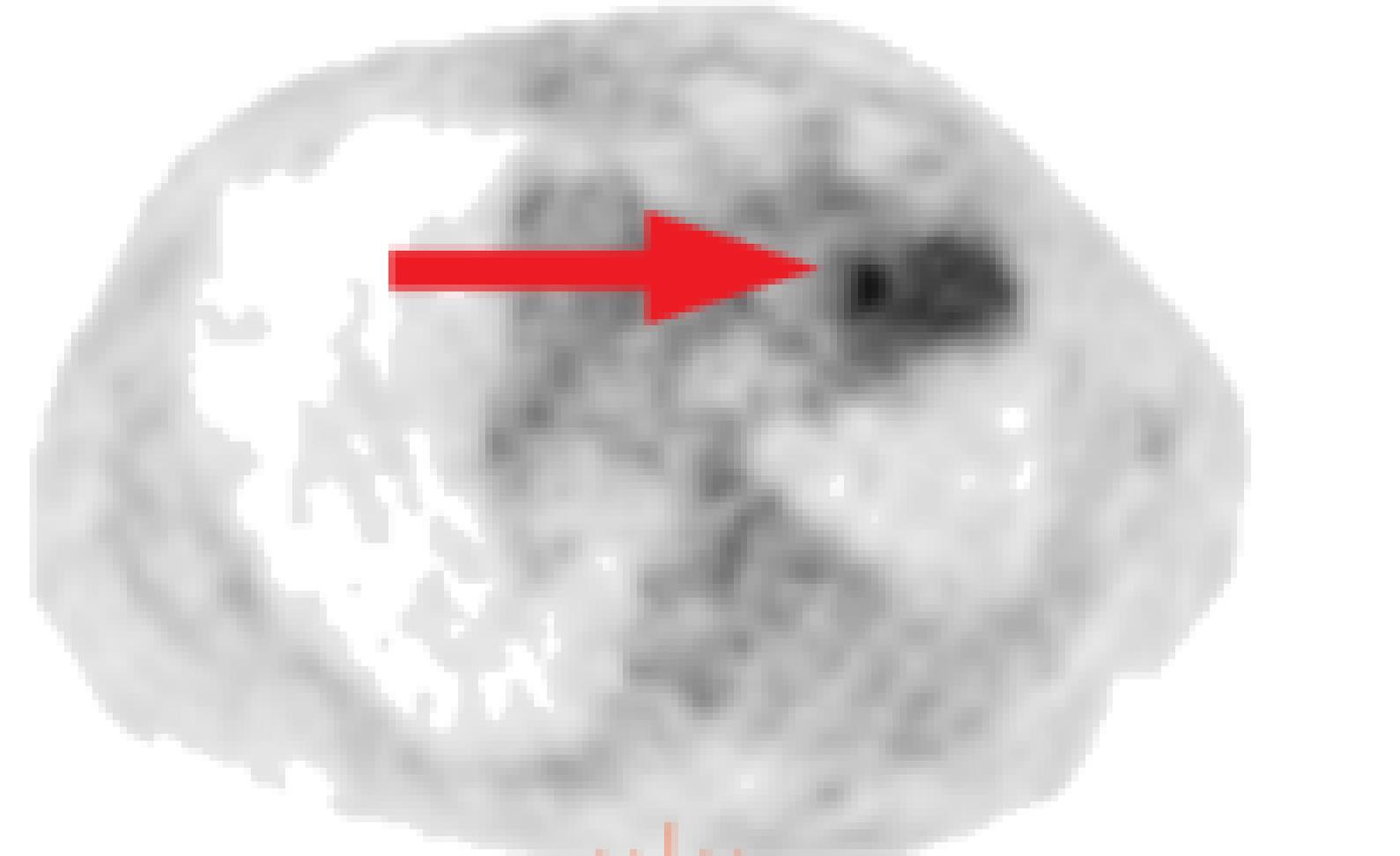
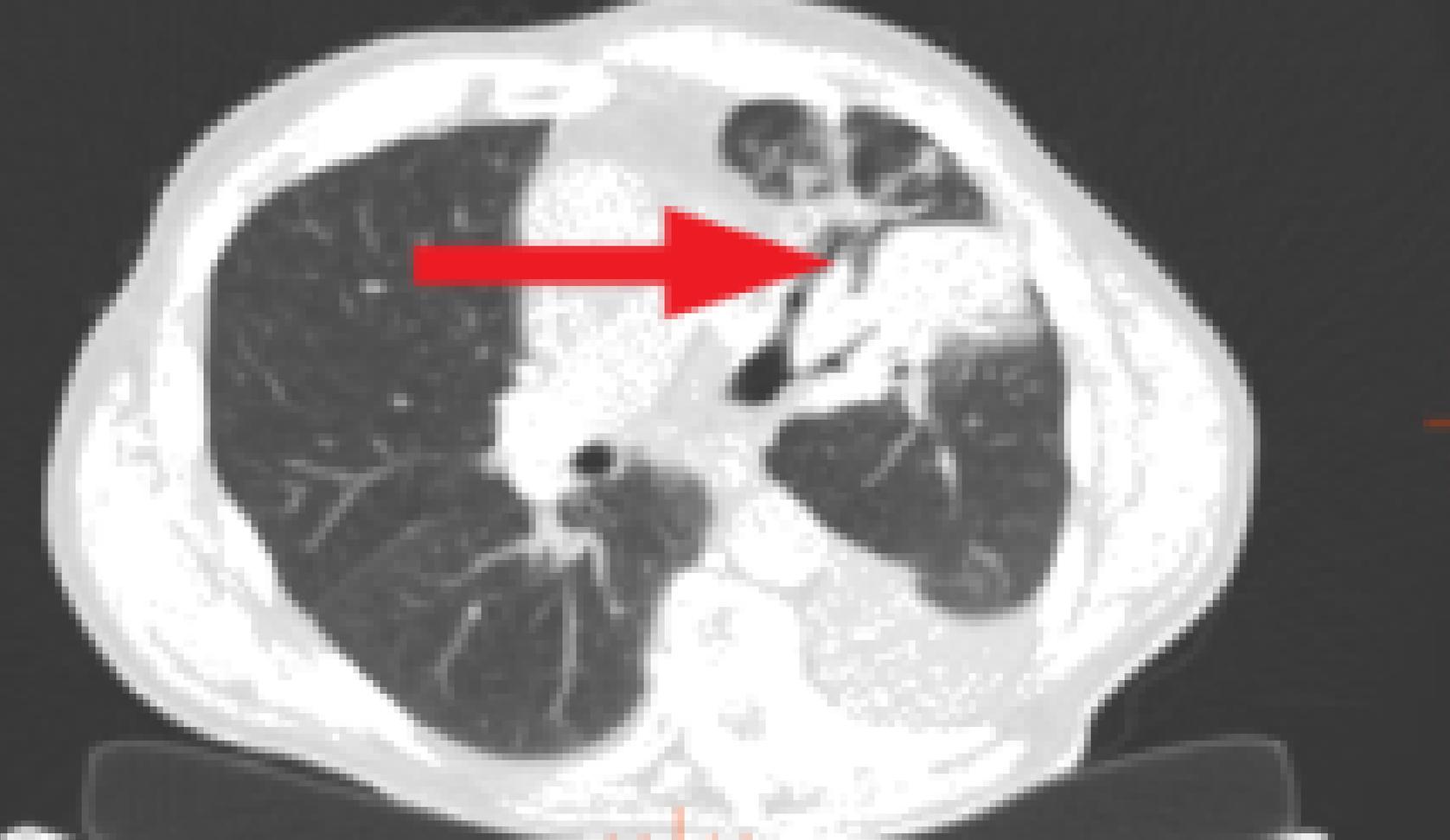
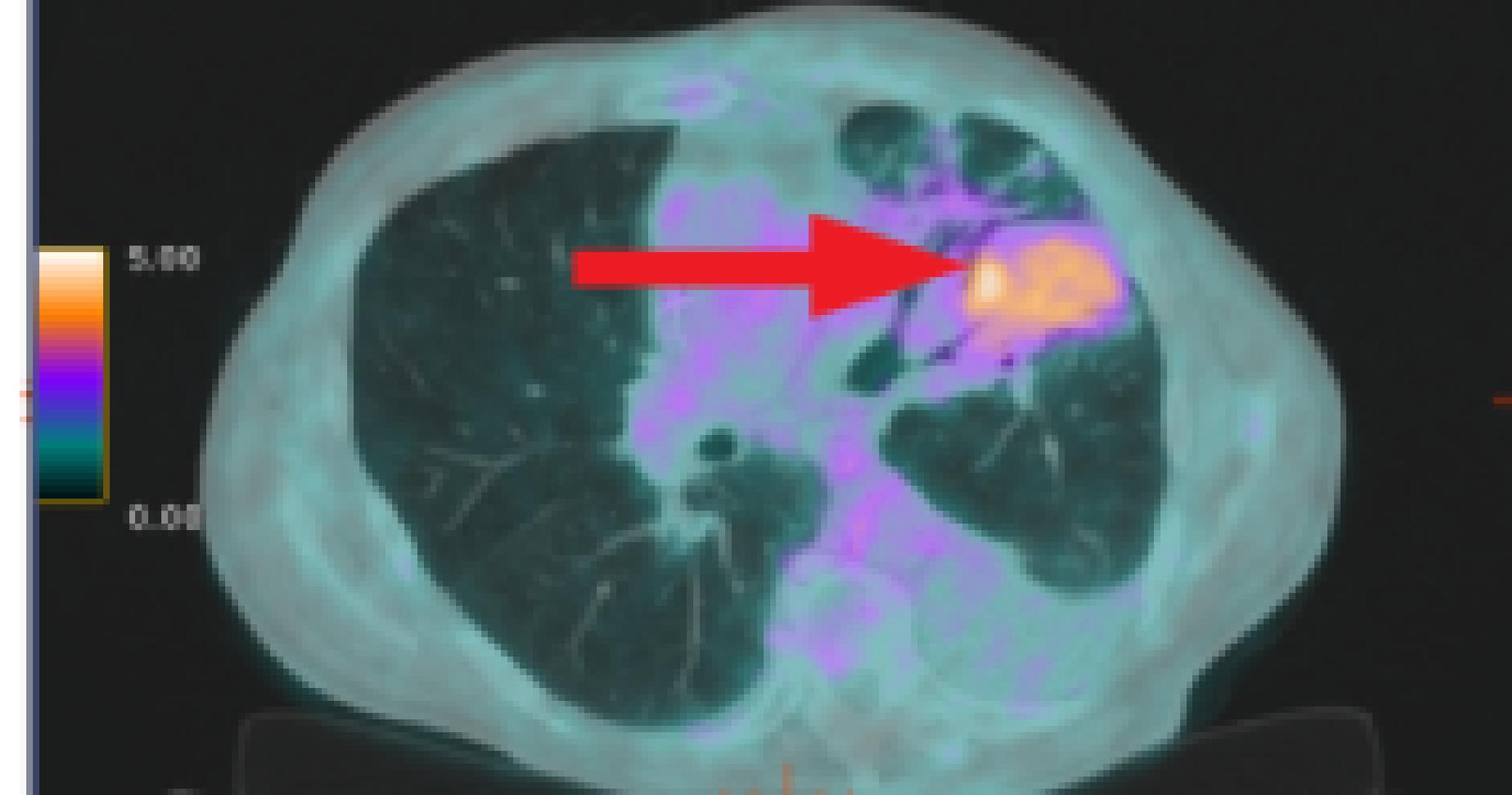
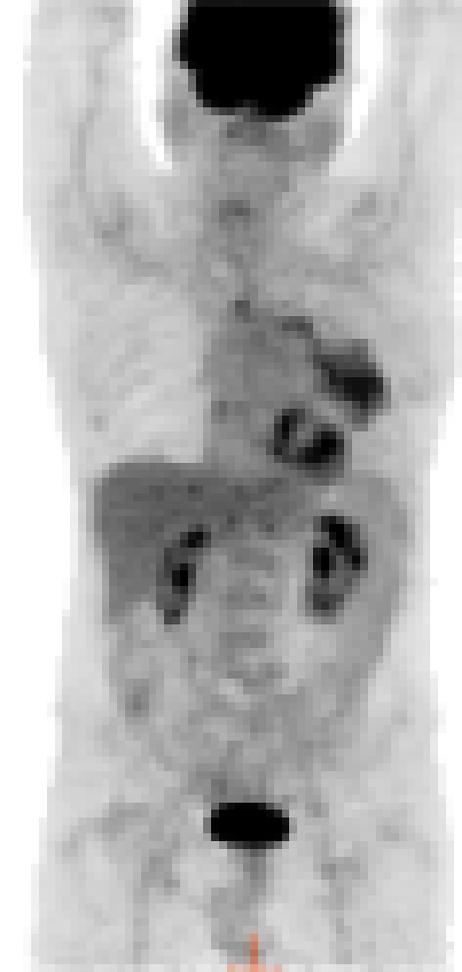
Figure legends

Figure 1. Illustration of the different possible timings of positron emission tomography combined with computed tomography for the evaluation of (chemo)radiotherapy.

Figure 2. Benefits of positron emission tomography scans for the evaluation of radiotherapy: example of examination of a patient with bronchial adenocarcinoma treated by chemoradiation. a: (^{18}F)-FDG PET/CT performed before treatment (yellow arrow: bronchial adenocarcinoma); b: (^{18}F)-FDG PET/CT performed 3 months after chemoradiotherapy (red arrow: appearance of a post-radiation inflammation); c: (^{18}F)-FDG PET/CT performed 9 months after chemoradiotherapy (green arrow: regression of pulmonary uptake confirming the post-radiation inflammation, orange arrow: appearance of a right lower lobar nodule with uptake, in favour of metastasis). PET/CT: positron emission tomography combined with computed tomography; FDG: fluorodeoxyglucose.







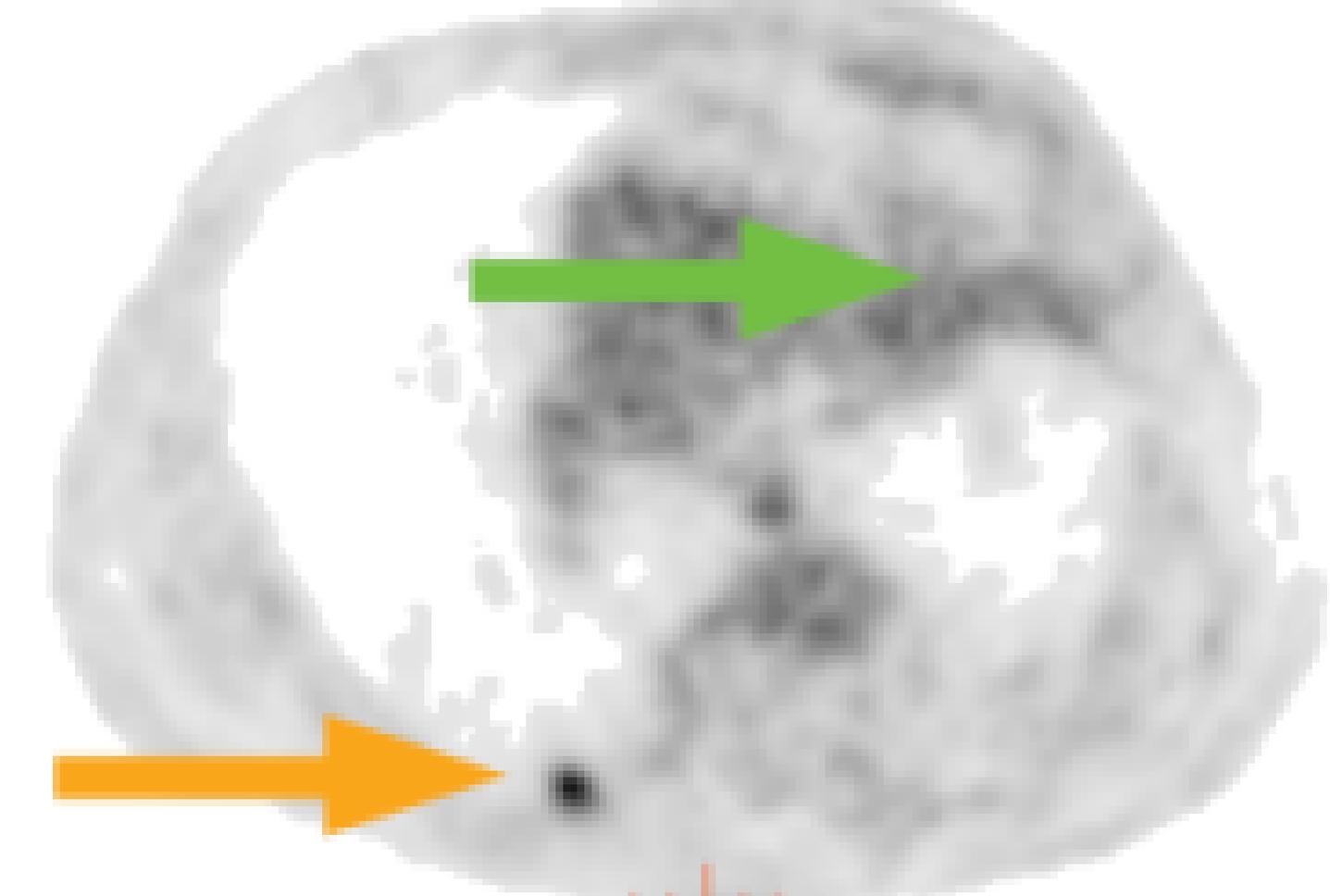
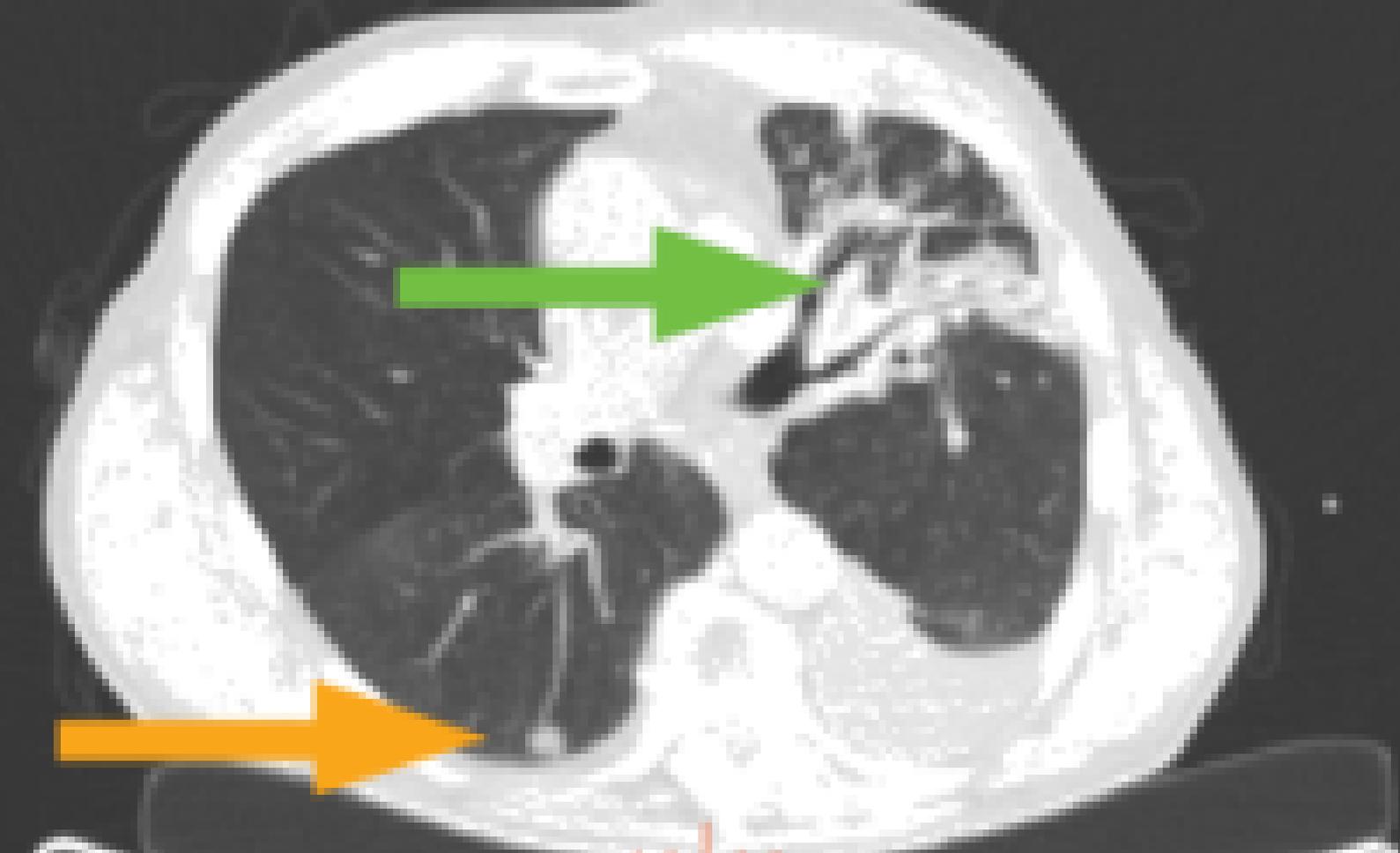
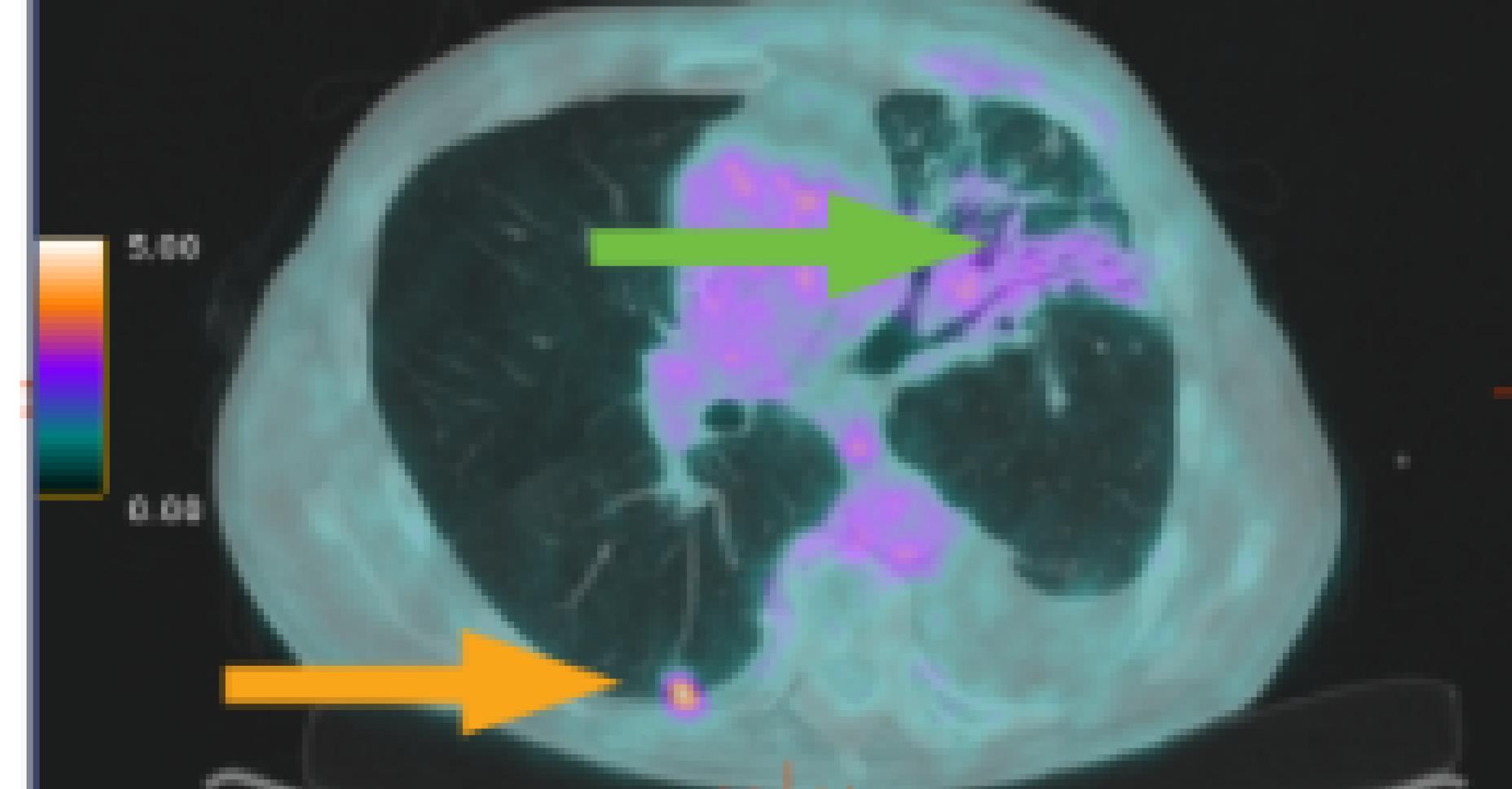
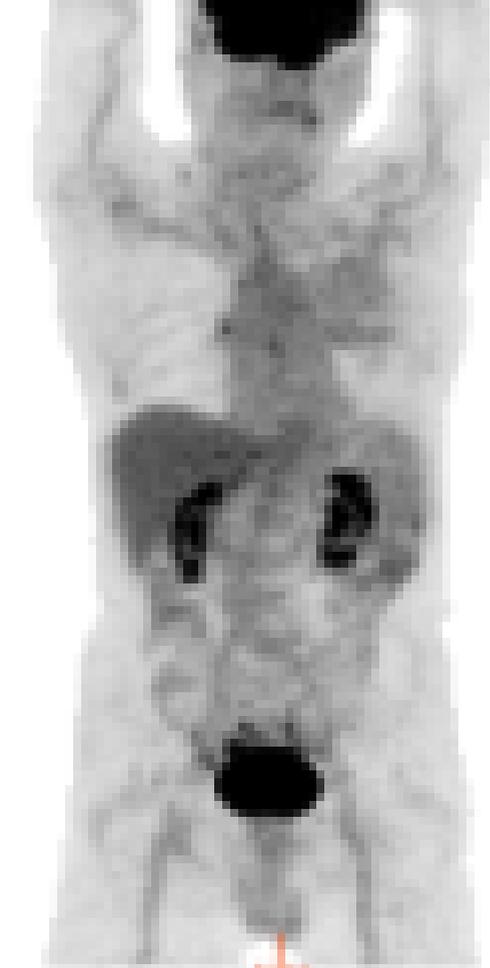


Table 1. Summary of the different recommendations of the National Comprehensive Cancer Network (NCCN) for the use of positron emission tomography combined with computed tomography in the evaluation of radiotherapy according to the timing and the type of cancer.

Examination time/type of cancer	Recommendation	NCCN version
<i>Interim evaluation</i>		
Lung cancer	Not recommended for clinical routine	7.2019
Oesophageal cancer	Not recommended for clinical routine	2.2019
Head and neck cancer	Not recommended for clinical routine	3.2019
<i>After neoadjuvant treatment</i>		
Rectal cancer	PET/CT not recommended. To date, the panel recommends chest CT, abdominal CT or MRI and pelvic MRI for restaging	2.2019
Oesophageal cancer	¹⁸ FDG PET/CT is useful for detecting distant lymph node or blood metastases. Must be done at least 5 to 8 weeks after the end of preoperative treatment. Endoscopy and upper gastrointestinal tract biopsy are also recommended. Oesophagectomy (preferably for adenocarcinomas) or surveillance (category 2B) are recommended for patients who show no signs of disease following preoperative radiochemotherapy	2.2019
<i>After definitive (chemo)radiotherapy</i>		
Lung cancer	Not recommended for clinical routine	7.2019
Head and neck cancer	In case of a clinical response, a ¹⁸ FDG PET/CT is recommended at least 12 weeks with, in case of positivity, a CT or MRI scan. Subsequent management (monitoring or dissection) depending on node size and PET/CT positivity	3.2019
Cervical cancer	¹⁸ FDG PET/CT recommended for patients with FIGO stage II-IV cancer within 3 to 6 months after the end of treatment. Possible also in patients with FIGO stage IB3 cancer who have required postoperative adjuvant radiotherapy or chemoradiotherapy due to high risk factors	4.2019
Oesophageal cancer	¹⁸ FDG PET/CT, endoscopy and upper gastrointestinal tract biopsy are also recommended	2.2019
<i>Follow-up</i>		

Lung cancer	Not recommended for clinical routine. However, many benign conditions (such as atelectasis, condensation and radiofibrosis) are difficult to differentiate from active neoplastic CT disease and ¹⁸ F-FDG PET/CT can be used in these settings. In case of positive PET, histopathological confirmation of disease recurrence must be performed (risk of false positive with areas already treated with radiotherapy that may remain avid for FDG for up to 2 years)	7.2019
Head and neck cancer	Not recommended for clinical routine	3.2019
Oesophageal cancer	Not routinely recommended, except for cancers classified T1b, regardless of N, treated with chemoradiotherapy where imaging (injected thoracoabdominal CT or ¹⁸ F-FDG PET/CT) must be considered every 6 to 9 months for the first two years and annually up to 5 years	2.2019
Cervical cancer	In case of suspicion of recurrence or metastasis	4.2019
Prostate cancer	Consider PET/CT or PET/MRI with (¹¹ C)-choline or (¹⁸ F)-fluciclovin PET/CT (in France, [¹¹ C]-choline is replaced by [¹⁸ F]-choline), especially in the case of bone scans with equivocal results (PET/CT or PET/MRI with [¹⁸ F]-Na can also be considered in this case)	4.2019
Rectal cancer	Not recommended. Consider the use of PET/CT in case of continuous carcinoembryonic antigen elevation or metastasis documented by CT, MRI and/or biopsy	2.2019

CT: computed tomography; FDG: fluorodeoxyglucose; FIGO: International Federation of Gynaecology and Obstetrics; MRI: magnetic resonance imaging; PET: positron emission tomography.