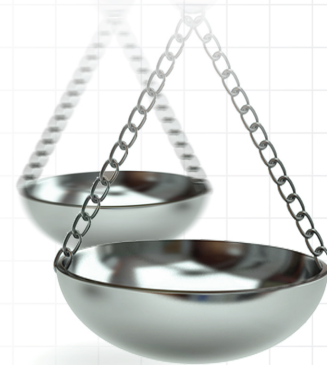




Population-based assessment of the National Comprehensive Cancer Network recommendations for baseline imaging of rectal cancer

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Aim: To examine the performance characteristics of alternative criteria for baseline staging, in a cohort of contemporary rectal cancer patients from the Surveillance, Epidemiology and End Results (SEER) database.

Methods: The SEER database (2010–2015) was accessed and patients with rectal cancer plus complete information on clinical T and N stages as well as metastatic sites were evaluated. We examined various performance characteristics of baseline imaging, including specificity, sensitivity, number needed to investigate (NNI), positive predictive value (PPV), negative predictive value and accuracy. **Results:** A total of 15,836 rectal cancer patients were included. Based on current guidelines that suggest cross-sectional chest and abdominal imaging for all cases of invasive rectal cancer, these recommendations would yield a PPV of 11.9% for the detection of liver metastases and 6.2% for the detection of lung metastases. This would translate to an NNI of 8.4 for liver metastases and an NNI of 16.1 for lung metastases. When patients with T1N0 were excluded from routine imaging, this resulted in a PPV of 6.4% and an NNI of 15.6 to identify one case of lung metastasis. Likewise, this resulted in a PPV of 12.3% and an NNI of 8.0 to detect one case of liver metastasis. Similarly, when patients with either T1N0 or T2N0 were excluded from routine imaging, the PPV and NNI for lung metastases improved to 6.6% and 15.1, respectively, and the PPV and NNI for liver metastases improved to 12.6 and 7.9%, respectively. **Conclusion:** Our study suggests that the specificity of the current imaging approach for rectal cancer staging is limited and that the omission of chest and abdominal imaging among selected early stage asymptomatic cases may be reasonable to consider.

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The initial assessment of newly diagnosed rectal cancer patients should entail a proper evaluation of disease biology, disease extent and patients' comorbidity burden and functional status [1]. The evaluation of disease extent is typically conducted by clinical, endoscopic and radiological examinations [2]. The current National Comprehensive Cancer Network (NCCN) guidelines for initial staging of rectal cancers recommend that chest, abdomen and pelvic computed tomography (CT) scans be performed for all cases of invasive rectal cancer [3]. This recommendation is made regardless of the clinical stage of rectal cancer, which contrasts the NCCN guidelines for other solid tumors (e.g., breast or prostate cancer) where there is a risk-stratified approach to initial staging investigations [4–6]. The rationale for such recommendations is to pick up cases with metastatic disease early so that they can be spared potentially aggressive, albeit futile, treatment interventions. Given that colorectal cancer is one of the most common solid tumors, the choice and intensity of baseline staging investigations may pose tremendous economic consequences for individual patients as well as for healthcare systems [7]. For this reason, we believe that these recommendations warrant scrutiny and their utility should be assessed in a population-based setting.

The primary hypothesis of the current study was that the universal recommendation to undergo chest and abdominal cross-sectional imaging in all cases of invasive rectal cancer may result in overinvestigation for a

Future
Medicine

considerable proportion of early stage patients. Our main aim was to examine the performance characteristics of alternative criteria for baseline staging in a cohort of contemporary rectal cancer patients from the SEER database.

Methodology

Selection of the study cohort

Records of patients evaluated in the current analysis were extracted from the SEER-18 registry [8] using the SEER*Stat software (Version 8.3.5).

Within the SEER database, we selected rectal cancer cases diagnosed from 2010 to 2015 with complete data on clinical T and N stages as well as on sites of metastases (liver, lung, bone or brain). Cases with noninvasive disease (Tis) were excluded. It should be noted that surgical pathological T and N stages were not considered in the current analysis. Determination of metastatic disease status was based primarily on clinical and/or radiological methods. In exceptional circumstances, this was supplemented by pathological information.

Evaluation of alternative staging recommendations

Two different analyses were conducted. Each one of them evaluated a different set of criteria for chest and abdominal imaging. The first set excluded patients with clinical T1N0 disease from routine imaging and the second set excluded all patients with clinical stage I disease (T1N0 and T2N0) from routine imaging.

Statistical considerations

Descriptive statistics (including frequencies and proportions) were explored for baseline parameters for the entire study population. These baseline parameters included age, sex, race, histology, clinical T and N stages, surgical treatment and the presence of liver, lung, bone and brain metastases.

We evaluated various performance characteristics for each group of criteria including positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, number needed to investigate (NNI) and accuracy. In order to calculate these performance characteristics, true positive observations, true negative observations, false-positive observations and false-negative observations were determined. The following equations were then used to calculate performance characteristics:

$PPV = \text{True positive} / (\text{true positive} + \text{false positive})$; $NPV = \text{True negative} / (\text{true negative} + \text{false positive})$; $\text{sensitivity} = \text{True positive} / (\text{true positive} + \text{false negative})$; $\text{specificity} = \text{True negative} / (\text{false positive} + \text{True negative})$; $NNI = 1 / PPV$ and $\text{accuracy} = (\text{true positive} + \text{true negative}) / \text{all observations}$.

All statistical calculations were performed using SPSS Statistics 20.0 (IBM, NY, USA).

Results

Patient characteristics

A total of 15,836 eligible rectal cancer patients were included in the study cohort. Among them, ages 40–69 years represented 66.4% of the cases, males 60.7% and white race 80.7%. The majority (73.8%) comprised adenocarcinoma. Patients with clinical stage T1N0 disease represented 7.9% of cases, those with clinical stage T2N0 represented 5.5%, and individuals with greater than T2N0 rectal cancer represented 86.6%. Among all patients, 33.5% had an elevated baseline CEA. More than half (54.6%) of the patients underwent primary tumor surgery (lower anterior resection or abdominoperineal resection; Table 1).

Liver metastases were reported in 11.9% of patients, lung metastases in 6.2%, bone metastases in 1.5% and brain metastases in 0.2%. Based on the current NCCN guidelines that suggest cross-sectional chest and abdominal imaging for all cases of invasive rectal cancer, these recommendations would yield a PPV of 11.9% for the detection of liver metastases and 6.2% for the detection of lung metastases. This would translate to an NNI of 8.4 for liver metastases and an NNI of 16.1 for lung metastases.

Evaluation of alternative baseline imaging criteria

The first group of alternative criteria that was assessed entailed excluding clinical T1N0 patients from routine chest and abdominal imaging. In the study cohort, 1246 patients had clinical T1N0 disease (i.e., chest and abdominal imaging would not be recommended when this hypothetical group of criteria was applied) while 14,590 patients had more advanced disease (i.e., chest and abdominal imaging would still be recommended).

Using this new, proposed criteria, 42 patients (0.2%) with lung metastases would have been missed and 91 patients (0.5%) with liver metastases would have been missed. Meanwhile, 13,652 patients (86.2%) would have

Table 1. Baseline characteristics of included patients in the study (N = 15836 patients).

Parameter	N (%)
Race:	
White	12,779 (80.7%)
Black	1511 (9.5%)
Others	1479 (9.3%)
Unknown	67 (0.4%)
Sex:	
Females	6229 (39.3%)
Males	9607 (60.7%)
Age:	
<40 years	700 (4.4%)
40–69 years	10,522 (66.4%)
≥70 years	4614 (29.2%)
Histology:	
Adenocarcinoma, not otherwise specified	11,690 (73.8%)
Other variants	4146 (26.2%)
Clinical stage:	
T1N0	1246 (7.9%)
T2N0	872 (5.5%)
>T2N0	13,718 (86.6%)
Surgery:	
Oncologic surgery	8635 (54.6%)
No oncologic surgery	7087 (44.7%)
Unknown	114 (0.7%)
CEA:	
Elevated	5302 (33.5%)
Normal	5273 (33.3%)
Unknown	5261 (Unknown)
Bone metastases:	
Yes	233 (1.5%)
No	15,603 (98.5%)
Brain metastases:	
Yes	32 (0.2%)
No	15,804 (99.8%)
Liver metastases:	
Yes	1880 (11.9%)
No	13,956 (88.1%)
Lung metastases:	
Yes	980 (6.2%)
No	14,856 (93.8%)

had chest imaging despite the absence of lung metastases, and 12,801 patients (80.8%) would have undergone abdominal imaging despite the lack of liver metastases.

This resulted in a PPV of 6.4% for the identification of lung metastases and an NNI of 15.6 to identify one case of lung metastasis. Likewise, this resulted in a PPV of 12.3% for the identification of liver metastases and an NNI of 8.0 to detect one case of liver metastasis.

Additional performance characteristics including specificity, sensitivity, accuracy and NPV are summarized in Table 2.

The second group of criteria that was evaluated comprised excluding clinical stage I (T1N0 and T2N0) patients from routine chest and abdominal imaging. In the study cohort, 2118 patients had clinical stage I disease (i.e. chest and abdominal imaging would not be recommended when these hypothetical criteria were applied) while 13,718 patients had more advanced disease (i.e. chest and abdominal imaging would still be recommended).

Using this alternative group of criteria, 71 patients (0.4%) with lung metastases would have been missed and 147 patients (0.9%) with liver metastases would have been missed. Conversely, 12,809 patients (80.8%) would have undergone chest imaging despite not being affected by lung metastases, and 11,985 patients (75.6%) would have had abdominal imaging despite not having liver metastases.

This resulted in a PPV of 6.6% for the identification of lung metastases and an NNI of 15.1 to identify one case of lung metastasis. Similarly, this resulted in a PPV of 12.6% for the identification of liver metastases and an NNI of 7.9 to detect one case of liver metastasis.

Table 2. Modified National Comprehensive Cancer Network recommendations for baseline chest and abdominal imaging for newly diagnosed rectal cancer patients (excluding T1N0 patients from routine imaging).

	Reference: Lung metastases as shown on chest imaging		NNI (1/PPV)
	Lung metastases (980 patients)	No lung metastases (14,856 patients)	15.6
Chest imaging recommended (14,590 patients)	TP N = 938 patients	FP N = 13,652 patients	PPV = TP/(TP+FP) 6.4%
Chest imaging not recommended (1246 patients)	FN N = 42 patients Sensitivity = TP/TP+FN 95.7%	TN N = 1204 patients Specificity = TN/FP+TN 8.1%	NPV = TN/(TN+FN) 96.6% Accuracy (TN+TP/All) 13.5%
	Reference: liver metastases as shown on abdominal imaging		NNI (1/PPV) 8
	Liver metastases (1880 patients)	No liver metastases (13,956 patients)	
Abdominal imaging recommended (14,590 patients)	TP N = 1789 patients	FP N = 12,801 patients	PPV = TP/(TP+FP) 12.3%
Abdominal imaging not recommended (1246 patients)	FN N = 91 patients Sensitivity = TP/TP+FN 95.2%	TN N = 1155 patients Specificity = TN/FP+TN 8.3%	NPV = TN/(TN+FN) 92.7% Accuracy (TN+TP/All) 18.5%

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. Modified National Comprehensive Cancer Network recommendations for baseline chest and abdominal imaging for newly diagnosed rectal cancer patients (excluding T1N0/T2N0 patients from routine imaging).

	Reference: Lung metastases as shown on chest imaging		NNI (1/PPV)
	Lung metastases (980 patients)	No lung metastases (14,856 patients)	15.1
Chest imaging recommended (13,718 patients)	TP N = 909 patients	FP N = 12,809 patients	PPV = TP/(TP+FP) 6.6%
Chest imaging not recommended (2118 patients)	FN N = 71 patients Sensitivity = TP/TP+FN 92.8%	TN N = 2047 patients Specificity = TN/FP+TN 13.8%	NPV = TN/(TN+FN) 96.6% Accuracy (TN+TP/All) 18.6%
	Reference: liver metastases as shown on abdominal imaging		NNI (1/PPV) 7.9
	Liver metastases (1880 patients)	No liver metastases (13,956 patients)	
Abdominal imaging recommended (13,718 patients)	TP N = 1733 patients	FP N = 11,985 patients	PPV = TP/(TP+FP) 12.6%
Abdominal imaging not recommended (2118 patients)	FN N = 147 patients Sensitivity = TP/TP+FN 92.2%	TN N = 1971 patients Specificity = TN/FP+TN 14.1%	NPV = TN/(TN+FN) 93.1% Accuracy (TN+TP/All) 23.3%

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.

Additional performance characteristics including specificity, sensitivity, accuracy and NPV are described in Table 3.

Discussion

Appropriate staging of rectal cancer provides helpful information that guides the decision-making process as it pertains to the management of individual patients. By determining the extent of metastatic disease, it can help to formulate a proper therapeutic strategy. The current staging approach endorsed by the NCCN and adopted by multiple other international organizations advocates for baseline cross-sectional chest, abdomen and pelvic imaging of all patients presenting with a new diagnosis of rectal cancer [1]. Our analysis, however, suggests that the specificity

of this approach may be limited and that the omission of chest and abdominal imaging in selected early-stage asymptomatic patients should be considered.

Importantly, our study also shows that the probability of brain or bone metastases is generally very low and supports the current NCCN recommendation that additional brain or bone imaging should only be considered in symptomatic individuals.

In contrast, the NCCN recommendation for universal cross-sectional chest and abdominal imaging for all rectal cancer patients was likely established at a time when local imaging modalities for T and N stages were less sensitive and thus accurate clinical staging was more difficult. With the introduction and widespread availability of more accurate local imaging modalities (e.g., endoscopic ultrasonography and rectal magnetic resonance imaging), it may be timely to reconsider the value of universal cross-sectional chest and abdominal imaging, especially among patients with clinically early stage disease [9].

One reason that justifies routine cross-sectional imaging is that some patients with apparent early stage colorectal cancer may have occult metastatic disease that is limited to the liver and/or lung. Importantly, such cases can still be approached curatively with appropriate local interventions (e.g., metastatic resection) and systemic therapies [10,11]. Of note, our study demonstrated that the rates of liver and/or lung metastases among asymptomatic T1N0/T2N0 patients are very low and that the omission of routine chest and abdominal imaging from these cases still resulted in an observed sensitivity for the entire cohort that remained acceptable.

Several limitations should be acknowledged when interpreting the conclusions of the current study. First, the SEER database is a population-based registry that captures information regarding the initial malignant diagnosis only. SEER database does not provide data regarding baseline imaging investigations that each patient has undergone. The current study is based on the assumption that all patients have been treated in a guideline-concordant fashion and they have undergone proper baseline assessment (given the fact that the vast majority of patients in the current study were treated within academic or community oncology centers in the USA). It is possible, however, that some of these patients were treated in a nonconcordant way with the guidelines. Second, it is important to note that the current analysis comprised cases that were solely diagnosed within the USA. Considering the differences in practice patterns between the USA and other countries, our findings may not be readily generalized to other jurisdictions.

Nonetheless, these limitations should be considered in the context of the study's strengths, namely the well-established data quality assurance mechanisms within the SEER database as well as the large cohort size.

It is also important to recognize that improving rectal cancer staging is not only about improving sensitivity or specificity. Other downstream benefits include reducing the economic burden on the healthcare system by minimizing futile imaging investigations and decreasing the risk of rare side effects to patients, such as the potential for contrast allergy or nephrotoxicity that may accompany contrast-enhanced imaging [12]. Moreover, unnecessary tests can also pose substantial psychological burden on patients, which is occasionally overlooked by physicians [13].

Another point that needs to be highlighted here is the potential financial burden associated with universal cross-sectional imaging even for patients with early stage rectal cancer. Omission of routine baseline staging for selected early stage patients might help relieve some of the economic strains on the healthcare system.

In conclusion, our study suggests that the specificity of the current baseline imaging approach for rectal cancer staging is limited and that the omission of chest and abdominal baseline imaging among selected early stage asymptomatic cases may be reasonable to consider.

Financial & competing interests disclosure

The authors have 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. As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

Summary points

- The SEER database (2010–2015) was accessed and patients with rectal cancer plus complete information on clinical T and N stages as well as metastatic sites were evaluated.
- We examined various performance characteristics of baseline imaging, including specificity, sensitivity, number needed to investigate (NNI), positive predictive value (PPV), negative predictive value and accuracy.
- Based on current guidelines that suggest cross-sectional chest and abdominal imaging for all cases of invasive rectal cancer, these recommendations would yield a PPV of 11.9% for the detection of liver metastases and 6.2% for the detection of lung metastases. This would translate to an NNI of 8.4 for liver metastases and an NNI of 16.1 for lung metastases.
- When patients with T1N0 were excluded from routine imaging, this resulted in a PPV of 6.4% and a NNI of 15.6 to identify one case of lung metastasis. Likewise, this resulted in a PPV of 12.3% and an NNI of 8.0 to detect one case of liver metastasis.
- Similarly, when patients with either T1N0 or T2N0 were excluded from routine imaging, the PPV and NNI for lung metastases improved to 6.6 and 15.1%, respectively, and the PPV and NNI for liver metastases improved to 12.6 and 7.9%, respectively.
- Our study suggests that the specificity of the current imaging approach for rectal cancer staging is limited and that the omission of chest and abdominal imaging among selected early stage asymptomatic cases may be reasonable to consider.

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