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Outcome after PET-CT based radiotherapy for non-small cell lung cancer

Wyniki radioterapii planowanej na podstawie badania PET-CT u chorych na niedrobnokomórkowego raka płuca

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Abstract

Introduction. The value of PET-CT in radiotherapy for non-small cell lung cancer (NSCLC) with regard to determination of target volumes is established. It is less clear whether its use can improve clinical outcomes of irradiated NSCLC patients compared to conventional staging. The outcome of NSCLC patients included in a previously published prospective study of the value of PET-CT in curative radiotherapy candidates was assessed.

Material and methods. Patients were treated according to the PET-CT findings. The survival data were compared between 67 patients treated curatively and 22 patients with palliative treatment given after upstaging based on the PET-CT findings. Survival of curatively treated stage III patients was compared with a previously published outcome of 173 stage III patients treated in the same institution with the same radiation schedule but without PET-CT.

Results. The 3-year overall survival was 42% and 0% (median: 21 months and 7 months), for curatively and palliatively managed patients, respectively ($p < 0.0001$). However, the median overall survival of 17 months for 50 stage III patients was the same as that in a previously published series of stage III patients treated with the same radiation schedule but without PET-CT. Three-year overall survival rates were 33% for the PET-CT group and 19% for historical group, $p = 0.1$. Twenty-one local recurrences and 21 distant metastases were reported. Three of 50 patients (6%) treated without elective nodal irradiation developed isolated nodal failure (without local recurrence).

Conclusions. The high early mortality rate in the patients excluded from curative radiotherapy after PET-CT suggests the potential value of PET-CT for improving the radiotherapy outcome. However, this benefit seems to be limited in stage III patients.

Key words: non-small cell lung cancer, radiotherapy, PET-CT, isolated nodal failure

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Introduction

The unquestioned role of positron emission tomography combined with computed tomography (PET-CT) in the diagnostics and treatment of non-small cell lung cancer (NSCLC) is related to its better accuracy in staging NSCLC in the mediastinum and in identification of distant metastases when compared to conventional diagnostic modalities, such as computed tomography (CT). The results of PET-CT scanning lead to changes in therapeutic strategies in many patients. The detection

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of distant metastases or locoregional disease upstaging results in disqualification from radical radiotherapy in 30% of patients [1]. Appropriate patient selection with PET-CT scanning can decrease the number of futile thoracotomies by 20% [2]. Many patients not eligible for radical interventions can avoid prolonged and toxic therapy owing to changes in treatment strategies after PET-CT. The inclusion of PET-CT scans in radical radiotherapy planning decreases the risk of geographical miss, especially within the mediastinum [3–5], and in some patients leads to a change of radiotherapy technique, including the decision about the use of elective nodal irradiation (ENI) [5].

Given the stage migration phenomenon [6] and high early mortality rate in radically treated patients who underwent conventional diagnostic procedures [7], the potential benefits of PET-CT qualification for radical therapy have been suggested, with potentially prolonged survival [1, 7, 8]. A trend towards improved overall survival in patients with PET-CT-based diagnostics and radiotherapy planning was observed in a Canadian prospective randomized study on disqualifications from radiochemotherapy after PET-CT when compared to CT alone in stage III NSCLC patients. Two-year overall survival rate of radically irradiated patients was 53% in the PET-CT arm and 41% in the CT arm (hazard ratio [HR] =0.7; 95% confidence interval [CI]: 0.5–1.0; p = 0.045) [9]. There are, however, no other randomized studies comparing the results of radical radiotherapy planned with PET-CT versus conventional CT-based radiotherapy. Considering the established impact of PET-CT on radiation target volumes design, such a randomized study could not be performed. The value of PET-CT in radiotherapy may be similar to that in surgically managed patients. In a Danish study, 200 patients with potentially resectable NSCLC were randomised to conventional radiological imaging (CT) and PET-CT scanning or CT alone. The percentage of futile thoracotomies was lower in the first group, but this did not translate into significant improvement in overall survival [10]. Therefore, the role of PET-CT in NSCLC patients treated with radiotherapy remains unknown. The therapeutic ratio of radiotherapy may be not that high in NSCLC and radiotherapy given to patients with metastases undetected by conventional diagnostic modalities may also affect overall survival. Further prospective studies on the survival of NSCLC patients treated with PET-CT are thus warranted.

The primary goal of a prospective study recently performed in our institution was to assess the changes after PET-CT in radiotherapy plans in NSCLC patients with a focus on the risk of geographical miss caused by a lack of PET-CT information in patients with and without planned ENI [5]. Patterns of failure of radically irradiated patients participating in that study was then prospectively assessed. Herein we report the outcomes and patterns of failure, including the incidence of isolated nodal failures (INF), in NSCLC patients treated within the framework of a prospective study, where, after PET-CT scanning, ENI was omitted only for minimal N disease (N0, N1, single N2 of not more than 3 cm in diameter). The survival data were compared between patients treated curatively and patients with palliative treatment given after upstaging based on the PET-CT findings. To assess the impact of PET-CT on radiotherapy outcomes, survival of curatively treated stage III NSCLC patients was compared with a previously published outcome of 173 stage III patients treated in the same institution within the framework of a prospective study with the same radiation schedule but without PET-CT.

Material and methods

The details of the material and methods, and the impact of PET-CT on therapeutic decisions and radiotherapy plans in the study group have been reported previously [5]. Briefly, 100 consecutive stage I-III NSCLC patients referred for radical radiotherapy underwent CT-based planning and then PET-CT-based planning. The patients for whom the decision about curative radiotherapy was maintained after PET-CT were treated according to the PET-CT-based plan. Patients with stage III NSCLC determined by conventional imaging had the ENI included in the CT-only based plans. After PET-CT, the stage III patients with minimal nodal disease (N0, N1, and single N2) had ENI omitted from the treatment plans. Before the onset of radiotherapy, fit stage III patients were administered two or three cycles of platinum-based chemotherapy. The decision about curative radiotherapy was maintained for 75 (75%) patients after PET-CT. Twenty-four patients were referred for palliative treatment: 19 because of distant metastases and five because of too extensive locoregional disease. A benign lesion was diagnosed in one patient.

According to the departmental protocols, the patients were irradiated using three distinct schedules as follows.

1. For early peripheral T1 to T3N0 tumors: 52 Gy in 13 fractions, five fractions per week; radiotherapy limited to the tumor with margins.
2. For early central T1 to T2N0–N1 and T3N0

tumors: 66 Gy in 30 fractions over 6 weeks; radiotherapy was limited to the tumor with margins with inclusion of the ipsilateral hilum, irrespective of hilar involvement.

3. For stage III tumors: 58.8 Gy over 4 weeks, including 39.9 Gy for limited ENI in 21 fractions, using a simultaneous boost technique (2.8 Gy per fraction including 1.9 Gy for limited ENI). The limited ENI was used for N2–3 disease, except for single N2 < 3 cm in diameter, and included only the lymph node stations with the highest probability for microscopic invasion, i.e. the uninvolved ipsilateral hilum, the 4R, 4L, 7, and for the left side, the 5 lymph node station. Details of this technique were published previously [11]. Lymph node stations were delineated according to the published guidelines [12] with local modification [13]. Stage III patients with N0, N1 or single N2 < 3 cm in diameter confirmed after PET-CT were treated with involved field radiotherapy (IFRT), covering only the tumor and pathological lymph node stations with margins, and ENI was omitted.

Gross tumour volume (GTV) consisted of pre-chemotherapy tumor volume, post-chemotherapy volumes could be used in exceptional cases. Nodal GTV was always based on pre-chemotherapy nodal involvement. If the uptake of 18F-fluorodeoxy-glucose ([18F]-FDG) was greater than its anatomic substrate on the fused image, the whole region of [18F]FDG enhancement was included in the GTV. To avoid errors, if the [18F]FDG uptake area was smaller than its anatomic substrate on CT, the whole concerned structure was included in the GTV. [18F]FDG-PET-negative lymph nodes measuring 1.5 cm or larger in short axis diameter were considered pathologic and included in the GTV.

After completion of the PET-CT-based radical radiotherapy, patients were followed up at 3-month intervals. Follow-up assessment included medical history, physical examination, chest X-ray, and chest CT. Other examinations were performed for symptomatic patients. PET-CT was not performed in the follow-up period. Local progression was defined as an increase in target disease of at least 20% in sum. Regional nodal recurrence in the initially uninvolved hilum, mediastinum, or supraclavicular areas without simultaneous or previous local progression, was defined as INF regardless of distant metastases. Histopathological verification of any recurrence was not mandatory. Local and distant recurrences were both recorded, irrespective of their time sequence.

Results of a prospective trial on the overall survival of 173 stage III NSCLC patients treated between 2001 and 2007 in the same institution with the same radiotherapy schedule (and for fit patients, sequential chemo-radiotherapy), but without PET-CT staging, were previously published [11]. Their survival was compared with that of the stage III patients treated with PET-CT use included in the current study; log-rank test was used for the comparison. Data concerning the outcomes of NSCLC stage I or II patients irradiated in DTR without PET-CT were not collected prospectively. Therefore, comparisons of the outcomes of early stage NSCLC patient treated with vs. without PET-CT were abandoned.

Patients who received palliative treatment after PET-CT were not systematically followed-up in DTR, and only data on their survival were available. These were 24 patients referred for palliative treatment because of distant metastases or locoregional disease too extensive for curative radiotherapy.

Current analysis concerns the pattern of treatment failure in the group that received radical radiotherapy after PET-CT. The overall survival, local progression-free survival, distant metastases-free survival and the cumulative incidence of INF were estimated using the Kaplan–Meier method. Time intervals were calculated from the first day of radiotherapy. The log-rank test was used to compare the overall survival rates for patients who received radical radiotherapy and those addressed for palliative treatment. In patients who did not receive radical radiotherapy, the survival rate was calculated from the date of PET-CT scanning.

The Wilcoxon test for age and the nonparametric Mann-Whitney U test for remaining parameters (gender, performance status, weight loss, clinical stage of disease, histological subtype, chemotherapy use) were used to determine the distribution of patient characteristics within each compared group (palliatively treated vs radically treated patients and the study stage III patients vs the historical group of stage III patients). A p-value of less than 0.05 was considered statistically significant.

Results

Among 75 patients with qualification for radical radiotherapy sustained after PET-CT, 67 were treated and followed-up in DTR in Warsaw. These patients were included in the analysis of the pattern of failure. The characteristics of this subgroup are shown in Table 1. Seventeen (25%) radical-

ly treated patients received ENI according to the study protocol because of massive nodal involvement (> 2 PET-positive lymph node stations or a single lymph node station > 3 cm). In the remaining 50 patients, IFRT was administered.

Median follow-up of living patients who received radical radiotherapy was 32 months (range: 15–41 months). Local recurrences were observed in 21 patients, and distant metastases were found in 21 patients. Brain was the most common site of metastatic disease; isolated cerebral metastases were identified in five of 67 patients (7.5%). Isolated brain metastases were found in five of 52 (9.6%) patients with stage III disease. Estimated 3-year overall survival was 42%, local progression-free survival was 55%, and distant metastases-free survival was 62%. Median overall survival was 21 months. Estimated three-year overall survival rates for stage III and stage I/II patients were 36% and 61%, respectively. Fifty-two stage III patients had a median overall survival of 17 months, whereas the median overall survival for stage I/II patients has not been reached. For comparison of overall survival of stage III patients with a historical cohort from the same institution, two patients treated out of protocol were excluded; one of them received 52 Gy in 13 fractions, and the other one 59.4 Gy in 33 fractions. Median and 3-year overall survival was 17 months and 33%, respectively. Median overall survival in 50 patients with stage III disease was identical to that in the previously published series of 173 patients treated in the same institution and according to the same protocol but without the inclusion of PET-CT in staging or radiotherapy planning. The difference in overall survival between these two patient cohorts was not statistically significant. Three-year overall survival rate was 19% in the historical group and 33% in the currently studied group ($p = 0.10$). Median follow-up for living patients in the historical group was 32 months (range: 18–84 months). The characteristics of stage III patients from the current study group and historical group are shown in Table 1. There were no statistically significant differences between both groups regarding median age and the distribution of remaining analysed clinical variables (sex, performance status, weight loss, clinical stage, histological subtype, use of chemotherapy).

Of the 24 patients referred for palliative treatment after PET-CT, seven received chemotherapy, 12 were treated with palliative radiotherapy and the remained five received supportive care only. Two patients were lost to follow-up. Twenty- two patients were included in the analysis of overall survival. Their median overall survival was 7 months (range: 2-26 months) and the estimated 2- and 3-year overall survival rates were 14% and 0%, respectively. These values compare unfavorably with those in curatively treated patients ($p < 0.0001$) (fig. 1). The characteristics of patients treated palliatively after PET-CT staging are shown in Table 3. There were no statistically significant differences between curatively and palliatively treated patients regarding median age and the distribution of remaining analysed clinical variables (sex, performance status, weight loss, clinical stage, histological subtype, use of chemotherapy).

Isolated nodal failures (INF) occurred in three of 67 patients (4.5%).In all these cases ENI had been omitted after PET-CT. In a group of 50 patients treated with IFRT the incidence of INF was 6%. Cumulative incidence of INF at three years was 10% (95% CI: 0–21%) for all irradiated patients and 12% (95% CI: 0–26%) for patients treated with IFRT.

Discussion

We have shown a relatively good survival of NSCLC patients managed with curative radiotherapy, although the rate of INF seems higher as that reported in other studies on PET-CT-based radiotherapy. The difference in survival between patients irradiated radically and those referred for palliation after PET-CT suggests that survival may be improved in curatively treated patients staged with PET-CT before radiotherapy. It may explain an improvement in survival seen in the contemporary studies on curative radiotherapy [14]. Short median overall survival in patients excluded from curative radiotherapy reflects the high mortality rate in this group of patients. If no PET-CT data had been available, those patients would have been treated with radical intention, which would compromise the overall outcome of radiotherapy.

The prospective randomised Positron Emission Tomography (PET) Imaging in Stage III Non-small Cell Lung Cancer (PET-START) study [9] included 310 patients with stage III NSCLC and showed a trend towards improved survival after PET-CT-based staging and radiotherapy planning, when compared to conventional imaging techniques. An Australian study [7] also showed an improvement in radiotherapy outcomes with the use of PET-CT. The outcomes of stage I–III NSCLC patients included in the prospective study on radio- and radiochemotherapy without PET-CT were compared to the results of PET-CT-staged patients included in another prospective study. A signifi-

Table 1. The characteristics of 67 patients treated radically after PET-CT staging

Characteristics	Number (percent) of patients
Age	Median 67 range 43–82
≤ 70	40 (59)
> 70	27 (41)
Gender	
Male	52 (78)
Female	15 (22)
Karnofsky performance status	
90–100	46 (69)
80	21 (31)
Weight loss in the six months preceding radiotherapy	
>10%	4 (6)
5–10%	8 (12)
No weight loss. or less than 5%	55 (82)
Histology	
Squamous	29 (43)
Adenocarcinoma	6 (9)
Large cell	1(2)
Non small-cell lung cancer without further specification	29 (43)
No pathologic confirmation	2 (3)
*Clinical stage after PET	
I	11 (16.5)
II	4 (6)
IIIA	21 (31)
IIIB	31 (46.5)
*T stage after PET	
T1	11 (17)
T2	21 (31)
T3	7 (11)
T4	27 (40)
rT0†	1 (1)
*N stage after PET	
N0	22 (33)
N1	10 (15)
N2‡	30 (45)
N3	5 (7)
Neoadjuvant chemotherapy	
Yes	34 (51)
No	33 (49)
Radiotherapy schedule	
13 × 4 Gy	8 (12)
30 × 2.2 Gy	8 (12)
21 × 2.8 Gy; IFRT	34 (51)
21 × 2.8 Gy; z ENI	16 (24)
33 × 1.8 Gy ^	1 (1)

*TNM stage according to the TNM classification UICC 5th edition (1997)
†Includes one relapse after surgery (rT0N2)
‡Includes one relapse after surgery (rN2)
^ Ower total dose and different fractionation schema for stage III patient resulted from location of the tumor close to the spinal cord; IFRT — involved-field radiotherapy

Table 2. The characteristics of stage III patients from the PET-CT group# and historical group

Characteristics	Number (percent) of patients	
	Study group	Historical group
Age	Median 64, range 43-80	Median 63, range 44-82
≤ 70	34 (68)	133 (77)
> 70	16 (32)	40 (23)
Gender		
Male	38 (76)	133 (77)
Female	12 (24)	40 (23)
Karnofsky performance status		
90–100	37 (74)	106 (61)
80	13 (26)	67 (39)
Weight loss in the six months preceding radiotherapy		
> 5%	7 (14)	28 (16)
No weight loss, or less than 5%	43 (86)	145 (84)
Histology		
Squamous	21 (42)	76 (44)
Adenocarcinoma	4 (8)	23 (13)
Large cell	1 (2)	2 (1)
Non small-cell lung cancer without further specification	22 (44)	72 (42)
No pathologic confirmation	1 (2)	0
*Clinical stage		
IIIA	21 (42)	96 (55)
IIIB	29 (58)	77 (45)
Neoadjuvant chemotherapy		
Yes	31 (62)	118 (68)
No	19 (38)	55 (32)

#50 patients included in the survival analysis
*TNM stage according to the TNM classification UICC 5th edition (1997)

cant reduction (45%) in NSCLC-related mortality was observed in patients treated after PET-CT when compared to the non-PET-CT group (p = 0.0075). Nevertheless, multivariate analysis stratified by whether chemotherapy was given and by the degree of the weight loss (there was statistically significant imbalance in the degree of weight loss between the two groups), revealed the reduction in an overall risk of death of 29% (HR = 71; 95% CI: 0.45–1.1; p = 0.06). A German study [8] analysed the impact of PET-CT on the outcomes of neoadjuvant radiochemotherapy (neoadjuvant radiochemotherapy, NARCT) in patients with stage III NSCLC, treated within the framework of the same prospective study.The first 115 patients underwent PET-CT scan before qualification for NARCT; in the remaining 78 patients only conventional imaging without PET-CT was performed, due to financial constraints. Thirty-one patients in the PET-CT group (27%) were excluded from curative treatment due to the presence of distant metastases or too extensive locoregional disease. Median overall survival for patients treated curatively with vs. without PET-CT was 22.3 vs. 11.3 months, respectively. Univariate analysis showed a significantly higher overall survival rate in the PET-CT group (p = 0.006). The use of PET-CT was a single independent prognostic factor influencing overall survival in multivariate analysis. Locoregional failure rates were similar in both groups, whereas the PET-CT group had a significantly lower incidence of distant metastases – distant metastases-free survival was significantly longer in that group. Thus, better treatment outcomes after PET-CT resulted from an appropriate patients' selection, with the exclusion of patients with N3 and/or M1 stage from curative treatment.

Contrary to the above mentioned results, in the current study median overall survival in stage III patients (17 months) was identical as in the historical group of patients with same stage of disease, treated in the same institution according to the same radiotherapy schedule (with or without chemotherapy) but without PET-CT [11]. In this group of patients there was no correlation between PET-CT and decrease in early mortality. Patients in the presen-

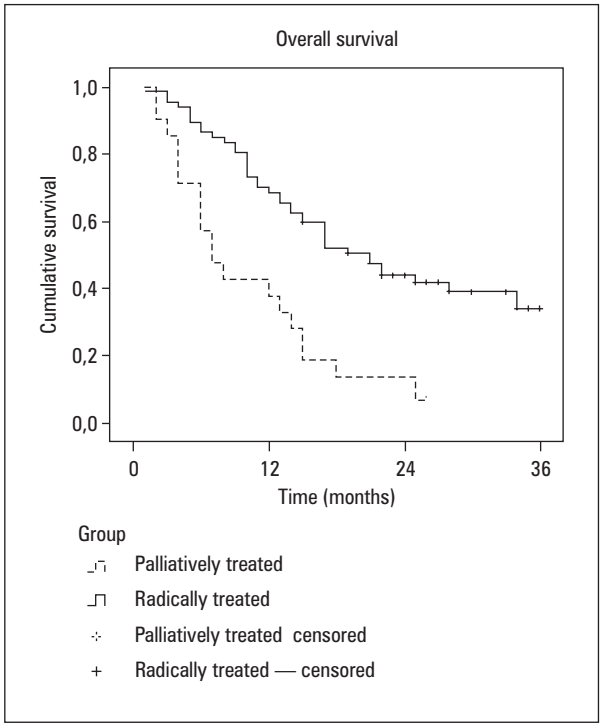

Figure 1. Overall survival for radically and palliatively treated patients

Table 3. The characteristics of 22# patients treated palliatively after PET-CT staging

Characteristics	Number (percent) of patients
Age	Median 64 range 50-82
≤ 70	16 (73)
> 70	6 (27)
Gender	
Male	16 (73)
Female	6 (27)
Karnofsky performance status	
90–100	16 (73)
80	6 (27)
Weight loss in the six months preceding radiotherapy	
>10%	1 (4.5)
5–10%	2 (9)
No weight loss. or less than 5%	19 (86.5)
Histology	
Squamous	10 (46)
Adenocarcinoma	1 (4.5)
Large cell	1 (4.5)
Non small-cell lung cancer without further specification	8 (36)
Carcinoid	1 (4.5)
No pathologic confirmation	1 (4.5)

#Among 24 patients qualified after PET-CT for palliative treatment two were lost from the follow-up; 22 patients were included in the survival analysis

ted study were not systematically evaluated for potential brain lesions prior to therapy. Standard PET-CT scan using fluorode-oxyglucose is unable to identify potential brain lesions. The incidence of isolated brain failures in a whole group of patients with stage III disease was 9.6% (5 out of 52 patients), so performing brain CT or MRI prior to radiotherapy could contribute to further improvement of the outcomes of curatively irradiated patients. The comparison with historical control and limited number of patients in the presented study represent its major limitations. That could contribute to the lack of statistically significant differences in survival between curatively treated stage III patients, with vs. without PET-CT. Patient qualification for curative radiotherapy based on PET-CT results, however, was associated with numerically improved three-year overall survival rate (33% vs. 19% with and without PET-CT, respectively). Therefore, PET-CT permits the selection of patients who can benefit most from curative treatment and achieve long-term survival, as supported by the above-mentioned German study results [8].

On the other hand, it is still possible that PET-CT has limited value for stage III patients, since more advanced locoregional disease carries a greater risk of micrometastases. This idea agrees with a recent mediastinoscopy study revealing that > 30% of patients with stage III NSCLC have nodal metastases undetected by PET-CT scan [15]. The sensitivity of the PET-CT scan performed shortly after completion of chemotherapy may be limited [16], but prospective data suggest a strong correlation of metabolic response to induction chemotherapy and treatment outcomes and failures [17]. An improvement in the outcomes of NSCLC patients treated with radiotherapy with the use of PET-CT is still to be demonstrated.

Three-year overall survival in stage I/II patients was 61% in the presented study. A retrospective analysis of treatment outcome in 132 patients with early stages of disease, irradiated in our centre according to various protocols before the PET-CT era, revealed three-year overall survival rate of 37% [18]. The retrospective character of this study and lack of a uniform treatment protocol limit our conclusions, but comparison of these data and the results of the presented study points to a possible survival benefit of the use of PET-CT for qualification for radiotherapy in early stage NSCLC patients as well.

An incidence of isolated nodal failures is higher in the presented study than in other series where ENI was omitted after PET-CT [19, 20]. It is an unexpected finding, especially when considered that IFRT was administered only in patients with low nodal stage (up to single N2 < 3 cm in size). It cannot be excluded that longer follow-up for living patients and prospective analysis of the

site of failure in the presented study led to a higher incidence of INF as compared to other publications.

Conclusions

In conclusion, the outcome of NSCLC patients managed with PET-CT-based irradiation shows a relatively good efficacy of curative radiotherapy. Despite a high rate of early mortality in patients excluded from curative radiotherapy after PET-CT, median survival in stage III patients does not differ from that of patients treated previously in the same institution with the same schedule but without PET-CT use. This would suggest that the use of PET-CT in diagnostics and treatment planning does not confer a survival advantage in stage III patients. Obviously, it does not compromise the utility of this imaging method in these patients, especially when considering a previously demonstrated broad range of advantages related to its use. Numerically improved three-year overall survival rate in patients irradiated after PET-CT suggests the possibility of better identification of potential long-term survivors. The rate of INF reported in this study seems meaningful and cannot be neglected, since the therapeutic options for NSCLC relapse are usually very limited.

Conflict of interest

The authors declares no conflict of interest.

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