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Systematic review

PET-CT use and the occurrence of elective nodal failure in involved field radiotherapy for non-small cell lung cancer: A systematic review

Lucyna Kepka [a,*], Joanna Socha [b]

[a] Radiation Oncology Department, Independent Public Health Care Facility of the Ministry of the Interior and Warmian & Mazurian Oncology Centre, Olsztyn; and [b] Radiation Oncology Department, Regional Oncology Centre, Czestochowa, Poland

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ABSTRACT

Aim: Current guidelines do not recommend the use of elective nodal irradiation for NSCLC, for several reasons. One of these is that PET-CT provides adequate nodal staging. We compared the published rates of elective nodal failures (ENFs) defined as regional failures that occur without local recurrence irrespectively of distant metastases status in patients who did or did not undergo PET-CT for staging.
Methods: Reports of the occurrence of ENFs were considered. Only studies that used involved fields and specified the number of ENFs in patients with and without PET-CT use were included. A chi-squared test was used for the comparison of the risk of ENF in patients staged with and without PET.
Results: Forty-eight studies were included; 2158 and 1487 patients with and without PET-CT performed before radiotherapy were identified. The proportion of patients treated with SBRT was higher in the group with PET-CT (71%) than it was in the group without PET-CT (20%; $p < .001$). There were 136 (6.3%) and 98 (6.6%) ENFs in patients with and without PET-CT, respectively ($p = .74$).
Conclusion: The failure to reduce ENF by PET-CT was demonstrated. These data should be regarded in the context of the adequacy of reporting the rate of ENF and recognized value of PET-CT in NSCLC treatment.
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Most current treatment guidelines do not recommend the use of elective nodal irradiation (ENI) in non-small cell lung cancer (NSCLC), for several reasons [1,2]. Shortly, these recommendations are funded on the basis that involved-field radiotherapy (IFRT) allows dose escalation and the rate of elective nodal failures (ENFs) is low in this technique, which is especially true for contemporary imaging, including positron-emission tomography–computed tomography (PET-CT) [1–5].

PET-CT has higher sensitivity and specificity than CT in the detection of mediastinal and hilar nodal metastases [4]. The value of PET-CT in radiotherapy for NSCLC with regard to the determination of target volumes is recognized [2]. It is claimed also that this may be an additional tool that facilitates IFRT in NSCLC. Better imaging is supposed to lead to better (i.e., more limited) treatment volume tailoring. Thus, the occurrence of ENF should be reduced with the use of PET-CT for staging, which supports the omission of ENI [5]. Historically, in the largest-ever published study on the occurrence of ENF, which did not employ ENI, there was no statistically significant difference in the risk of ENF between patients who had PET-CT for staging and those who did not. Among 524 patients, 32 ENFs (6.1%) were identified. Three hundred twelve patients with pretreatment PET-CT had an actuarial 2-year ENF risk of 8.6% compared with 6% in 212 patients who were staged without PET-CT ($p = .73$) [6]. Recently, in the report of the outcome of a large pooled cohort of patients undergoing stereotactic body radiation therapy (SBRT), no impact of PET-CT on the occurrence of ENF was demonstrated. Among 505 patients with early-stage lung cancer, 88% had PET-CT for staging. There were 12% and 3% regional recurrences in patients who did or did not undergo PET-CT staging, respectively ($p = .06$) [7]. These conflicting data regarding the value of PET-CT in the reduction of the risk of ENF incited us to perform a search of the literature to compare the frequency of the occurrence of ENF after IFRT between patients who had and those who did not have PET-CT for staging.

Methods

Studies that reported the occurrence of ENF were selected via a comprehensive literature search using the "PubMed" and "Google Scholar" databases. The search terms included were: "Elective nodal failure," "Isolated nodal failure," "Non-small cell lung cancer," "Involved-field radiotherapy," "PET-CT and radiotherapy," "Radiotherapy and NSCLC," "pattern of failure," "SBRT and NSCLC," and "ENI and NSCLC." The reference lists of relevant articles were further explored.

* Corresponding author at: Independent Public Health Care Facility of the Ministry of the Interior and Warmian & Mazurian Oncology Centre, Al. Wojska Polskiego 37, 10-228 Olsztyn, Poland.
E-mail address: lucynak@coi.pl (L. Kepka).

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For the purpose of this review, ENF was defined as the relapse in initially uninvolved lymph nodes that were not intentionally included in the radiation volume, without simultaneous or previous local relapse. Regional relapses in the initially uninvolved lymph nodes that occurred simultaneously with distant metastases without local relapse were also considered as ENF.

Only studies that included clear statements regarding the use (or not) of PET-CT for staging (±planning) were included. In a few cases, e-mails were sent to the corresponding authors with a request of details on the number of patients in whom PET-CT was used for staging before radiotherapy and its relation to the reported number of ENFs. Studies in which the exact number of patients and ENFs in groups with and without PET-CT was not established were excluded. Patients who received ENI were excluded. The crude number of ENFs was derived from respective studies with and without PET-CT. A chi-squared test was used to compare the rate of ENF in patients for whom PET-CT was performed before radiotherapy with that observed in patients who did not have PET-CT for baseline staging or planning. In addition, the rate of ENF in patients who underwent SBRT was compared between groups of patients with and without PET-CT. A similar comparison was performed after excluding patients treated with SBRT.

Results

In total, 65 studies that reported the occurrence of ENF after radiotherapy for NSCLC were found. Seventeen studies were excluded for the following reasons: use of ENI in all patients (2) [8,9]; lack of information on the occurrence of ENF in relation to the use (or not) of ENI (2) [10,11]; the exact number of ENFs in groups of patients with and without PET-CT or the number of patients with PET-CT performed before radiotherapy was not specified (10) [6,7,12–19]; repeated reports on subgroups of patients from previous publications (2) [20,21]; and doubt on the isolated character of regional relapse in a small subgroup of patients without PET-CT (1) [22]. Finally, 48 studies were included in this review [23–70]. For one study, details on the use of PET-CT in relation to the occurrence of ENF were provided by personal communication from the corresponding author [23].

The characteristics of the studies included in this review are provided in Table 1. There were 28 groups (2158 patients) with PET-CT and in 24 groups (1487 patients) without PET-CT performed before radiotherapy. The distribution of clinical stages in patients with and without PET-CT performed before radiotherapy was: early (stage I or II): 1605 (74%) and 856 (57.5%); locally advanced (stage III): 400 (19%) and 486 (32.5%); and unknown: 153 (7%) and 145 (10%), respectively. The provided follow-up period for patients staged with PET-CT ranged from 12.4 to 50.2 months (median: 18 months) and for patients staged without PET-CT ranged from 9.4 to 86 months (median: 20.5 months).

The crude occurrence of ENF varied among these studies from 0% to 12.5% (median: 5.9%) in patients staged with PET-CT and from 0% to 36.3% (median: 3.6%) in patients staged without PET-CT (Fig. 1). There were 136 (6.3%) and 98 (6.6%) ENFs in patients with and without PET-CT performed for staging before IFRT, respectively ($p = .74$). In relation to the technique of radiotherapy used, 1541 (71.4%) patients with PET-CT and 293 (19.7%) without PET-CT received SBRT ($p < .001$). There were 125 ENF (6.8%) in 1834 patients treated with SBRT and 109 ENF (6%) in 1811 patients treated with other techniques. In the group of patients who were treated with SBRT without PET-CT, there were 19 (6.5%) ENFs compared with 106 (6.9%) ENFs in SBRT patients with PET-CT ($p = .82$). After excluding patients who were treated with SBRT, we detected 79 ENFs (6.6%) in 1194 patients without PET-CT, and 30 (4.9%) ENFs in 617 patients with PET-CT performed before radiotherapy ($p = .16$).

Discussion

No difference in the reported rate of ENF between patients who had PET-CT for staging before IFRT and those who did not was demonstrated in this literature review. This indicates that, despite the recognized higher sensitivity and specificity of PET-CT over CT for mediastinal and hilar nodal staging of lung cancer [4], the pattern of regional failure after IFRT for NSCLC may not be modified by the use of PET-CT. In other words, the safety of ENI omission is not strongly supported by the use of PET-CT itself for staging.

On the other hand, the findings of our study support neither the use of ENI nor its omission. The dilemmas that are usually pointed out by the debaters of ENI persist, one of which is the risk of an underestimation of the rate of ENF (ascertainment bias, e.g., in the case of distant relapse) [3,71]. One may argue that the rate of ENF, which appears to be independent of the diagnostic tool used, undermines the estimation of the value of PET-CT using the evaluation of the risk of ENF. We agree with this reasoning; however, the purpose of our study was limited to this end-point only, and we acknowledge all limitations related to the complexity of the detection of ENF. Nevertheless, we conclude that the use of PET-CT does not change this risk, as postulated in the guidelines [1,2,5]. The risk of 5–12% associated with this type of relapse is considered by some as being low, especially in the context of high risk of local relapse [5,43], and by others as being meaningful, thus precluding an opportunity for a cure in a proportion of patients, because an even lesser survival benefit associated with the addition of chemotherapy to radiotherapy changed clinical practice guidelines [71,72].

We should acknowledge a number of limitations of our analysis. Besides limitations related to the reporting of ENF we acknowledge that we were not able to derive from most studies included in the review any data on the diagnostic tools used in the follow-up period. One may only speculate that patients staged with PET-CT before radiotherapy had more often PET-CT performed during follow-up and this contributed to the higher number of detection of regional relapses in such patients. Also, due to the growing evidence of the value of PET-CT for radiotherapy planning and its increased availability, patients treated without PET-CT were treated in the higher proportion in earlier era. Thus patients with PET-CT used for staging would have falsely higher rate of ENF due to better post-treatment staging. This may undermine the value of our findings. Nevertheless, also in the studies in which patients were treated with and without PET-CT for staging in the same time period, there was no difference in the rate of ENF in favor of the PET-CT use [6,23,37,63]. One may think also that patients staged with PET-CT survived longer than patients without PET-CT due to stage migration thus a rate of detected ENF would be higher. However, the lengths of follow-up period of patients in the groups with and without PET-CT were similar in our study.

We reported the significantly higher proportion of PET-CT staging for SBRT patients than for patients treated with conventional techniques. However, the benefit of the use of PET-CT for staging was not disclosed for any techniques used. Patients treated with SBRT have probably a lower risk of ENF due to the earlier stages of their disease. Surprisingly, the rate of ENF was very similar in patients treated with SBRT and in those treated with conventional techniques. This may be related to the steeper dose distribution and related to that a lack of incidental irradiation [73]. We still do not have firm data that enable us to incorporate the phenomenon of incidental irradiation into treatment planning, to prevent regional failures. However, there is growing evidence that, in the absence of ENI, incidental irradiation reduces the risk of ENF. Recently, it was demonstrated that doses higher than 20 Gy delivered to ipsilateral hilum decreased the rate of ENF in patients treated with SBRT [23]. This may explain the absence of differences in the reported

Table 1
Studies included in the review that reported on the risk of ENF (elective nodal failure) in patients staged with or without PET.

Study: First author [Ref.]; type of the study	Number of patients evaluated	Number of ENF (%)	Details on treatment	Patient/tumor characteristics	Median follow-up [in months]; unless otherwise stated
Patients staged without PET					
Lao [23]; prospective	23*	0 (0)	SBRT**	T1-T2N0	20 months
Slotman [24]; retrospective	31	1 (3.2)	12 × 4 Gy;	T1-T2N0	Not specified
Krol [25]; retrospective	108	2 (1.9)	2.5–3.0 Gy/fraction to 60–65 Gy	Peripheral tumors	Not specified
Robertson [26]; prospective	30	1 (3.3)	Dose escalation up to 92.4 Gy	Stage II and III	Not specified
Hayakawa [27]; retrospective	26	1 (3.8)	60–81 Gy	Stage I	Range: 3–18 years
Cheung [28]; retrospective	103	4 (3.8)	52.5 Gy in 20 fr	T1-T4N0 (5 × N1)	86
Rosenzweig [29]; retrospective	171	11 (6.4)	Dose escalation up to 81 Gy	86% stage III; 14% stage I and II	21
Hayman [30]; prospective	63	2 (3.2)	Dose escalation up to 102.9 Gy	All stages	9.4
Cheung [31]; retrospective	33	2 (6.1)	48 Gy in 12 fractions	T1T2N0	22.5
Senan [32]; prospective	43	0 (0)	Sequential CHT-RT	Stage III; only patients who received at least 50 Gy	16
Hof [33]; retrospective	10	0 (0)	SBRT single fraction	Stage I	14.9
Bradley [34]; prospective	33	2 (6)	Dose escalation (median dose: 70 Gy)	Stage I	20
Onishi [35]; prospective	35	2 (5.7%)	SBRT	Stage I	13
Bradley [36]; prospective	179	14 (8)	Dose escalation up to 70–90 Gy; in stage III combined with sequential CHT	Stage I–III	Range of median for subgroups: 13.3–18.7
Belderbos [37]; prospective	21	0 (0)	Dose escalation from 50 to 94 Gy (median: 80 Gy); 18% induction CHT	Stage I–III	17
Baumann [38]; retrospective	138	6 (4.3)	SBRT	Stage I	33
Urbanic [39];	35	0 (0)	80.5 Gy in 35 fractions	Stage I and II	33
Yuan [40]; prospective	100	7 (7)	68–74 Gy with concomitant CHT	Stage III	27
Mostafa [41]; prospective	32	1 (3.1)	66 Gy with concomitant CHT	Stage III	13.5
Yu [42]; prospective	80	29 (36.3)	66.6 Gy; IMRT	Stage I and II	72
Sulman [43]; retrospective	29	0 (0)	Most concurrent RT (64 Gy)-CHT	All stages	18
Nakayama [44]; retrospective	45	2 (4.4)	66–84 Gy with sequential or concomitant CHT	Stage III	Not specified
Onishi [45]; retrospective	87	11(12.6)	SBRT	Stage I	55
Chen [46]; prospective	32	0 (0)	Median RT dose of 60 Gy with induction and concomitant CHT	Stage III	33
Patients staged with PET					
Lao [23]; prospective	156*	19 (12.2)	SBRT	Stage I	20
Zimmermann [47]; retrospective	30	2 (6.7)	SBRT	Stage I	18
De Ruysscher [48]; prospective	44	1 (2.3)	61.2–64.7 Gy in 34/37 fractions	All stages	16
Belderbos [37]; prospective	67	2 (3)	Dose escalation from 50 to 94 Gy (median: 80 Gy); 18% induction CHT	All stages	17
Hoopes [49]; prospective	57	6 (10.5)	SBRT	Stage I	42.5
Klopp [50]; retrospective	35	3 (8.5)	60–70 Gy; 70% with concurrent CHT	All stages	13
Chang [51]; retrospective	13	1 (7.7)	SBRT	Stage I	17
Sulman [43]; retrospective	86	2 (2.3)	Most concurrent RT (mean: 64 Gy)-CHT	All stages	18
Stephans [52]; retrospective	86	7 (8.1)	SBRT	Stage I	15.3
Collins [53]; retrospective	20	0 (0)	SBRT (cyberknife)	Stage I (“small, peripheral”)	25
Fakiris [54]; prospective	70	4 (5.7)	SBRT	Stage I	50.2
Bradley [55]; retrospective	91	4 (4.4)	SBRT	Stage I and II (+6 T1N0M1)	18
Fernandes [56]; retrospective	48	6 (12.5)	60–84 Gy with concurrent or sequential CHT	Stage III (including 3 oligometastatic)	16.2
Kimura [57]; retrospective	50	4 (8)	60–80 Gy; in 72% with sequential or concurrent CHT	Stage II – 28% Stage III – 72%	Not specified
Ricardi [58]; prospective	62	7 (11.3)	SBRT	Stage I	28
Timmerman [59]; prospective	55	2 (3.6)	SBRT	Stage I	34.4
Grills [60]; retrospective	55	4 (7.3)	SBRT	Stage I	30
Fleckenstein [61]; prospective	23	1 (4.3)	66.6 Gy with concurrent CHT	Stages II and III	27.2
Bral [62]; prospective	40	2 (5)	SBRT	T1-T3N0	16
Kolodziejczyk [63]; prospective	50	3 (6)	RT 58.7 – 66 Gy with or without sequential CHT	All stages	32
Bradley [64]; prospective	47	1 (2)	Different curative doses with or without CHT	Stages II (6%) and III (94%)	12.9
Tada [65]; prospective	22	1 (4.5)	Hyperfractionated dose escalation concurrent CHT	Stage III	Not specified
Senthi [66]; retrospective	676	37 (5.5)	SBRT	Stage I and II	32.9
Van Baardwijk [67]; prospective	132	6 (4.5)	Concurrent RT-CHT	Stage III	30.9
Zhang [68]; retrospective	68	6 (8.8)	SBRT	Stage I	31
Chen [46]; prospective	13	0 (0)	Median RT dose of 60 Gy with induction and concomitant CHT	Stage III	33
Samuels [69]; retrospective	46	4 (8.7)	SBRT	Stage I	12.4
Kim [70]; retrospective	16	1 (6)	SBRT	Stage I	14

* Numbers provided by personal communication of Dr. Cho [23].
** SBRT – Stereotactic-body Radiotherapy.

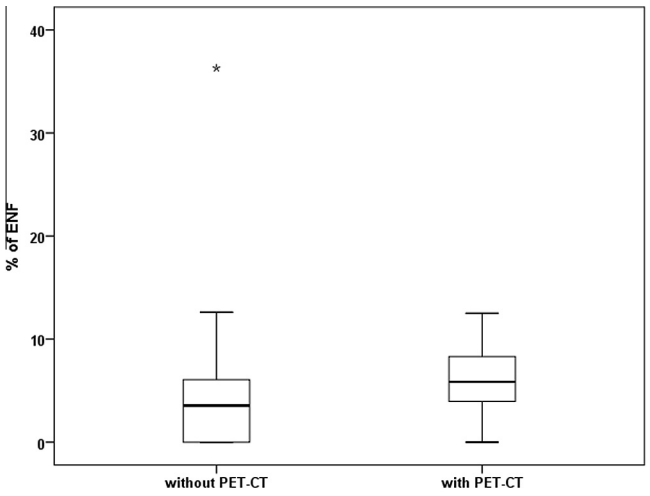

Fig. 1. Median and range values of the rate of elective nodal failures (ENF) in 28 groups (2158 patients) with PET-CT and in 24 groups (1487 patients) without PET-CT performed before radiotherapy.

rate of ENF between patients with early peripheral tumours who were treated with SBRT and patients treated with other techniques, in whom central and larger tumors are at a potentially higher risk of regional relapse. Even low radiation doses (i.e., lower than 40 Gy) may reduce regional relapses in both SBRT and non-SBRT techniques [23,74]. Probably, a rapid dose decrease outside PTV in the SBRT technique led to the increased risk of ENF. PET-CT should not render us overconfident about the real disease extent, because this diagnostic tool is not able to detect microscopic disease. Here, we do not promote ENI use in SBRT, because the results obtained with this technique to date are very encouraging; however, we should still closely monitor such patients and continue to gather data on this issue [75,76].

Unfortunately, we were not able to demonstrate the proportion of ENF in relation to the clinical stage of the disease. Most reports included in this review did not specify the exact distribution of ENF in this regard. One may expect that the risk of ENF increases with more advanced clinical stage, as it was demonstrated in other reports [8]. Also, the value of PET-CT may be more limited in more locoregionally advanced NSCLC. Videtic et al. [77] demonstrated that 39% of 87 stage III NSCLC patients had nodal metastases identified by mediastinoscopy that were undetected by PET-CT.

The heterogeneity of included studies is another limitation of our findings. We have included prospective and retrospective studies performed within different periods of time. However, we were not able to find better way of looking for these data, because even in the prospective studies, the pattern of failure was not usually considered as the main end-point of the study and these data were also often recorded retrospectively. Different times of performing radiotherapy might have led to the use of different types and techniques of PET scanning. We cannot exclude that the modern PET-CT machines would contribute to the higher accuracy of mediastinal staging. Also, most studies did not provide details on delineation, i.e. how the PET-CT findings modified radiation target volumes. Included studies did not provide data on the policy of pathologic verification of PET-CT findings. However, pathologic staging is not mandatory for radiotherapy purposes and is not routinely used in clinical practice [2]. We are aware that if we had all these data our analysis would have more scientific impact. On the other, we think that a large number of included studies compensates for these uncertainties.

Our rate of ENFs (6.5%) differs slightly from this provided in the guidelines (usually below 5%). This may be related to our definition of ENF in which regional failures were not excluded if they occurred simultaneously with distant metastases. The guidelines refer to the reports in which, mostly, isolated nodal failures (INFs) instead of ENFs were considered. INFs were defined as outside clinical target volume regional failures that occurred in the absence of local and distant relapse. We consider that regional failures may be a source of distant seeding and, at times, distant metastases represent failure in regional control. For that reason, our definition of ENF seems to be more suitable for evaluation of the value of PET-CT in terms of regional control.

In conclusion, we have demonstrated that, despite the recognized value of PET-CT in the diagnostic and radiotherapy of NSCLC, its value in the reduction of ENF in radiotherapy of lung cancer should not be overestimated.

Conflict of interest statement

No conflict of interest from any authors. No financial funding received for this study.

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