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Brief Opinion

Estimating changes in the rate of synchronous and metachronous metastases over time: Analysis of SEER data

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Introduction

Cancers are typically staged at diagnosis on the basis of the anatomic extent of disease. A cornerstone of the formal staging systems used for most cancers is the absence or presence of clinically evident distant metastatic spread (ie, the M-term of the TNM staging system).[1] Typically, patients who present without evidence of distant metastases are considered potentially curable, and patients who present with evidence of distant metastases are considered largely incurable.

However, staging systems and these generalizations are imperfect. Tools used for staging (eg, clinical history, physical examination, imaging studies, and sometimes invasive methods) are often inadequate. Many patients who present without clinical evidence of metastatic disease (cM0) indeed harbor occult distant disease that leads to subsequent mortality. Thus, distant metastases that are actually present at the time of diagnosis may be broadly considered to be either overt (eg, diagnosed synchronously with the primary lesion) or covert (diagnosed metachronously; ie, after definitive local/regional therapy).

Over the last several decades, there have been marked advances in the tools available to define the anatomic extent of disease at presentation (eg, computed tomography [CT] and positron emission tomography [PET]) and thus may alter the stage of patients. A particular strength of PET is its ability to detect previously occult distant metastatic cancer[2]; thus, it potentially increases the ratio of patients with synchronous/metachronous distant metastases. PET imaging was approved by Medicare for the staging of various diseases starting in approximately 1998.[3] There have been improvements in CT scanning during the last few decades as well.[4,5] The potential impact of newer staging tools (that evolve over time) on the fraction of patients who have synchronous versus metachronous metastases is schematically illustrated in Figure 1.

We herein use data from a large population-based registry to estimate the magnitude of the impact of advances in staging (eg, imaging) on the ratio of patients diagnosed with synchronous versus metachronous metastases. We hypothesize that despite these advances, the ratio of synchronous/metachronous metastases has changed only modestly for most diseases over time.

Methods and materials

All data used in this analysis were extracted from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. SEER has been collecting data on cancer cases in the United States since 1973, and the SEER-9 and SEER-18 databases cover approximately 9.4% and 27.8% of the US population, respectively.[6] The present analysis considers data from 1973 to 2008 and is an update of a prior similar analysis that considered data from 1973 to 1998.[7]

Conflicts of interest: The authors declare that there are no conflicts of interest with regard to the publication of this paper.

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The 15 sites studied represent all primary disease sites for solid tumors (ie, excluding leukemia and lymphoma) with available data. Several tumor types with low incidence rates (eg, cancers of bones and joints, soft tissue, and testis) or where routine clinical care has included unique staging methods (eg, laparotomy for lymphoma and ovarian cancer) were excluded from the analysis. Similarly, prostate cancer was excluded due to the lack of staging data in the SEER database.

For each of the 15 solid tumor types, the crude rates for several metrics were extracted for patients diagnosed in each year from 1973 to 2008, with 2 exceptions. The data available for larynx cancer were from 1973 to 2003 and the data for lung cancer were from 1988 to 2008. All extracted data were based on the SEER historic stage A system because this was recorded consistently across the time period considered. The extent of disease at diagnosis was defined as localized (for cancer limited to the organ in which it began and without evidence of spread), regional (for cancer that has spread beyond the original [primary] site to nearby lymph nodes or organs and tissues), and distant (for cancer that has spread from the primary site to distant organs or distant lymph nodes).

SEER*Stat Version 8.3.2 software was used for the extraction of the data. The "rate" application of the SEER-9 database was used to calculate crude rates. The "survival" application within the SEER-18 database was used to calculate survival rates. Site recode ICD-0-3/WHO 2008 was used to define disease sites. Specific rates extracted from the SEER registry are as follows (see Fig 1):

1. The fraction of patients with invasive cancer who have overt clinically detected synchronous metastases (with or without pathologic confirmation) at initial diagnosis (herein termed "cM1pM1"). Mathematically, this is the rate of (Distant / [Localized + Regional + Distant]) in the SEER registry. Patients categorized as having unstaged disease were excluded from this calculation. We acknowledge that a modest fraction of these patients could be inaccurately staged (eg, false positive scans for metastases) but submit that this group is relatively small. We further acknowledge that this rate can be affected by the use of screening (eg, with mammography).
2. Among patients without overt metastases at the time of diagnosis (cM0), the 5-year mortality rate (equal to 1 minus the relative survival rate [reported in SEER as the actuarial survival] for cM0 patients at 5 years) was noted. This rate (multiplied by the fraction of patients who were cM0 at presentation) was taken as a reflection of the fraction of all patients with metachronous metastasis (assuming that most deaths were due to distant metastases; herein termed "cM0pM1"). We acknowledge that many patients can succumb to uncontrolled localized disease (eg, for cancers of the lung) rather than metastatic cancer and that this rate is thus not a perfect surrogate for the rate of metachronous metastases (eg, due to improvements in adjuvant systemic therapies curing some patients with overt subclinical metastatic disease at diagnosis and due to prolonged survival in patients who develop overt metastatic disease after initial treatment).
3. The fraction of patients who have no metastases (either clinically or pathologically) at presentation (herein termed "cM0pM0"). This is computed as the product of the fraction of patients who were cM0, and the 5-year overall survival rate in these patients. We acknowledge that this is an imperfect approach because patients can succumb to distant disease beyond 5 years, especially in the setting of effective systemic therapies.

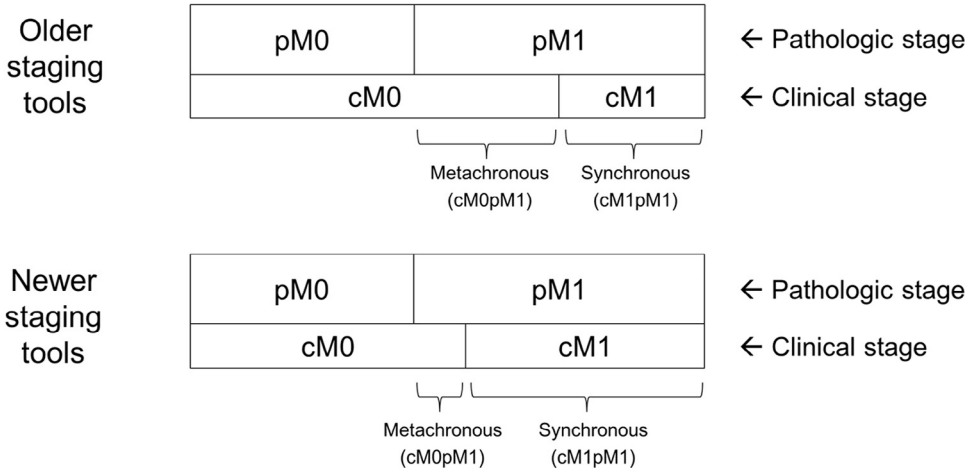

Figure 1 Idealized diagram (not to scale) depicting the concept that improvements in staging tools (that evolve over time) would be expected to increase the ratio of patients with synchronous versus metachronous metastases. Note that improvements in staging alter the clinical but not the pathological staging. Some patients who were cM0pM1 with older staging tools could be moved to cM1pM1 with advances in staging.

These rates were computed for 15 different solid tumors for each individual year from 1973 to 2008. Although these estimation methods used are imperfect, because the same approach was taken across time, the trends inferred by the results are perhaps still valid. For display purposes, data from representative years are shown, and data from ranges of years (eg, 5-year intervals) are pooled. Due to the descriptive and imperfect nature of the data, the results are displayed primarily in a series of graphs without a formal statistical analysis. A formal statistical analysis would imply a level of certainty in the data that we believe is not warranted.

Results

The extracted data for the different disease sites for the representative years 1973, 1998, and 2008 are shown in Table 1. The ratios of the rates of synchronous/metachronous metastases from 1973 to 2008 for 15 different cancer types are shown in Figure 2. The manner in which the years are grouped does not meaningfully affect the trends observed.

Discussion

The data shown are consistent with the hypothesis that improvements in staging methods may be associated with a modest increase in the ratio of synchronous/metachronous distant metastases seen over time. The apparent increase in the ratio of synchronous/metachronous distant metastases is perhaps greatest for the diseases for which PET was first widely adopted clinically (eg, lung, colorectal, esophagus, breast). Indeed, the timing of the changes in the ratio of synchronous/metachronous distant metastases (seen largely, but not exclusively, after 2002) appears to suggest that this was due to PET because PET was approved by Medicare for initial staging for lung (non-small cell lung cancer) in 1998, esophagus in 2001, colorectal in 2001, and breast in 2002.

The magnitude of the changes observed over time are relatively modest (see Fig 2, far right). This observation emphasizes that our modern staging tools are still suboptimal—that is, relatively insensitive. For a lesion to be seen on CT or PET, it typically needs to be ≥0.5 to 1 cm in size, which might represent $10^{8\text{-}9}$ cells and maybe $10^{6\text{-}9}$ cancer cells.[8] Thus, by the time a lesion is detectable on imaging, it has already been through perhaps 20 to 30 cell doublings (eg, $2^{20} \approx 10^6$). During this time of growth, the lesion is likely undetectable by imaging. Thus, a meaningful fraction of patients without evidence of distant metastases (cM0) actually do harbor subclinical metastatic cancer (cM0pM1), and most of these patients have metastatic deposits that contain fewer than $10^{6\text{-}9}$ cancer cells. Thus, the addition of PET imaging (for example) might identify additional patients with previously-occult distant disease, but these additional patients represent a modest fraction of all patients with distant metastases. Nevertheless, for diseases with a high metastatic rate (eg, lung, esophagus), even modest changes in the ratio might represent a large fraction of the patient population.

The impact of improving the accuracy of systemic staging at the time of diagnosis is difficult to quantify. Superficially, one would suspect that the use of more accurate staging might reduce costs and improve overall outcomes (eg, because patients might more consistently receive the most appropriate therapy). However, these benefits need to be balanced against the increased costs and associated (sometimes unexpected) consequences of increased testing (eg, possible false positives, costs for additional testing/biopsies) and further tempered by the realization that the available therapies for many diseases are somewhat limited. An in-depth assessment of this issue is beyond the scope of this analysis, but others have considered some of these issues.[9-11]

There are several limitations of this report. First, the data are population based, and there are inherent inaccuracies in these data (eg, related to variations in data input). Similar problems exist in most population-based studies. Second, there are other changes in clinical care (eg, screening patterns or the use/efficacy of systemic therapy) that can influence the results. An increasing rate of screening will tend to shift the overall patient population to earlier stages and an overall lower number of patients with distant metastases.[12,13] This does not necessarily influence the ratio of synchronous/metachronous metastases. Indeed, for breast cancer, where screening rates have generally been increasing over the years considered,[14] the "apparent" ratio of synchronous/metachronous metastases appears to have increased, possibly due to more aggressive staging at diagnosis and improved efficacy of systemic therapy.

Third, the method of estimating cM0pM1 is inexact because patients can die of local/regional disease (rather than distant metastases) and other patients can live with distant metastases beyond 5 years after initial diagnosis.[15,16] This is a shortcoming of the present analysis because improvements in adjuvant systemic therapies, for example, may cure some patients with covert subclinical metastatic disease at diagnosis, and therapeutic improvements for patients who develop overt metastatic cancer (eg, therapeutic systemic therapies or radiosurgery) may prolong survival beyond 5 years.

The analysis was repeated using the 10-year mortality data as a surrogate for metachronous metastasis, and the interpretation of the results was qualitatively unchanged. One can argue that the 10-year mortality might be a better surrogate than the 5-year mortality rate because improvements in palliative chemotherapy and supportive care might be less likely to affect the 10-year data versus the 5-year data. However, using the 10-year data reduces the available data to consider because a longer follow-up is obviously needed to assess this. Indeed, when using the 10-year

Table 1 List of tumor sites and associated rates of metastases and mortality

Tumor site	1973			1998			2008		
	Synch. (cM1pM1)	Metach. (cM0pM1)	5-year mortality for cM0	Synch. (cM1pM1)	Metach. (cM0pM1)	5-year mortality for cM0	Synch. (cM1pM1)	Metach. (cM0pM1)	5-year mortality for cM0
Breast	7.64%	21.52%	23.3%	5.53%	6.33%	6.7%	6.82%	5.31%	5.7%
Lung	52.65%[a]	34.42%[a]	72.7%[a]	52.02%	33.73%	70.3%	55.39%	27.75%	62.2%
Stomach	42.26%	44.69%	77.4%	37.53%	37.73%	60.4%	39.83%	31.17%	51.8%
Colon	26.81%	26.35%	36.0%	19.74%	17.26%	21.5%	21.61%	14.03%	17.9%
Rectum	21.81%	32.92%	42.1%	15.55%	18.92%	22.4%	16.76%	17.15%	20.6%
Anal	9.88%	25.41%	28.2%	8.92%	21.68%	23.8%	15.61%	22.79%	27.0%
Bladder	3.92%	25.75%	26.8%	3.54%	15.82%	16.4%	4.46%	17.96%	18.8%
Or. ca.&ph.	14.97%	36.65%	43.1%	10.27%	34.82%	38.8%	14.87%	25.96%	30.5%
Pancreas	61.25%	36.54%	94.3%	62.91%	34.23%	92.3%	55.76%	38.18%	86.3%
Larynx	7.83%	31.89%	34.6%	6.87%	30.64%	32.9%	6.01%[b]	33.37%[b]	35.5%[b]
Esophagus	33.85%	62.18%	94.0%	32.47%	55.04%	81.5%	41.52%	43.28%	74.0%
Cervix uteri	8.16%	25.35%	27.6%	8.71%	19.54%	21.4%	11.94%	21.49%	24.4%
Corpus uteri	7.33%	8.80%	9.5%	8.21%	9.55%	10.4%	9.95%	9.55%	10.6%
Kidney&ren.	31.00%	22.49%	32.6%	21.52%	14.60%	18.6%	15.79%	10.44%	12.4%
Melanoma	10.38%	17.12%	19.1%	3.84%	5.38%	5.6%	3.45%	4.73%	4.9%

Kidney&ren., kidney and renal pelvis; Metach., metachronous; Or. ca.&ph., oral cavity and pharynx; Synch., synchronous.

[a] Lung data, 1988.

[b] Larynx data, 2003.

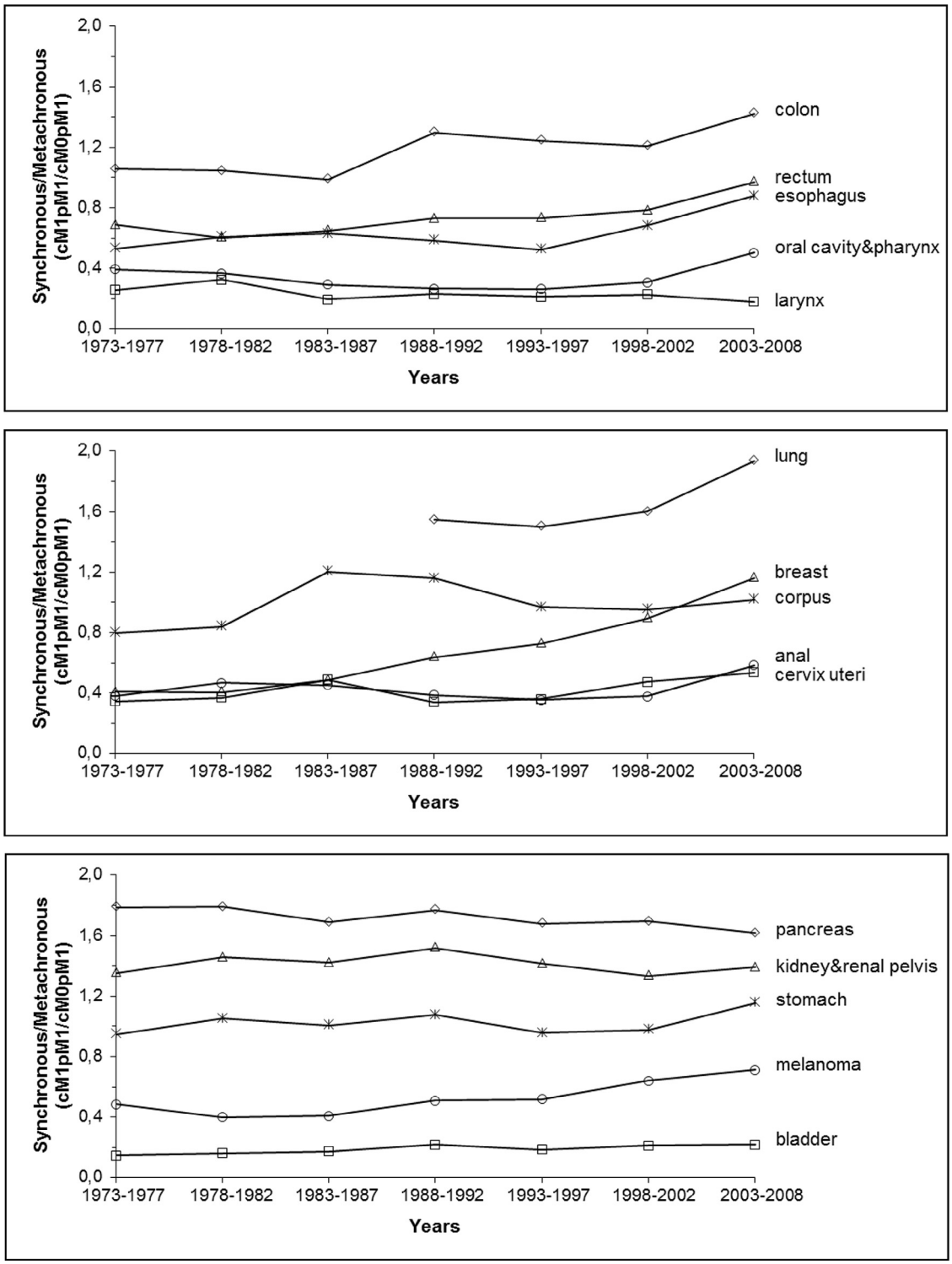

Figure 2 The estimated ratio of the rates of synchronous/metachronous metastases from 1973 to 2008 for 15 different types of cancers.

mortality data (to estimate the metachronous metastatic rate), the modest increases in the ratio that there were observed when using the 5-year data were generally less evident.

Interestingly, because of the degree to which improvements in systemic therapy may tend to increase the perceived ratio of synchronous/metachronous metastases over time, this imperfection in our methods would tend to overestimate the impact of changes in staging techniques on this ratio. In other words, increases in this ratio that are due to improvements in systemic therapy may be inappropriately attributed to improvements in the accuracy of staging. Therefore, we believe that the conclusion that these

advances in systemic staging techniques only modestly affect the ratio of synchronous/metachronous metastases over time remains valid.

Fourth, a formal statistical analysis was not applied to the collected data. Given the inherent uncertainties in the data collected, this seemed prudent. Nevertheless, we believe that one can still draw broad implications from these imperfect data, such as that the ratio of synchronous/metachronous metastases has had a modest increase over recent years.

In conclusion, this analysis provides some support that changes in staging tools (eg, novel imaging methods) are associated with an increase in the ratio of synchronous/metachronous distant metastases observed over time for several types of cancers. However, the magnitude of the changes that were observed are modest and thus emphasize that our modern staging methods remain relatively imperfect.

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