Research Article

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Is routine baseline brain imaging needed for all newly diagnosed non-small-cell lung cancer patients?

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Aim: Dedicated brain imaging is advocated by the National Comprehensive Cancer Network guidelines for newly diagnosed non-small-cell cancer (NSCLC) patients beyond stage I. The current study assessed the performance characteristics of this recommendation. **Methods:** Through accessing the Surveillance, Epidemiology and End Results (SEER) registry (2010–2015), all patients (regardless of stage) with newly diagnosed NSCLC and complete information about TN stages and presence or absence of brain metastases were extracted. In the current study, the following performance characteristics of the above recommendation were assessed: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), number needed to investigate (NNI) and accuracy. **Results:** A total of 182,977 NSCLC patients were included. For the overall cohort, PPV (for the recognition of brain metastases) was 13.8% and NNI to detect one case of brain metastasis was 7.2. Likewise, NPV (for the exclusion of brain metastases) was 97%, sensitivity was 92.1%, specificity was 31.1% and overall accuracy was 37.6%. When stratified by histology, patients with adenocarcinoma have PPV of 17.2% and NNI to detect one case with brain metastasis of 5.8. NPV (for the exclusion of brain metastases) was 97%, sensitivity of 91.4%, specificity of 35.4% and overall accuracy of 32.6%. On the other hand, patients with squamous cell carcinoma have PPV of 6.3% and NNI to detect one case with brain metastasis of 15.8. NPV (for the exclusion of brain metastases) was 98.9%, sensitivity of 94.6%, specificity of 26.3% and overall accuracy of 29.7%. **Conclusion:** In view of the poor specificity, the current study calls for reconsideration of the universal recommendation of dedicated brain imaging (in addition to PET/CT scan) among NSCLC patients beyond stage I.

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Reasonable use of resources in the setting of baseline staging of solid tumors is a tricky job. On one hand, proper determination – at the start of treatment – of whether a patient has distant metastatic disease would spare the patient unnecessary and potentially aggressive radical treatments [1]; on the other hand, overuse of staging investigations to nonindicated patients has its own dire medical and economic consequences [2].

Non-small-cell lung cancer (NSCLC) is one of the most commonly diagnosed and treated solid tumors [3]. PET/CT scan has been advocated as an indispensable staging modality among all patients planned for radical treatment [4]. Brain metastases are particularly more common with lung cancer (compared with other solid tumors) and PET scans are notoriously less sensitive to detect brain metastases compared with other distant sites of metastases [5].

The addition of dedicated brain imaging (particularly brain MRI) was additionally advocated by the National Comprehensive Cancer Network (NCCN) guidelines for patients beyond stage I NSCLC (according to NCCN NSCLC guidelines version 4.2018) [6]. This universal recommendation was made independent of the histological subtype within NSCLC.

External validation of these recommendations within a real-world setting is of paramount significance to examine its performance characteristics and to re-question the relevance and the need for a change in these recommendations.

Moreover, external validation would allow assessment of the performance of these guidelines in specific contexts (including different histological subtypes and diverse staging approaches).

Objective

To assess the performance characteristics of routine baseline brain imaging among newly diagnosed NSCLC patients in a population-based setting.

Methodology

After querying Surveillance, Epidemiology and End Results (SEER)*Stat software (Version 8.3.5), the cases assessed in this study were extracted by the SEER-18 registry [7].

Selection of the study population

Within the SEER database, all NSCLC patients (including those with adenocarcinoma, squamous cell carcinoma, large cell carcinoma or NSCLC, NOS) diagnosed from 2010 to 2015 with complete information about TN stage and brain metastases were selected. To be noted, the SEER database represents almost 28% of cancer patients in USA and it covers a variety of academic and community treatment centers.

Data collection

The following information was selected from each patient wherever available: age at diagnosis, race, gender, histology, subsite, laterality, TN stage, tumor size, extension, bone metastases, brain metastases, liver metastases, lung metastases, surgical treatment, radiotherapy and chemotherapy. Because the reported TN stages in the SEER database were of the 7th AJCC system, TN stages were transformed into comparable AJCC 8th TN stages (using tumor size and extension information).

Evaluation of the NCCN recommendations

One primary analysis was conducted which relates to the ability of the NCCN recommendations to identify brain metastases. An initial analysis was conducted for all patients regardless of their histology. A subsequent analysis was added for two of the principal histological subtypes of NSCLC (namely; adenocarcinoma and squamous cell carcinoma).

Statistical considerations

Descriptive statistics (including frequencies and proportions) were performed for baseline clinicopathological characteristics and received treatments for the entire cohort.

In order to properly evaluate performance characteristics, the following parameters were used including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), number needed to investigate (NNI) and accuracy. All the analyses were done using SPSS Statistics 20.0 (IBM, NY, USA).

Results

Patients characteristics

After excluding patients with incomplete information about brain metastases, and TN stages, a total of 182,977 patients (84.2%) were included in the study. Adenocarcinoma constituted the majority of cases (59.9%). Age group $\geq$ 70 years represented 50.4% of the cases. White race represented 80.9% and male patients represented 52.5%. Distribution of patients according to AJCC 7thTN stages was reported in Table 1. 72.1% of the cases were staged clinically while 27.2% of the cases were staged pathologically. 70.5% of the patients did not undergo radical surgery. 10.7% of the patients have brain metastases at the time of diagnosis.

Evaluation of NCCN recommendations in all patients

Among the included patients in the study, 52,411 patients have T1–T2a N0 (i.e., brain scan is not recommended); while 130,566 patients have more advanced stages (i.e., brain scan is recommended).

Using the NCCN recommendations, 1551 patients (0.8%) with brain metastases would have been missed; while 112,463 patients (61.4%) would have brain imaging despite having no brain metastases. This results in a PPV (for the recognition of brain metastases) of 13.8% and NNI to detect one case of brain metastasis of 7.2. Likewise, this means NPV (for the exclusion of brain metastases) of 97%, sensitivity of 92.1%, specificity of 31.1% and overall accuracy of 37.6% (Table 2).

Table 1. Baseline characteristics of included patients in the study (n = 182,977 patients).

Parameter	n (%)
Race	
– White	148,055 (80.9%)
– Black	21,779 (11.9%)
– Others	12,768 (7%)
– Unknown	375 (0.2%)
Sex	
– Females	86,919 (47.5%)
– Males	96,058 (52.5%)
Age	
– <40 years	1117 (0.6%)
– 40–69 years	89,592 (49%)
– ≥70 years	92,268 (50.4%)
Subsite	
– Main bronchus	6483 (3.5%)
– Upper lobe	101,088 (55.2%)
– Middle lobe	8775 (4.8%)
– Lower lobe	51,974 (28.4%)
– Overlapping lesion	1822 (1%)
– Unknown	12,835 (7%)
Laterality	
– Right	105,487 (57.7%)
– Left	74,250 (40.6%)
– Bilateral	1721 (0.9%)
– Unknown	1519 (0.8%)
Histology	
– Adenocarcinoma	109,688 (59.9%)
– Sqaumous cell carcinoma	56,144 (30.7%)
– Large cell carcinoma	1722 (0.9%)
– NSCLC, NOS	15,423 (8.4%)
T stage (AJCC 7th)	
– T1	49,552 (27%)
– T2	54,899 (30%)
– T3	38,530 (21%)
– T4	39,996 (22%)
N stage (AJCC 7th)	
– N0	85,237 (46.6%)
– N1	16,264 (8.9%)
– N2	59,639 (32.6%)
– N3	21,837 (11.9%)
Staging approach	
– Clinical	131,836 (72.1%)
– Pathological	29,814 (27.2%)
– Unknown	1327 (0.7%)
Surgery	
– Pneumonectomy	2145 (1.1%)
– Lobectomy/sublobar resection	51,169 (27.9%)
– No surgery	129,073 (70.5%)
– Unknown	590 (0.5%)
Chemotherapy	
– Yes	78,326 (42.8%)
– No/unknown	104,651 (57.2%)
Radiotherapy	
– Yes	78,177 (42.8%)
– No/unknown	104,800 (57.2%)
Bone metastases	
– Yes	28,619 (15.6%)
– No	153,565 (83.9%)
– Unknown	793 (0.5%)
Brain metastases	
– Yes	19,654 (10.7%)
– No	163,323 (89.3%)
Liver metastases	
– Yes	13,237 (7.2%)
– No	168,860 (92.3%)
– Unknown	880 (0.5%)

Table 2. Recommendations for brain imaging according to NCCN NSCLC guidelines (all patients; T1-4 N0-3).

	Reference: brain metastases as shown on brain imaging		NNI (1/PPV)7.2
	Brain metastases (19,654 patients)	No brain metastases (163,323 patients)	
Brain imaging recommended (130,566 patients)†	TP N = 18,103 patients	FP N = 112,463 patients	PPV = TP/(TP+FP) 13.8%
Brain imaging not recommended (52,411 patients)†	FN N = 1551 patients	TN N = 50,860 patients	NPV = TN/(TN+FN) 97%
	Sensitivity = TP/TP+FN 92.1%	Specificity = TN /FP+TN 31.1%	Accuracy (TN+TP/All) 37.6%

†Brain imaging not recommended: T1–T2a N0; Brain imaging recommended: all other patients.
FN: False negative; FP: False positive; NNI: Number needed to investigate; NPV: Negative predictive value; PPV: Positive predictive value; TN: True negative; TP: True positive.

Table 3. Recommendations for brain imaging according to NCCN NSCLC guidelines (all adenocarcinoma patients; T1–4 N0–3).

	Reference: brain metastases as shown on brain imaging		NNI (1/PPV)5.8
	Brain metastases (14,071 patients)	No brain metastases (95,617 patients)	
Brain imaging recommended (74,543 patients)†	TP N = 12,865 patients	FP N = 61,678 patients	PPV = TP/(TP+FP) 17.2%
Brain imaging not recommended (35,145 patients)†	FN N = 1206 patients	TN N = 33,939 patients	NPV = TN/(TN+FN) 97%
	Sensitivity = TP/TP+FN 91.4%	Specificity = TN /FP+TN 35.4%	Accuracy (TN+TP/All) 32.6%

†Brain imaging not recommended: T1–T2a N0; Brain imaging recommended: all other patients.
FN: False negative; FP: False positive; NNI: Number needed to investigate; NPV: Negative predictive value; PPV: Positive predictive value; TN: True negative; TP: True positive.

Evaluation of NCCN recommendations according to histological subtype

Adenocarcinoma

Among patients with adenocarcinoma, the performance characteristics of the NCCN recommendations for brain scan were as follows: PPV was 17.2% and NNI to detect one case with brain metastasis was 5.8. NPV (for the exclusion of brain metastases) was 97%, sensitivity of 91.4%, specificity of 35.4% and overall accuracy of 32.6% (Table 3).

Squamous cell carcinoma

Among patients with squamous cell carcinoma, the performance characteristics of the NCCN recommendations for brain scan were as follows: PPV was 6.3% and NNI to detect one case with brain metastasis was 15.8. NPV (for the exclusion of brain metastases) was 98.9%, sensitivity of 94.6%, specificity of 26.3% and overall accuracy of 29.7% (Supplementary Table 1).

Evaluation of NCCN recommendations according to staging approach

Given the fact that some patients have been staged clinically and other patients have been staged pathologically (according to AJCC criteria for staging); and given the expected effect of staging approach on performance characteristics of the NCCN recommendations, the performance characteristics were repeated separately for clinically versus pathologically staged patients. Among clinically staged patients, NCCN recommendations were characterized by high sensitivity (92%) and low specificity (18.1%). On the other hand, and among pathologically staged patients, NCCN recommendations were characterized by lower sensitivity (73.4%) and higher specificity (61.4%) (Supplementary Table 2).

Evaluation of different imaging thresholds

Given the observed modest specificity for detection of brain metastasis (compared with sensitivity), another threshold for imaging was hypothesized and tested (this hypothesis includes patients with T2b N0 among patients not recommended for staging). This threshold for brain imaging leads to a modest improvement in specificity (33.5% for all patients; 37.5% for adenocarcinoma and 29.4% for squamous cell carcinoma) (Supplementary Table 3).

An additional threshold (that is compatible with the NICE guidelines in the UK [8]) was examined that does not offer routine brain imaging to stage I or stage II patients. This threshold leads to an even higher specificity (46.6% for all patients; 50.1% for adenocarcinoma and 43.9% for squamous cell carcinoma) (Supplementary Table 4).

Discussion

Proper staging of NSCLC provides important information with regard to the therapeutic decision-making process for each individual patient. Determination of whether any patient has a localized versus metastatic disease as well as the distribution of distant metastases should fundamentally change the treatment options/approaches that a patient may have. Although PET/CT scan is currently considered a standard imaging procedure for newly diagnosed patients with NSCLC (particularly those planned for potentially curative treatment), the additional role of specific brain imaging with different stages is a subject of ongoing debate. The NCCN guidelines advocated universal brain imaging for patients with >stage I disease. However, to the best of our knowledge, the performance of this recommendation was not examined in a population-based database with a big enough cohort of patients, as in the current study.

The current analysis revealed a number of important findings. Although the current NCCN recommendations showed very satisfactory NPV (≥97%) regardless of the histological subtype, PPV was, however, variable depending on the histological category (PPV for adenocarcinoma patients is almost triple that of squamous cell carcinoma patients). This difference might be related to the reported higher rates of distant metastases (including brain metastases) among adenocarcinoma compared with squamous cell carcinoma. These findings result in NNI for squamous cell carcinoma triple that of adenocarcinoma. Sensitivity was generally satisfactory among the overall cohort as well as both histological subtypes (≥91%). On the other hand, specificity was not satisfactory for the overall cohort as well as both histological subtypes (≤35%). This is related to the significant proportion of patients who will be investigated with brain imaging without having brain metastases. When modifying the threshold for brain imaging to exclude stage IIA or whole stage II from routine imaging, there is a modest increase in specificity and – as expected – lower sensitivity.

Overall, the current analysis shows that the current NCCN recommendations for brain imaging among NSCLC patients need to be revisited given the significant number of patients hypothetically investigated without having subsequent brain metastases.

This question is even more relevant now given the universal recommendation of having baseline whole-body PET/CT scan for all curatively treated patients (although PET/CT scan is not as accurate as dedicated brain MRI in detecting cerebral metastases, it can still detect some cases of brain metastases particularly if the brain was included in the PET/CT field; thus, minimizing further the added benefit of a dedicated brain imaging [9,10]).

The above discussion about the additional role of dedicated brain MRI should be relevant only for asymptomatic patients with a potentially curative treatment plan. Symptomatic patients should be offered dedicated brain imaging regardless of T and N stages. On the other hand, asymptomatic patients with no plans for a potentially curative treatment should probably be spared unnecessary additional brain imaging [11].

Several weaknesses should be acknowledged in the current study. Because of the specific nature of the SEER database as a population-based registry and because of the retrospective nature of this study, the current analysis did not separately identify cases that might have been imaged for brain metastatic disease (and subsequently diagnosed with it) based on symptomatology (e.g., headache or seizures). Moreover, this study represents the performance characteristics of the NCCN guidelines within academic/community settings in USA; confirmatory analyses are needed from community settings in other geographic areas/other treatment settings to ensure reproducibility and consistency of the findings of the current study. Additionally, exact staging investigations done for each included patient were not detailed in the SEER dataset. However, given the fact that all included patients were treated in one of the US cancer hospitals, it is expected that most (if not all) of them underwent appropriate standard-of-care staging assessment at the time of diagnosis. These weaknesses should be looked at in the context of the strengths of the current study. In particular, the use of a large patient cohort and the established quality assurance program within the SEER database are specific features within the current study.

While performance characteristics of the current staging paradigms for lung cancer are reasonable end points, other aspects should be respected. These include the economic costs of universally recommending an additional staging investigation for such a common malignancy as lung cancer and potential side effects of the contrast imaging (despite being rare, they still should be considered as part of the overall picture) [12]. Moreover, the psychological burden added to the patients from an additional staging investigation should never be underestimated [13]. Another

important aspect is the potential impact of a positive finding for a metastatic disease on the overall treatment strategy for patients planned for radical/potentially curative treatment.

In conclusion, the current study calls for the reconsideration of the universal recommendation of dedicated brain imaging (in addition to PET/CT scan) among NSCLC patients beyond stage I. Further studies incorporating cost–effectiveness analyses of this recommendation are warranted.

Summary points

- Through accessing the Surveillance, Epidemiology and End Results (SEER) registry (2010–2015), all patients (regardless of stage) with newly diagnosed non-small-cell lung cancer (NSCLC) and complete information about TN stages and brain metastases were extracted.
- In the current study, the following performance characteristics were assessed: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), number needed to investigate (NNI) and accuracy.
- A total of 182,977 NSCLC patients were included.
- For the overall cohort, PPV (for the recognition of brain metastases) was 13.8% and NNI to detect one case of brain metastasis was 7.2. Likewise, NPV (for the exclusion of brain metastases) was 97%, sensitivity was 92.1%, specificity was 31.1% and overall accuracy was 37.6%.
- When stratified by histology, patients with adenocarcinoma have PPV of 17.2% and NNI to detect one case with brain metastasis of 5.8. NPV (for the exclusion of brain metastases) was 97%, sensitivity of 91.4%, specificity of 35.4% and overall accuracy of 32.6%.
- On the other hand, patients with squamous cell carcinoma have PPV of 6.3% and NNI to detect one case with brain metastasis of 15.8. NPV (for the exclusion of brain metastases) was 98.9%, sensitivity of 94.6%, specificity of 26.3% and overall accuracy of 29.7%.
- In view of the poor specificity, the current study calls for the reconsideration of the universal recommendation of dedicated brain imaging (in addition to PET/CT scan) among NSCLC patients beyond stage I.
- Further studies incorporating cost–effectiveness analyses of this recommendation are warranted.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This article does not contain any studies with human participants or animals performed by the author. Informed consent: as this study is based on a publicly available database without identifying patient information, informed consent was not needed.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2018-0148

References

Papers of special note have been highlighted as: • of interest;

1. Liam CK, Andarini S, Lee P, Ho JC, Chau NQ, Tscheikuna J. Lung cancer staging now and in the future. *Respirology* 20(4), 526–534 (2015).
2. Yasufuku K, Fujisawa T. Staging and diagnosis of non-small cell lung cancer: invasive modalities. *Respirology* 12(2), 173–183 (2007).
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68(6), 394–424 (2018).
4. Postmus PE1, Kerr KM2, Oudkerk M *et al.* ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 28(Suppl. 4), iv1–iv21 (2017).
5. Kitajima K, Nakamoto Y, Okizuka H *et al.* Accuracy of whole-body FDG-PET/CT for detecting brain metastases from non-central nervous system tumors. *Ann. Nucl. Med.* 22(7), 595–602 (2008).
6. NCCN guidelines for non-small-cell lung cancer. Version 4, 2018. (2018). www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

• **National Comprehensive Cancer Network guidelines 2018.**

7. Surveillance, Epidemiology and End Results Program. About the SEER Program. (2016). http://seer.cancer.gov/about

8. National Institute for Health and Care Excellence (2011). Lung cancer: diagnosis and management (NICE Guideline 121). www.nice.org.uk/guidance/cg121/chapter/1-Guidance

- **NICE guidelines for workup of diagnosis and management of lung cancer.**

9. Bochev P, Klisarova A, Kaprelyan A, Chaushev B, Dancheva Z. Brain metastases detectability of routine whole body ^{18}F-FDG PET and low dose CT scanning in 2502 asymptomatic patients with solid extracranial tumors. *Hell. J. Nucl. Med. 1* 5(2), 125–129 (2012).

10. Manohar K, Bhattacharya A, Mittal BR. Low positive yield from routine inclusion of the brain in whole-body ^{18}F-FDG PET imaging for noncerebral malignancies: results from a large population study. *Nucl. Med. Commun. 3* 4(6), 540–543 (2013).

11. Vansteenkiste J, Crino L, Dooms C *et al.* 2nd ESMO consensus conference on lung cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann. Oncol. 2* 5(8), 1462–1474 (2014).

12. Andreucci M, Solomon R, Tasanarong A. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. *BioMed Res. Intern. 2* 014, 20 (2014).

13. Andersen BL. Psychological interventions for cancer patients to enhance the quality of life. *J. Consult. Clin. Psychol.* 60(4), 552–568 (1992).