

American Society of Clinical Oncology Identifies Five Key Opportunities to Improve Care and Reduce Costs: The Top Five List for Oncology

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INTRODUCTION

Advancements in the prevention, diagnosis, and treatment of cancer have contributed to improved survival, better quality of life, and declining death rates in the United States. With these successes have come increases in cost to a level that is now causing serious financial burdens to patients, families, and society at large. If current trends remain unchanged, the Centers for Medicare and Medicaid Services (CMS) project that US health care spending will reach \$4.3 trillion and account for 19.3% of the nation's gross domestic product by 2019.¹ Although cancer care represents a small proportion of the health care costs in the nation, its cost is rising precipitously^{2,3} and will increase as our population ages and the disease becomes more prevalent.

The basis for the rising cost of care is complex and is due, in part, to unnecessary use of health care resources. The Congressional Budget Office estimates that up to 30% of care delivered in the United States goes toward unnecessary tests, procedures, physician visits, hospital stays, and other services that do not improve a patient's health.⁴ Substantial regional variations in health care costs have been documented; there is good reason to believe that physicians in lower cost regions order and provide evidence-based tests and treatments just as often as their colleagues in higher cost regions, but they tend to avoid providing care whose usefulness is not well supported by existing data. It can be concluded that if physicians in higher cost regions ordered tests and treatments in a pattern similar to that followed by physicians in lower cost regions, substantial savings could be realized.¹ In short, US physicians could do a great deal to control the costs of health care if there were more broad-based adherence to evidence-based guidelines.⁵⁻⁷

Although few disagree with the importance of using high-level evidence in making medical decisions, there are competing factors that are often brought to bear on the problem. Cancer is a terrifying diagnosis that elicits appropriate anxiety in anyone hearing the words "you have cancer." Patients

and family members understandably want "everything done," despite not having sophisticated awareness of the evidence base that should be guiding the physician. Concerns about litigation regularly factor into physician's decision making, especially in situations in which the outcome might be limited survival. The economics of health care delivery are also misaligned with respect to the shared goal of using appropriate testing or intervention for the appropriate clinical circumstance—no more and no less.

As the leading medical professional oncology society committed to conquering cancer through research, education, prevention, and delivery of high-quality patient care, the American Society of Clinical Oncology (ASCO) has identified the rising cost of cancer care as an opportunity to sharpen the focus on the need to ensure high-quality care while reducing unnecessary expense for our patients, their families, and society at large.

To address this issue, ASCO established the Cost of Care Task Force in 2007 to assess the magnitude of the problem in cancer medicine and develop strategies to address these challenges. In 2009, ASCO first addressed this issue with the release of a policy statement that identified multiple factors that contribute to the high cost of cancer care⁸ and a companion booklet that was designed as a resource for our patients.⁹ Since that time, ASCO has been actively engaged in initiatives to promote evidence-based decision making and more active engagement between physicians and their patients regarding the provision of high-value care.

In January 2010, Howard Brody, MD, challenged the organized medical community at large to address the problem of waste and inefficiency in the delivery of health care by suggesting that each specialty identify the top five practices that are costly, widely used, and for which no evidence exists to support their value.⁵ ASCO's Cost of Care Task Force found this to be a compelling suggestion and undertook an initiative to identify diagnostic tests or treatment interventions that are commonly ordered, expensive, and of unproven clinical benefit.

Taking its cue from the “Top Five” challenge, in 2011 the American Board of Internal Medicine Foundation began to organize a national effort to promote awareness about the importance of stewardship of health care resources. The effort, entitled, “Choosing Wisely®: The Five Things Physicians and Patients Should Question,” is intended to promote conversations between physicians and patients about using the most appropriate tests and treatments, as well as avoiding care that is unnecessary or whose harm may outweigh the benefits. ASCO, along with other medical specialty organizations, agreed to participate in this effort and has taken its guidance from the Cost of Care Task Force in developing its list.

After careful consideration by experienced oncologists, ASCO highlights five practices that are in common use despite the absence of evidence supporting their clinical value (Table 1).¹⁰⁻²⁴ It is understood that the Top Five list discussed in this article is no substitute for the individualized decision making that is the essence of the doctor-patient relationship. Furthermore, the elements of the Top Five list may not be appropriate in certain situations, as could be the case when a patient is enrolled in a clinical trial that demands tests or interventions that are not part of the standard of care.

These items are provided solely for informational purposes and are not intended to replace a medical professional’s independent judgment or as a substitute for consultation with a medical professional. Patients with any specific questions about the items on this list or their individual situation should consult their health care provider. New evidence may emerge following the development of these items. ASCO is not responsible for any injury or damage arising out of or related to any use of these items or to any errors or omissions.

METHODS

Each participating organization in the American Board of Internal Medicine Foundation’s Choosing Wisely® initiative was charged with identifying five tests or procedures commonly used in their field whose necessity is not supported by high-level evidence. Each society was free to determine how to create its own list, provided that it used a clear methodology and adhered to the following set of shared guidelines:

- Each item should be within the specialty’s purview and control.
- The tests and/or interventions should be used frequently and/or carry a significant cost.
- Each recommendation should be supported by generally accepted evidence.
- The selection process should be thoroughly documented and publicly available on request.

To guide ASCO in this effort, the Cost of Care Task Force worked for several months to identify a list for ASCO to consider as its Top Five. Initially, a subcommittee of Task Force members suggested a number of practices they believed were overused or misused. A literature search was performed to ensure that the items identified were supported by available evidence; ultimately they were approved by the full Task Force. Once an initial Top Five list was drafted, it was presented to the ASCO Clinical Practice Committee, a group composed of community-based oncologists and the presidents of the 48 state/regional oncology societies in the United States. Advocacy groups were asked to weigh in as well to ensure that the recommendations will achieve their intended purpose of increasing physician-patient communication and changing practice patterns. A plurality of more than 200 clinical oncologists reviewed and supported the Top Five list. Ultimately, it was presented to, discussed by, and approved by the Executive Committee of the ASCO Board of Directors.

RESULTS

The Top Five List: Practices or Interventions That Are Costly, Widely Used, and Not Supported by High-Level Clinical Evidence

1. *Do not use cancer-directed therapy for patients with solid tumors who have the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and with no strong evidence supporting the clinical value of further anticancer treatment.* Studies show that cancer-directed treatments are likely to be ineffective for patients with solid tumors who meet the above-stated criteria. Exceptions include patients with functional limitations caused by other conditions that result in a low performance status (PS) or those with disease characteristics (eg, mutations) that suggest a high likelihood of response to therapy. Implementation of this approach should be accompanied by appropriate palliative and supportive care.

The recommendation against chemotherapy in patients with poor Eastern Cooperative Oncology Group PS (ie, ≥ 3 , defined as “3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours”²⁵) dates to the early 1980s, when PS was found to be a predictor of poor survival, reduced response, and worsened toxicity from chemotherapy.^{26,27} The evidence for treatment benefit or harm has rarely been quantified in patients with poor PS, as new drug clinical trials have concentrated on patients with good PS who have the most chance of showing a substantial benefit.

Among patients with non-small-cell lung cancer (NSCLC), the number with poor PS ranges from 29% at presentation^{27a} to near-universal prevalence as the disease progresses. The available data suggest that chemotherapy use in patients with poor PS or multiply relapsed disease is common. At one large US health maintenance organization, 49% of patients with NSCLC and PS of 3 or 4 received chemotherapy.^{27a}

There have been few trials of newer drugs with optimal supportive care in patients with poor PS, and no randomized trials of chemotherapy with or without best supportive care. Weekly gemcitabine, docetaxel, or vinorelbine in 63 patients with NSCLC and PS of 3 yielded a response rate of 19%, the same as for patients with PS of 1 to 2. Quality of life and breathlessness improved, and the toxicity of weekly treatment was acceptable, but the overall survival was 3.4 months, half that of patients with PS of 1 to 2, and progression-free survival was only 1.8 months.²⁸ Single-agent gemcitabine caused responses in 8% of patients with NSCLC and PS of 3, but median survival was just 65 to 83 days.²⁹ Neither of these studies had a control group. There are no published trials of chemotherapy in patients with other common cancers and poor PS.

The available guidelines established by expert panels have all concluded that if a patient’s cancer has grown during three different regimens, the likelihood of treatment success is so poor and toxicity so high that further anticancer treatment is not recommended. There are few comparative trials of chemotherapy versus best supportive care in patients whose cancer has grown despite treatment with multiple regimens. The available data for NSCLC show a documented response rate of 2% for third-line and 0% for fourth-line chemotherapy in the largest series at MD Anderson Cancer Center.³⁰ The available evidence demonstrates that lack of response to the last regimen and development of new metastases predict little chance of response to subsequent

Table 1. Top Five List in Oncology

The American Society of Clinical Oncology (ASCO) is a medical professional oncology society committed to conquering cancer through research, education, prevention and delivery of high-quality patient care. ASCO recognizes the importance of evidence-based cancer care and making wise choices in the diagnosis and management of patients with cancer. After careful consideration by experienced oncologists, ASCO highlights five categories of tests, procedures and/or treatments whose common use and clinical value are not supported by available evidence. These test and treatment options should not be administered unless the physician and patient have carefully considered if their use is appropriate in the individual case. As an example, when a patient is enrolled in a clinical trial, these tests, treatments, and procedures may be part of the trial protocol and therefore deemed necessary for the patient's participation in the trial.

1. Don't use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment.¹⁰⁻¹⁵

- Studies show that cancer directed treatments are likely to be ineffective for solid tumor patients who meet the above stated criteria.
- Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g. mutations) that suggest a high likelihood of response to therapy.
- Implementation of this approach should be accompanied with appropriate palliative and supportive care.

Sources:

- Azzoli CG, Temin S, Aliff T, et al: 2011 focused update of 2009 American Society of Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 29:3825-3831, 2011.
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- Engstrom PF, Benson AB 3rd, Chen YJ, et al: Colon cancer clinical practice guidelines. *J Natl Compr Canc Netw* 3:468-491, 2005.
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2. Don't perform PET, CT and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.¹⁶⁻¹⁸

- Imaging with PET, CT or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.
- Evidence does not support the use of these scans for staging of newly diagnosed low grade carcinoma of the prostate (stage T1c/T2a, PSA < 10 ng/ml, Gleason score ≤ 6) with low risk of distant metastasis.
- Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

Sources:

- Makarov DV, Desai RA, Yu JB, et al: The population level prevalence and correlates of appropriate and inappropriate imaging to stage incident prostate cancer in the Medicare population. *J Urol* 187:97-102, 2012.
- National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology (NCCN guidelines)—Prostate cancer. Version 4.2011.
- Thompson I, Thrasher JB, Aus G, et al: Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 177:2106-2130, 2007.

3. Don't perform PET, CT and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.¹⁹

- Imaging with PET, CT or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.
- In breast cancer, for example, there is a lack of evidence demonstrating a benefit for the use of PET, CT or radionuclide bone scans in asymptomatic individuals with newly identified DCIS, or clinical stage I or II disease.
- Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

Source:

- Carlson RW, Allred DC, Anderson BO, et al: Invasive breast cancer. *J Natl Compr Canc Netw* 9:136-222, 2011.

4. Don't perform surveillance testing (biomarkers) or imaging (PET, CT and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.^{12,20-23}

- Surveillance testing with serum tumor markers or imaging has been shown to have clinical value for certain cancers (e.g. colorectal). However, for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measurement of serum tumor markers in asymptomatic patients.
- False-positive tests can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

Sources:

- Locker GY, Hamilton S, Harris J, et al: ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 24:5313-5327, 2006.
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- Carlson RW, Allred DC, Anderson BO, et al: Breast cancer. *J Natl Compr Canc Netw* 7:122-192, 2009.
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- Harris L, Fritsche H, Mennel R, et al: American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 25:5287-5312, 2007.

5. Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20% risk for this complication.²⁴

- ASCO guidelines recommend using white cell stimulating factors when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is approximately 20% and equally effective treatment programs that do not require white cell stimulating factors are unavailable.
- Exceptions should be made when using regimens that have a lower chance of causing febrile neutropenia if it is determined that the patient is at high risk for this complication (as a result of age, medical history, or disease characteristics).

Source:

- Smith TJ, Khatcheressian J, Lyman GH, et al: ASCO 2006 update of recommendations for the use of white blood cell growth factors: An evidence based clinical practice guideline. *J Clin Oncol* 24:3187-3205, 2006.

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Abbreviations: CT, computed tomography; DCIS, ductal carcinoma in situ; PET, positron emission tomography; PSA, prostate-specific antigen.

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regimens.³¹ When data are available to show benefit from fourth-line chemotherapy, such as eribulin in metastatic breast cancer, it has been from trials that excluded patients with poor PS.³² Despite the evidence for lack of effect, *n*-th line chemotherapy is common. In a large community practice, 26% of patients with NSCLC received fourth-line chemotherapy, including 20% within 2 weeks of their death,³³ and in Germany, 10% of similar patients received fourth-line chemotherapy.³⁴ At a large university center, 50% of patients with solid tumors received chemotherapy within 14 days of their death.³⁵ In Sweden, 23% of patients with solid tumors received chemotherapy in their last 30 days of life.³⁶ These findings suggest that this practice is driven not by profit, but by the desire to help patients and the inability of patients, families, and their oncologists to make end-of-life transitions.³⁷

Some may argue that lack of evidence does not preclude lack of benefit, as so few fourth-line chemotherapy trials have been reported. However, ASCO has always recommended that treatment not be given unless there is a definable benefit.³⁸ In a retrospective study of patients with lung cancer who survived at least 3 months from the time of diagnosis, patients who received chemotherapy within 2 weeks of their death did not survive longer than those whose chemotherapy was discontinued earlier,³⁹ and in a randomized study, less use of intravenous chemotherapy in the last 2 months of life was strongly associated with better survival.⁴⁰ A dramatic reduction in fourth-line chemotherapy in patients with NSCLC⁴¹ and colorectal cancer⁴² led to no changes in overall survival and markedly lower cost. Despite the lack of trials in patients with poor PS and those with multidrug resistant cancers, the relative contraindication against chemotherapy for patients has been recommended by all the expert panels addressing colon,¹³ lung,^{10,11,43} and breast cancer^{19,44,45} guidelines. It was also strongly endorsed by ASCO in attempting to define the benefits of continued chemotherapy versus nonchemotherapy-based palliative care.¹⁴

Exceptions to this guideline include patients with functional limitations caused by other conditions or those with disease characteristics that suggest a high likelihood of response to therapy (eg, highly chemotherapy-responsive disease such as newly diagnosed myeloma, *HER2* amplification in chemotherapy-naïve breast cancer, or cancers with molecular targets such as *ALK* mutations in signet ring NSCLC.⁴⁶)

Smith and Hillner¹⁵ suggested the simple rule that patients must be well enough to walk unaided into the clinic to receive chemotherapy. When oncology practitioners receive direct feedback about overuse and misuse of chemotherapy in the end-of-life setting, they quickly improve practice, with chemotherapy in the last 14 days of life falling from 50% to less than 20% in one quarter.³⁵ Stopping anticancer treatment should always be accompanied by appropriate palliative and supportive care and referral to hospice, and the best practice would be continuation of palliative care started concurrently at the time of diagnosis for “any patient with metastatic cancer and/or high symptom burden.”^{47(p880)}

2. *Do not perform PET, CT, and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.* Imaging with positron emission tomography (PET), computed tomography (CT), or radionuclide bone scan can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival. Evidence does not support the use of these scans for staging of newly diagnosed low-grade carci-

noma of the prostate (stage T1c/T2a, prostate-specific antigen [PSA] < 10 ng/mL, Gleason score ≤ 6) with low risk of distant metastasis. Unnecessary imaging can lead to harm through unnecessary invasive procedures, overtreatment, and misdiagnosis.

In the past 30 years, there has been a substantial shift in the patterns of management of early-stage (clinically nonmetastatic) prostate cancer, most heavily influenced by the introduction of PSA screening into widespread clinical use. Although randomized clinical trials have failed to show a survival benefit from community-wide screening of asymptomatic patients, the practice has been a clinical standard for two decades and has led to the identification of a large reservoir population of men with occult prostate cancer. Thus large numbers of patients have been identified with clinically occult prostate cancer, predominantly stages I-II, who are frequently at low risk for subsequent tumor-related mortality.

It had previously been known from autopsy studies that more than 60% of patients older than 70 years have occult foci of prostate cancer, but that the vast majority of these occult cases did not contribute to mortality. Thus it has become clear that there are at least two patterns of early-stage prostate cancer, a predominant one that is clinically indolent and poses little threat to survival, and another variant that has the capacity to invade and metastasize, eventually resulting in death.

Because of the heterogeneous natural history of early-stage prostate cancer, a “cookie cutter” approach to staging became the standard of care. With this approach, many patients routinely have undergone bone scan and sometimes [¹⁸F]fluorodeoxyglucose (FDG) PET or PET/CT scans at presentation, purportedly to identify occult metastases and thus to avoid unnecessary and inappropriate local definitive therapy, such as radiation or radical prostatectomy.

However, because low-risk prostate cancer has a small propensity to metastasize, aggressive clinical staging provides no clinical benefit, despite considerable expense. For example, in their authoritative review of the costs of care of early-stage prostate cancer, Saigal and Litwin⁴⁸ estimated that 99% of men with newly diagnosed prostate cancer, with a serum PSA of less than 10 μg/L and a Gleason score less than 7, do not benefit from CT scans, magnetic resonance imaging (MRI), or bone scans, and cited cost savings as high as \$40 to \$80 million per year if rational use algorithms were to be followed. Although a fiscally responsible approach to medical management is important, patient safety must remain a crucial factor. It is important to emphasize that the domain of available information is clear that staging tests for low-risk prostate cancer are unnecessary. Choi et al,⁴⁹ in an analysis of Surveillance, Epidemiology, and End Results–Medicare linked data regarding men with low-risk prostate cancer who presented in 2004 to 2005, reported that 36.2% of 6,444 men underwent cross-sectional imaging (MRI or CT scans), bone scan, or abdominal ultrasound, and that there was substantial geographic variation in patterns of practice (inconsistent with rational use of level 1 evidence). They noted a less than 1% chance of positive results when imaging men with low-risk prostate cancer, data that are consistent in many nations.^{50–52} Others have reported similar levels of overuse of staging techniques for low-risk prostate cancer,^{16,53} despite clear published national guidelines that recommend against such testing protocols.^{17,18}

We conclude that routine use of CT, MRI, or radionuclide imaging for early-stage, low-risk prostate cancer is not indicated as this

approach provides no clinical benefit but is associated with substantial expense.

3. *Do not perform PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.* Imaging with PET, CT, or radionuclide bone scan can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival. In breast cancer, for example, there is a lack of evidence demonstrating a benefit for the use of PET, CT, or radionuclide bone scans in asymptomatic individuals with newly identified ductal carcinoma in situ (DCIS), or clinical stage I or II disease. Unnecessary imaging can lead to harm through unnecessary invasive procedures, overtreatment, unnecessary radiation exposure, and misdiagnosis.

Early-stage breast cancer (including DCIS, clinical stages I and II) is a potentially curable disease and a common problem faced by surgical, medical, and radiation oncologists.⁵⁴ Curative treatment of localized breast cancer can be accomplished by excision of the primary tumor followed with radiation therapy, or by mastectomy. Depending on a variety of factors, including the biomarkers associated with the primary cancer, systemic treatment—including hormonal therapy, chemotherapy, and biologic therapy—may be appropriate. Because the staging determination is critical to appropriate application of surgical, radiation, and systemic treatment with their associated short-term and long-term toxicities, there is great pressure to accurately assess disease stage in each patient.

Clinical staging (based on history and a physical examination by an oncology-trained physician), combined with serum tests of liver function and alkaline phosphatase, is the standard method to separate early breast cancer from metastatic or locally advanced breast cancer. Patients with locally advanced breast cancer (eg, stage III) have a higher risk of occult metastatic disease, which may be discovered by FDG PET or PET/CT scanning, and use of these tests in this setting is appropriate.

The available evidence-based guideline does not recommend FDG PET or CT scanning for patients with stages I, IIa, and IIb breast cancer who are asymptomatic and have no findings on routine clinical and pathologic staging to suggest a more advanced stage.^{19,44} The guideline is based on information available from retrospective studies of imaging in early-stage breast cancer. These studies show that the low incidence of occult liver and bone metastases (< 6%) is mostly in patients with stage III cancer, not in those with stages I and II,^{55,56} and many of the findings are falsely positive (ie, not due to metastatic cancer).⁵⁷ FDG PET is inferior to physical examination and sentinel lymph node biopsy for detecting axillary lymph node metastases.^{58,59} In patients with large, stage III tumors or inflammatory breast cancer, FDG PET detects occult metastases in 10% to 21% of patients.⁶⁰⁻⁶⁴

The list price of an FDG PET with concurrent CT scan varies between \$2,500 and \$5,000 depending on the type of scan and location of the facility. As a possible benchmark, Medicare payment to facilities and the interpreting physicians varies according to a fee schedule, based on the facility type (freestanding or hospital outpatient) and region of the country. For example, in urban northern California, the fee schedule amount for concurrent FDG PET and CT scan payment is approximately \$1,450, for CT scans of the chest approximately \$425 to \$550, and for CT scans of the abdomen \$300 to \$730.^{65,66} Patients with third-party payment coverage (including the Medicare program) are directly responsible for a portion of these costs as their copayment.

These prices are provided for reference only as the CMS provides reimbursement for FDG PET imaging for the initial treatment strategy for male and female breast cancer only when used in staging distant metastasis. Thus, absent clinical information to suggest distant metastases, FDG PET imaging is not covered for early-stage breast cancer. FDG PET imaging for diagnosis and initial staging of axillary nodes is also not reimbursable by the CMS.⁶⁷ More important than the monetary cost, unwarranted testing leads to needless exposure of the patient to dangers of invasive procedures stimulated by false-positive results, the inherent anxiety and uncertainty associated with a false-positive result, and unjustified exposure to ionizing radiation in women at low risk of dying as a result of breast cancer.⁶⁸

4. *Do not perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic patients who have been treated for breast cancer with curative intent.* Surveillance testing with serum tumor markers or imaging with PET, CT, and radionuclide bone scans has been shown to have clinical value for certain cancers (eg, colorectal). However for breast cancer that has been treated with curative intent, several studies have shown there is no benefit from routine imaging or serial measurement of serum tumor markers in asymptomatic patients. False-positive tests can lead to harm through unnecessary invasive procedures, overtreatment, and misdiagnosis.

The majority of patients with breast cancer diagnosed today present with early-stage, node-negative disease that is found on screening mammography.⁵⁴ As a result of earlier diagnosis and the efficacy of adjuvant therapies (chemotherapy, radiation, endocrine therapy), most of these women have a normal life expectancy and a low risk for recurrence. Surveillance for breast cancer recurrence in this setting is particularly low yield given the low prevalence of recurrence. For a surveillance or screening test to be considered useful, it must have high sensitivity and specificity, as well as a significant positive predictive value, the latter being highly dependent on the prevalence of the condition. Furthermore, screening tests need to add value through detecting early-stage disease for which treatment will improve survival outcomes. To date, there is no evidence from randomized trials that earlier detection of asymptomatic breast cancer recurrence (outside of the breast, as a local recurrence, or new primary) improves survival outcomes.^{22,23,69-71} In addition, these studies suggest that most breast cancer recurrence is detected through clinical symptoms and not through screening. Thus, making patients aware of the potential symptoms of a breast cancer recurrence (eg, pain, new lumps, dyspnea) is an important strategy in breast cancer surveillance.

A surveillance test that is useful after breast cancer is mammography, in that women who undergo breast-conservation treatment are at persistent risk of local recurrence in the involved breast. In addition, over their remaining lifetime, women with retained breasts may have a risk of new cancer in the ipsilateral or contralateral breast as high as 1% per year. Combining surveillance mammography with clinical breast examination in this setting makes sense, given the prevalence of both local recurrence and new primaries. These two surveillance strategies are complementary, given that not all breast cancers are detected by mammography. When new breast cancers are identified through this screening practice, they are likely to be smaller and amenable to better treatment outcomes, as has been demonstrated with primary screening mammography. Thus, adherence to annual screening mammography is a valuable surveillance strategy in breast cancer survivors. In contrast, breast MRI screening has not been evaluated in this setting

and is currently only recommended for women at extraordinarily high risk, such as *BRCA1/2* mutation carriers.⁷² There is a high false-positive rate associated with breast MRI, and it is thus not recommended for routine surveillance. However, there are individual circumstances in which this may be ordered, as in women with very dense breasts or a strong family history of breast cancer.

Other imaging strategies such as standard chest radiograph, bone scans, and abdominal ultrasound did not change survival outcomes in the two randomized trials conducted in the 1990s,^{70,71} and thus are not recommended for routine surveillance. Chest and abdominal CT scans or whole-body PET scans have not been evaluated as surveillance strategies for follow-up of early-stage breast cancer, even though they may be of value for the diagnostic evaluation of clinically evident recurrent breast cancer.²² Given the low prevalence of distant recurrence in early-stage breast cancer, and the high likelihood of false-positive findings and/or incidental findings that will lead to further testing, there is no evidence to support the use of these imaging strategies.^{22,69}

With regard to tumor markers, there have been no prospective studies conducted that support the use of tumor markers such as carcinoembryonic antigen, CA 15-3, or CA 27.29 in the monitoring of patients with breast cancer after primary treatment.²³ These tests may be associated with false-positive changes that may precipitate extensive diagnostic work-ups as well as cause considerable anxiety among breast cancer survivors, and thus their use should be discouraged. Conversely, false-negative tests may provide a false sense of security.

Careful attention to patient history and physical examination, as well as targeted diagnostic evaluation of new symptoms, should be the mainstay of surveillance for recurrence in breast cancer survivors. Patients should be encouraged to report any persistent symptoms that are not explained by an intercurrent illness or injury. Effective communication between the patient and her health care providers should play a central role in monitoring for breast cancer recurrence, which is fortunately a rare event for many women.

5. Do not use white cell-stimulating factors for primary prevention of febrile neutropenia for patients with less than 20% risk for this complication. ASCO guidelines recommend using white cell-stimulating factors when the risk of febrile neutropenia (FN) secondary to a recommended chemotherapy regimen is approximately 20% and equally effective treatment programs that do not require white cell-stimulating factors are unavailable. Exceptions should be made when using regimens that have a lower chance of causing FN if it is determined that the patient is at high risk for this complication (as a result of age, medical history, or disease characteristics).

Since the approval of myeloid colony-stimulating factors by the US Food and Drug Administration in the early 1990s, the use of granulocyte colony-stimulating factors (G-CSFs) has been widely accepted into routine clinical practice to reduce the risk of FN associated with cytotoxic chemotherapy.⁷³ FN is a medical emergency and is associated with a substantial risk of morbidity, mortality, and hospitalization, which ultimately increase the cost of cancer care.⁷⁴⁻⁷⁷ G-CSFs have been demonstrated to reduce the risk of FN in adults when administered immediately after chemotherapy.^{77,78} One recent meta-analysis demonstrated that the use of G-CSFs as primary prophylaxis for FN reduced both the risk of FN and early mortality, but another meta-analysis showed no reduction in short-term or infection mortality.^{78a,79} Guidelines for G-CSF use in the appropriate clinical

setting have been endorsed by ASCO, the National Comprehensive Cancer Network, and the European Organization for Research and Treatment of Cancer.^{24,80,81} Yet there remains wide variation in the appropriate use of G-CSFs for primary prophylaxis of FN in clinical practice.^{73,82} This variation from guideline standards results in increased use of these costly agents when the risk of FN is low. Conversely, the risk and morbidity of FN are increased when these agents are withheld as primary prophylaxis, contrary to guidelines.^{73,82}

The 2006 ASCO Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Guideline states that primary prophylaxis with a white cell growth factor is recommended for the prevention of FN in patients who have a high risk of developing this complication of therapy.²⁴ High risk is defined as a risk greater than 20%. Adult patients receiving cytotoxic chemotherapy may be at this degree of risk based on the myelotoxicity of the regimen itself, or from a combination of the therapy and age greater than 65 years, poor PS, or comorbidities, including prior treatment for the cancer itself.^{83,84} It is estimated that approximately half of all adult patients who receive low-risk (< 10% risk of FN) and intermediate-risk (10% to 20% risk of FN) treatment are at a personal risk of greater than 20% for developing FN on the basis of factors other than the chemotherapy regimen itself and should receive primary prophylaxis with G-CSFs.^{85,86}

Despite the widespread use of G-CSFs, their use as primary prophylaxis of FN in the clinical setting varies widely and is inconsistent with guidelines. The CanCORS (Cancer Care Outcome Research and Surveillance Consortium) study evaluated a large Medicare cohort of patients with lung and colorectal cancer and demonstrated that only 17% of patients treated with high-risk chemotherapy regimens received appropriate G-CSFs. Yet 18% of patients with intermediate risk of FN and 10% of patients with low risk of FN received G-CSFs.⁸² Similarly, Naiem et al⁸⁷ found that of 423 patients treated with a high-risk regimen in 47 community-based practices, only 42% (176 patients) received primary prophylaxis with G-CSF. In an older study of community-based practices, G-CSFs were administered as primary prophylaxis 49.4% of the time with chemotherapy; however, treatment was not stratified by risk of FN, making comparisons difficult.⁷³ These data point to inconsistent use of G-CSFs in the primary prophylaxis setting, both when appropriate according to guidelines and when inappropriate.

The ASCO Guidelines Panel states that the use of any drug requires a balance of the benefits and risks to be included in a guideline recommendation. The drug must improve overall or disease-free survival, improve quality of life, decrease toxicity, and improve cost effectiveness.²⁴ The use of G-CSFs meets these criteria, but not under every circumstance. Myeloid growth factors have been proven essential in the delivery of dose-dense chemotherapy for patients with estrogen receptor (ER)–negative, node-positive breast cancer.⁸⁸ Yet this regimen has demonstrated no significant benefit for patients with ER-positive disease compared with standard regimens with lower risk of FN.^{89,90} Despite this evidence, dose-dense chemotherapy remains a widely accepted and recommended standard for all women with breast cancer in the adjuvant setting.⁸⁰ Similarly, dose escalation in small-cell lung cancer, non-Hodgkin's lymphoma, NSCLC, and other solid tumors has not demonstrated improved survival in the first-line or curative intent setting.⁹¹⁻⁹⁶ Yet the use of G-CSFs in this setting occurs routinely in clinical practice.⁸² Randomized trials have demonstrated that use of G-CSFs to support dose escalation or relative dose

intensity is feasible and successful. However, the proof of principle that the dose can be escalated has not translated into improved survival for most patients with solid tumors.⁹⁷ In the palliative setting, dose escalation has not been demonstrated to improve outcomes or quality of life, and no study has been able to demonstrate an improvement in overall survival with increased dose intensity. Thus it is hard to justify the use of G-CSFs in this clinical context.⁸²

What is the practicing clinician to make of these data? The guidelines are clear: primary prophylaxis with a myeloid stimulating factor is recommended for treatment regimens associated with a high risk of FN such as dose-dense chemotherapy for women with ER-negative, node-positive breast cancer, and for patients at high risk for FN as a result of age and comorbidities, even when using less myelosuppressive therapy. Because the use of a supportive modality such as G-CSF is dependent on the chemotherapy treatment program chosen, evidence-based decision making coupled with open patient-physician communication about risks and benefits of proposed therapy is essential. This will promote the delivery of high-quality care while ensuring appropriate use of costly—sometimes necessary and sometimes unnecessary—drugs such as the G-CSFs.¹⁵

DISCUSSION

Over the past several decades, there has been substantial progress in the prevention, early diagnosis, and treatment of many forms of cancer. These gains represent hard-fought “wins,” arrived at largely through an exacting clinical trials process. Evidence-based oncology has formed a body of knowledge that guides physicians toward the optimal approach to addressing the many variations by which this disease presents. ASCO, representing the nation’s cancer treating physicians, fully acknowledges the existential challenges a cancer diagnosis poses to a patient and family and the strong temptation to do everything there is to be done in the process of staging, treating, and providing follow-up care. At the same time, ASCO recognizes that inappropriate use of diagnostic and surveillance testing approaches can and does lead to false-positive results, which invariably lead to interventions that are unnecessary, costly, and potentially harmful. For this reason, clinical guidance—derived, evidence-based studies represent the acme in high-quality patient care. Adherence to evidence-based medicine also will serve the national interest by constraining the runaway costs of health care, in this case, cancer care.

The items discussed in ASCO’s Top Five list cover diagnostic, surveillance, and therapeutic interventions that are frequently used to address common oncologic problems. A vast percentage of the health care budget is expended during the final months of life.⁹⁸⁻¹⁰⁰ Cancer is no exception, as chemotherapy for advanced disease is often administered in clinical settings characterized by poor PS in patients for whom multiple prior therapies failed to provide benefit. In situations in which further chemotherapy is almost certain to be futile (absence of an actionable mutation for which there is a targeted agent that has promise, an appropriate clinical trial for which the patient is eligible, or a disease that is uniquely sensitive to a particular agent), treatment should be directed at symptom palliation and psychological support.

Included within the Top Five are two items that relate to staging of early breast and prostate cancers. Without clinical evidence demonstrating benefit from routine imaging with PET, CT, or radionuclide scanning, these tests provide no additional value to the care of the patient; waste resources needlessly; and most seriously of all, stimulate

evaluations such as further invasive testing that pose a risk of unnecessary morbidity. In parallel, the discussion of post-treatment surveillance in early-stage breast cancer finds no support for routine imaging with PET, CT, or radionuclide scanning, or breast MRI and tumor markers. The low risk of systemic recurrence in this setting limits the positive predictive value of such testing.

The decision to address the use of G-CSFs in the Top Five list acknowledges the clear overuse of these agents and the absolute value that they add when used for appropriate clinical indications. Much has been written about the use and misuse of these cytokines, and major professional organizations have recognized the opportunities and challenges their availability represents by promulgation of guidelines that describe their recommended use. ASCO views implementation of these guidelines as an achievable goal that will help ensure the proper use of CSFs in the indicated circumstance while realizing significant cost savings through controlling their use in patients at low risk for FN or those receiving palliative chemotherapy for advanced disease.

The Top 5 list represents a series of practices in frequent use in common clinical scenarios that are not supported by strong evidence. Reconsidering their use, one patient at a time, is likely to improve the value of care that is provided, which in this case means the desired clinical outcome at the lowest cost to the patient and society. Nonetheless, ASCO recognizes that the care of every person with a life-threatening disease is challenging and must be responsive to unique features of that particular individual’s circumstances. For that there will never be a substitute.

FUTURE DIRECTIONS AND NEXT STEPS

The Top Five list contributed by ASCO to the Choosing Wisely[®] campaign provides not only a set of specific practices that should be questioned, but also—and perhaps more importantly—an opportunity to emphasize the importance of evidence-based medicine in arriving at clinical decisions. Over the coming months, ASCO will be devoting significant attention to implementation of the Top Five list in practice by educating both physicians and patients about the effort and providing them with the tools and resources they need to consider the issues fully and make sound medical decisions as a result. In addition, ASCO is planning to measure the impact of this campaign on practicing cancer physicians. Each of the Top Five items has been selected not only because it is important from a clinical care and value perspective, but also because it is measurable. Resources such as Medicare and insurance company databases, the ASCO Quality Oncology Practice Initiative, and the planned rapid learning system to which ASCO is committed will represent the means by which these and other practice improvement initiatives can be assessed.

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Appendix

The statement was reviewed and transmitted to the ASCO Board of Directors by ASCO's Cost of Cancer Care Task Force: Lowell E. Schnipper, MD, Chair (Beth Israel Deaconess Medical Center, Boston, MA); Joseph Bailes, MD (American Society of Clinical Oncology, Alexandria, VA); Douglas W. Blayney, MD (Stanford University School of Medicine, Stanford, CA); Diane Blum, MSW (Lymphoma Research Foundation, New York, NY); Nancy Davidson, MD (University of Pittsburgh Cancer Institute and UPMC Cancer Centers, Pittsburgh, PA); Patricia Ganz, MD (University of California, Los Angeles School of Medicine and Public Health, Los Angeles, CA); J. Russell Hoverman, MD, PhD (Texas Oncology, PA, Dallas, TX); Robert Langdon, MD (Nebraska Cancer Specialists, The Physicians of Oncology Hematology West, PC, Omaha, NE); Allen Lichter, MD (American Society of Clinical Oncology, Alexandria, VA); Gary Lyman, MD (Duke University, Durham, NC); Neal J. Meropol, MD (Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH); Therese Marie Mulvey, MD (Southcoast Center for Cancer Care, Southcoast Health System, Fairhaven, MA); Lee Newcomer, MD (UnitedHealthcare, Edina, MN); Jeffrey Peppercorn, MD, MPH (Duke University, Durham, NC); Derek Raghavan, MD, PhD (Levine Cancer Institute, Carolinas HealthCare, Charlotte, NC); Gregory Rossi, PhD (AstraZeneca, Macclesfield, United Kingdom); Deborah Schrag, MD (Dana-Farber Cancer Institute, Boston, MA); Richard Schilsky, MD (The University of Chicago Medical Center, Chicago, IL); Thomas J. Smith, MD (Sidney Kimmel Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD).