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# The Journal of COMMUNITY and Supportive ONCOLOGY

— RESEARCH AND REVIEWS FOR THE PRACTICING ONCOLOGIST —



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# Improving cancer care through modern portfolio theory

By Kevin B Knopf, MD, MPH

We struggle daily to improve cancer care – to improve our therapeutic outcomes in cancer – as individual physicians and as researchers. We work collectively to disseminate information and collaborate, and there are welcome calls for open data sharing to accelerate progress.[1] We enroll patients on clinical trials, or we work in a basic science lab to discover mechanisms of carcinogenesis and potential therapeutic targets. We discuss "n of 1" trials and the "paradigm shift of precision oncology," and we are optimistic about the future of cancer care.

Leaving the world of biology and clinical trials for a minute, we also can apply economic theory in our never-ending quest to improve cancer outcomes. One area of interest may be modern portfolio theory (MPT), which the economist Harry Markowitz introduced in an essay in 1952 and later won the Nobel Prize for his work.

MPT is complex, but it states that one's expected rate of financial return depends on how assets are allocated. There is even discussion of an "efficient frontier": an optimal way to allocate assets for a given system. We can apply MPT to how we think about allocating economic assets in cancer care – with the goal of maximizing return for all cancer patients – by following the principal of distributive justice.[2]

At least 71 billionaires live in the San Francisco Bay Area, where I live, but 14,000 children (13%) in the area live below the poverty line.[3] When there is a range of asset allocations in health care, results can vary not on the basis of the underlying disease state or the quality of the provider, but on access to care. As an example, most pediatric cancers are curable, yet a recent retrospective analysis of data in the SEER-Medicare registry showed that mortality within 1 month of diagnosis of childhood cancer related in part to socioeconomic factors – those patients with a lower socioeconomic status (which correlates with being an ethnic minority in the United States) were more likely to die within a month of diagnosis of their cancer than were patients with a higher socioeconomic status.[3] Here is where MPT can transform the cancer outcomes landscape at no additional investment in basic science or costly precision medicine[5]: by triaging these patients according to their disease state rather than their ability to pay, they could be administered curative chemotherapy, placed on the appropriate clinical trial, and be cured of their cancer like other children of higher socioeconomic status.

My colleagues and I observed a similar trend when we looked at treatment of diffuse large-cell non-Hodgkin lymphoma in Medicare recipients.[6] Although the cure rate is as high as 60%-80% with the use of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or R (rituxin)-CHOP chemotherapy, we found that many patients had received suboptimal chemotherapy. Upon closer examination, we found that there were variations in care by socioeconomic status even in a single-payer system. Thus aspects of cultural literacy and additional efforts for triage need to be developed, but again, application of MPT could be instrumental in improving cancer cure rates by reducing disparities in care by allocating assets to solve access-to-care issues, and curing these patients of their non-Hodgkin lymphoma.

A physician at a Bay Area health care system notes that the open slots in his schedule are triaged by his employer by the patient's ability to pay – well-insured patients are seen within a few days, but there are very few slots for Medicaid patients, who have to wait weeks or longer to be seen. During this time, their malignancies have time to grow, and potentially metastasize. This may provide suboptimal outcomes for some patients in his community.

We solved this problem at a local hospital where all patients were on Medicaid or uninsured. We triaged patients according to severity of illness, with patients with rapidly growing cancers, particularly curable ones, were brought in as soon as possible and patients with stable benign hematologic conditions seen on a less urgent basis. A social worker and I saw patients together. She would find them resources such as transportation, food, copay assistance to help them through their treatment, and I would

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optimize their cancer care clinically. On a small scale, this application of MPT (or asset allocation) worked quite well. Perhaps it can be reproduced on a much larger scale. Return on investment relates largely to how you allocate your assets. What's nice about these applications of MPT is that the return on investment – increasing the cure rate of cancer - is quite large for just a minimal change in asset allocation.

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# Prehabilitation for lymphedema in head and neck cancer patients at a community cancer center

Andrew Sember, BA; Cheryl Pranskevich, PT, CLT; Susan T Scott, BSN, RN, OCN; Ian V Hutchinson, PhD, DSc; and Rex Hoffman, MD

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Patients with head and neck cancer often develop morbidities as a result of their treatment with surgery, radiation, and chemotherapy. One of the most prevalent side effects of the treatment is lymphedema, the accumulation of interstitial fluid in tissues that have inadequate lymph drainage. Secondary lymphedema, an acquired abnormality in the lymphatic network, is commonly caused by cancer and/or its treatment. Lymphedema is both under-recognized and under-treated in head and neck cancer. While recent advances in radiation therapy techniques have resulted in a corresponding drop in other treatment-related morbidities, an estimated 50% of treated head and neck cancer patients will develop lymphedema. Indeed, at some places the incidence is much higher, at 75%, following treatment with surgery and radiation. Clearly, there is an unmet need to recognize and treat lymphedema in head and neck cancer patients. This article describes an early intervention prehabilitation program that was established for the early identification and treatment of patients at risk of lymphedema and compares the observed outcomes before and after the initiation of the program.

Lymphedema is the swelling of tissue caused by the accumulation of interstitial fluid in any area of the body where lymphatic flow has been compromised.[1] Secondary lymphedema is an acquired abnormality in lymph drainage[1,2] and is the type commonly seen in cancer patients. Secondary lymphedema can be described as external or internal. Internal lymphedema, swelling of deep structures and tissues, is very difficult to quantify.

## Lymphedema in patients with head and neck cancers

Lymphedema is a complicating morbidity frequently seen in head and neck cancer patients who have undergone treatment with surgery, radiation, and chemotherapy. However, although it is one of the most prevalent side effects of treatment, it is both under-recognized and under-treated.[3]

In head and neck cancer patients, internal swelling may develop in the soft tissues of the upper aerodigestive tract,[4] affecting articulation and swallowing. Currently, there does not seem to be an effective practical and reliable tool with which to measure internal lymphedema. In addition, it is generally accepted that there is no effective way to treat internal lymphedema. By contrast, external lymphedema is more readily observed, but both subjective and objective assessments are difficult. External swelling may occur in the face, jaw, and neck. However, the subjective scales currently available are insufficient to capture very important characteristics of external lymphedema.[5] The Edge Task Force on Head and Neck Cancer in 2015 was not able to recommend any outcome measures for objectively quantifying external edema.[6] Furthermore, objective measurements of head and neck lymphedema can be expensive and time consuming.

## Extent and risk

A combination of both internal and external swelling is seen in more than 50% of patients.[7] Risk factors include "throat" tumors, multicancer treatment approaches, higher total radiation dose, a greater number of radiation procedures, and radiation at the surgical site.[5] More than 500,000 survivors of head and neck cancer in the United States are at risk of lymphedema.[5] Although recent advances in treatment have reduced the incidence of other morbidities, 50% of patients who are treated for head and neck cancer may still develop lymphedema.[1,8] The reported incidence in some centers may be much higher, with up to 75% of patients developing lymphedema following treatment.[9]

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### Measurement modalities for clinical evaluation

There is little current research into lymphedema of the head and neck, despite the high prevalence of the condition.[8] According to Deng and colleagues, measurement of head and neck lymphedema is a challenge, which has an impact on clinical assessment, diagnosis, and treatment of this under-recognized, under-reported and under-addressed problem in head and neck cancer patients.[10] In a review of the literature, Deng and colleagues identified three measurement modalities available for clinical evaluation: patient-reported outcomes, clinician-reported outcomes, and technology.[10] One major factor, though, in detecting lymphedema, is physician awareness: physicians, health care professionals, and even some lymphedema therapists are not well educated about this problem.[8]

### Treatment

The effectiveness of traditional lymphedema treatment is not well defined.[8] Currently, complete decongestive therapy (CDT), is considered the standard of care for lymphedema. The National Lymphedema Network has stated that modifications of CDT, especially manual lymphatic drainage and modified compressive garments for external lymphedema, have been shown to be beneficial for the treatment of lymphedema in head and neck cancer patients.[11] Most findings in lymphedema research, mainly in breast cancer patients, have shown that early intervention is the best management and yields the best outcomes. As with other chronic conditions, early identification and timely, appropriate treatment of lymphedema is critical to improve clinical outcomes, to decrease symptom burden and functional impairment, and to improve overall quality of life in head and neck cancer patients.[10]

### Improving recognition and treatment

Head and neck oncologic treatment is increasingly offered outside the network of specialist academic hospitals, at hospitals serving more localized communities where the neediest, sickest patient groups may be receiving less than optimal care.[3] This challenges community hospitals to provide optimal treatment, similar to that being offered at nationally recognized institutions. In January 2012, we implemented a prehabilitation program in our community hospital cancer center to provide early intervention for our patients based on the understanding that proper and prompt treatment for patients with early signs of lymphedema should be a priority.[12] In this article, we outline how we implemented the program and the describe improvements we observed before and after the implementation of the program.

## The prehabilitation program

### The role of the nurse navigator

Before the introduction of the prehabilitation program, our pattern of practice was to refer patients to oncology rehabilitation for lymphedema management after they had completed their medical treatment with surgery, radiation, and chemotherapy. In 2012, that was changed to a prehabilitation model of care that was overseen by a head and neck nurse navigator. This focus on prehabilitation begins with patients being referred to oncology rehabilitation at the time of cancer diagnosis for baseline assessment of head and neck swelling. In addition, there is assessment of the many possible other side effects associated with head and neck cancer and its treatment, namely loss of range of motion of the neck, jaw (trismus), and/or shoulders, postural deficits, functional loss, pain, balance dysfunction with fall risk, weakness, and fatigue. Therapeutic interventions are initiated as needed and appropriate. This process also raises awareness of a condition that has been described as under-recognized and under-treated.[3]

The nurse navigator sits in on each radiation oncology consultation and aids in "navigating" patients through their treatment. The nurse ensures that each patient is referred to different ancillary services from the outset, such as seeing a dietician, social worker, physical/occupational therapist and certified lymphedema therapist, speech pathologist, and financial assistance advisor, if necessary (Table 1).

### Assessment of lymphedema

Measurement of head and neck lymphedema is a challenge.[10] In our program, the physical therapy assessment also includes the evaluation of several other morbidities associated with head and neck cancer and its treatment,

**TABLE 1** Prehabilitation assessments and preparationa

| |
|---|
| **Assessment of possible concomitant side effects** |
| ■ Loss of motion of the neck, jaw and shoulders |
| ■ Postural deficits |
| ■ Functional lossb |
| ■ Pain |
| ■ Balance dysfunction with fall risk |
| ■ Weakness |
| ■ Fatigue |
| **Preparation** |
| ■ Education in basic lymphatic anatomy/ physiology and lymphedema risk |
| ■ Home exercise program established if indicated |
| ■ Plan for follow-up reassessment and/or treatment established |

[a]Patients are referred for prehabilitation at the time of cancer diagnosis, to provide a baseline assessment of head and neck swelling, and of various dysfunctions. [b]Functional losses include deficiencies in self-care, sleeping, concentration, driving, reaching and lifting, ability to work or participation in recreational activities.

such as range of motion, weakness, fatigue, radiation fibrosis, balance dysfunction, and risk of falling (Table 2).

Patient-reported outcomes are essential to fully capture observable and unobservable symptoms (eg, sensations) as well as the functional impacts of lymphedema.[10] In addition to lymphedema, there are many other morbidities that may be assessed on the basis of patient-reported outcome tools, such as upper extremity function with QuickDASH.[13] At our clinic for head and neck cancer patients we use the Neck Disability Index (NDI)[14] and Care Connections (CC)[15] survey for the patient-reported outcomes. The Quick DASH, NDI, and CC tools all assess standard functional outcomes that are not specific to lymphedema, but are useful in documenting changes related to lymphedema. We initially used the CC survey and later transitioned to using the NDI. Neck pain is common with lymphedema in the head and neck region, and the NDI is a valid, reliable, responsive and internally consistent clinical tool to measure self-reported disability in patients with neck pain.[16] These questionnaires were completed by the patients at their initial assessment, at reassessment, and at time of discharge.

Although objective criteria for external lymphedema have not been established, simple measurements such as using a tape measure to record neck circumference, allow a useful longitudinal assessment. Digital photography may be effective in the documentation and subjective evaluation of changes of external lymphedema.[10,17] However, there are some limitations with photography because although external photographs (including digital photography and three-dimensional imaging) can capture some features, such as changes in contours, symmetry, and changes in skin quality and color, they do not detect changes in skin and soft tissue texture and compliance (Table 3).[10]

**TABLE 2** Clinical evaluation of lymphedema in head and neck cancer patients

| |
|---|
| **Patient-reported outcomes** |
| Self-reporting of swelling symptoms |
| Neck pain |
| Other observable and non-observable symptoms (such as sensations) |
| Quick Dash questionnaire (for upper-extremity functional assessment) |
| Care Connections questionnaire<br>Neck Disability Index questionnaire |
| **Clinician-reported outcomes** |
| Physical examination to assess external lymphedema |
| Visual inspection, pitting or non-pitting edema, tissue texture |
| Endoscopy to assess internal lymphedemaa |
| **Functional testing** |
| Range of musculoskeletal motion |
| Neck, jaw (trismus) and shoulders |
| Weakness and fatigue |
| Spinal accessory nerve palsy |
| Peripheral neuropathy (chemotherapy induced) |
| Balance dysfunction (with fall risk) |
| Radiation-induced fibrosis |
| Swallowing (dysphagia) |
| **Technical (objective) measurements** |
| Tape measurements |
| Digital photography |

[a]Not available at Disney Family Cancer Center.

### Impact on clinical outcomes

We retrospectively reviewed the medical records of 230 head and neck cancer patients who had been treated at our center between June 2008 and June 2015. Complete clinical data were available for 190 patients. The following information was extracted from each patient's chart: whether they developed lymphedema, tumor stage, had surgery, radiation dose, type of chemotherapy given, their smoking history, if they had had a neck dissection and the primary site of the tumor (Table 3).

**Incidence in different time periods.** Of the 190 patients with complete records 78 (41%) were found to have lymphedema. These were all patients undergoing treatment for head and neck cancer during June 2008-June 2015. The prehabilitation program was initiated with the hiring of a nurse navigator for head and neck cancer, starting in January 2012. It is interesting to note that the incidence of lymphedema was 27% before the program was started, but after nurse navigator joined the team, the incidence increased significantly to 48% ($P$ = .0002), in line with published expectations. This increase in recorded incidence may be attributable to the greater awareness of lymphedema intentionally fostered by the prehabilitation program.

**Smoking history.** Patients' lifetime smoking history was retrieved from their medical records, based on their verbal admission of tobacco use. Most of the patients (n = 110) self-reported a history of smoking. Of those with a history of smoking, 36 (33%) developed external lymphedema after treatment for head and neck cancer, and 74 (67%) did not. However, this difference was not statistically significant. Hence, although smoking is a risk factor for head and neck cancer, it was not associated with the development of external lymphedema in our cohort of patients.

**TABLE 3** Clinical observations

| Parameter | No. of patients (%) | Lymphedema status, n (%) | | Significance |
|---|---|---|---|---|
| | | With | Without | |
| Period | | | | |
| June 2008- June 2015 | 190 (100) | 78 (41) | 112 (59) | NS |
| June 2008- December 2011 | 62 (33) | 17 (27) | 45 (73) | NS |
| January 2012- June 2015 | 128 (67) | 61 (48) | 67 (52) | $P = .0002^1$ |
| Self-reported lifetime smoking history | 110 (58) | 36 (33) | 74 (67) | NS |
| Squamous-cell carcinoma | 156 (82) | 70 (45) | 86 (55) | NS |
| Tumor stage 3 or 4 | 121 (64) | 51 (42) | 70 (58) | NS |
| Position of tumor | | | | |
| Oral cavity[a] | 26 (14) | 12 (46) | 14 (54) | NS |
| Pharynx | 111 (58) | 50 (45) | 61 (55) | NS |
| Nasopharynx | 13 (7) | 1 (8) | 12 (92) | $P = .017^1$ |
| Oropharynx | 87 (46) | 47 (60) | 40 (36) | $P = .044^1$ |
| Base of tongue | 45 (24) | 25 (56) | 20 (44) | NS |
| Tonsil | 38 (20) | 20 (53) | 18 (47) | NS |
| Other | 4 (2) | 2 (50) | 2 (50) | NS |
| Hypopharynx | 11 (6) | 2 (18) | 9 (82) | $P = .04^1$ |
| Larynx | 2 (1) | 1 (50) | 1 (50) | NS |
| Parotid gland | 14 (7) | 1 (7) | 13 (93) | $P = .012^1$ |
| Other | 37 (19) | 14 (38) | 23 (62) | NS |
| Treatment | | | | |
| No resection or neck dissection[b] | 95 (50) | 25 (26) | 70 (74) | $P = .015^1$ |
| Resection of primary tumor[b] | 65 (34) | 35 (54) | 30 (46) | $P = .0004^2$ |
| Resection plus neck dissection[b] | 26 (14) | 18 (69) | 8 (31) | $< .0001^2$ |
| Neck dissection only[b] | 4 (2) | 4 (100) | 0 (0) | $P = .006^2$ |
| Radiation, no surgery[b] | 121 (64) | 43 (36) | 78 (64) | NS |
| Radiation plus surgery[b] | 69 (36) | 35 (51) | 34 (49) | $P = .04^3$ |
| Radiation <60 cGy | 28 (15) | 7 (25) | 21 (75) | NS |
| Radiation 60-69.6 cGy | 55 (29) | 24 (44) | 31 (56) | NS |
| Radiation >70 cGy | 105 (55) | 45 (43) | 60 (57) | NS |
| Radiation dose unknown | 2 (1) | 2 (100) | 0 (0) | NS |
| Chemotherapy | 131 (69) | 58 (44) | 73 (56) | NS |

Significance determined using Pearson chi-square test of association. NS means not statistically significant (significant = $P < .05$). The groups compared are shown in the superscripts: *P*1 values are comparisons with the whole cohort (2008-2015); *P*2 values are in comparison with the 'no dissection or resection' patients; and the *P*3 value is a comparison with the 'radiation no surgery' patients.

[a]Oral cavity includes the oral tongue, buccal mucosa, retromolar trigone, and floor of the mouth. [b]The term surgery includes both resection of the primary tumor and neck dissection, the term resection refers to resection of the primary tumor.

### Type of tumor

Most of the patients (n = 156, 82%) had squamous cell carcinomas (SCC). Of those, 45% developed external lymphedema and 55% did not. Therefore, having SCC did not predispose to lymphedema. The other cancers were mixed type, mainly adenocaricoma, but their numbers were too small to draw statistical conclusions.

**Stage of the tumor**
About two thirds of the patients (n = 121, 64%) had stage 3 or 4 cancer. However, treatment of more advanced cancers was not associated with lymphedema development.

**Site of the tumor**
The literature suggests that patients with a primary tumor in the throat are at increased risk for lymphedema.[5] The American Cancer Society has defined cancers of the oropharynx (throat) as including the base of the tongue (back third of the tongue), the soft palate, the tonsils, and the side and back walls of the throat.[18] In our head and neck cancer cohort, patients with primary tumors of the oropharnyx were, perhaps, more susceptible to lymphedema ($P$ = .044, Table 3). By contrast, in our cohort of patients, those with nasopharyngeal, hypopharyngeal, and parotid gland tumors were significantly less likely to develop lymphedema ($P$s = .017, .04, .012, respectively).

**No surgery**
Half of our patients (n = 95) were not treated with surgery. In the patients who did not have surgery, 25 (26%) developed lymphedema, whereas 70 (74%) did not. Hence, although the incidence of lymphedema was significantly lower in patients who did not have surgery ($P$ = .015), lymphedema did develop in patients who did not have a surgical procedure.

**Resection of primary tumor without neck dissection**
Of the 64 patients who had surgery, but without neck dissection, 35 (55%) developed external lymphedema. Compared with the no-surgery patients, the doubling of the incidence (from 26% to 55%) was highly significant ($P$ = .0004). These findings are compatible with the literature reports that surgery increases the incidence of lymphedema, which is not surprising because surgery and subsequent scarring is known to compromise the lymphatic system.

**Resection of primary tumor with neck dissection**
The incidence of external lymphedema was increased to 69% when patients were subjected to both surgery and neck dissection. Compared with the June 2008-June 2015 cohort, there was a significant increase in the incidence of lymphedema in the neck dissection group ($P$ = .007). Neck dissection involves the removal of lymph nodes and disruption of the lymphatic vessels, so it is not surprising that there is a higher incidence of external lymphedema. In our practice, neck dissections increased in frequency every year from June 2008 until December 2011, when 8 patients underwent neck dissections, 6 (75%) of whom developed lymphedema. Since January 2012, when the prehabilitation program was implemented, the number of neck dissections have declined, with more patients receiving chemoradiation and surgery being reserved for surgery. Hamoir and colleagues have reported that neck dissection is no longer justified unless there is clinically residual disease in the neck.[19]

**Radiation**
Lymphedema occurred in patients regardless of the dose of radiation received. Although the incidence of lymphedema seemed to be higher in patients who received more than 60 cGy, that difference was not statistically significant (Table 3). We had expected a relationship between radiation damage and greater lymphedema, but that was not evident in our patients.

**Chemotherapy**
The majority of patients (n = 131, 69%) received chemotherapy. The exposure to chemotherapy was not correlated with the risk of external lymphedema in our cohort of patients, with 58 of the 131 treated patients (44%) developing lymphedema, compared with 73 (56%) of treated patients who did not (Table 3).

**Complete decongestive therapy**
All patients with documented lymphedema were evaluated for complete decongestive therapy (CDT). Contraindications to CDT included congestive heart failure, renal failure, acute infection, peripheral artery disease, upper-quadrant deep vein thrombosis, and carotid artery stenosis. Eligible patients were referred to a certified lymphedema therapist for CDT. As the program evolved, patients at risk for lymphedema were referred for CDT early on, usually at the time of diagnosis, to improve early identification and surveillance of lymphedema.

CDT included manual lymph drainage, compression bandaging (Figure), decongestive exercises, skin care, and education in swelling self-management. Manual lymph drainage is a specialized light pressure hands-on technique that reduces swelling by enhancing lymphatic reabsorption and flow. Compressive bandaging/garments increase venous and lymphatic drainage and soften fibrotic tissue. Continued use of compression depends on progress. In head and neck cancer patients, the need for lifelong compression is not evident when they are treated early and there is good patient compliance.[8] Therapeutic exercise enhances lymphatic and venous circulation, and good skin care reduces the risk of infection.

Patients' responses to CDT were documented with digital photographs that were taken at each visit and, more recently, use of the NDI.

**Communication and education**
The head and neck cancer nurse navigator attends the cancer center's multidisciplinary head and neck tumor board, which has representation from otolaryngology, diagnostic

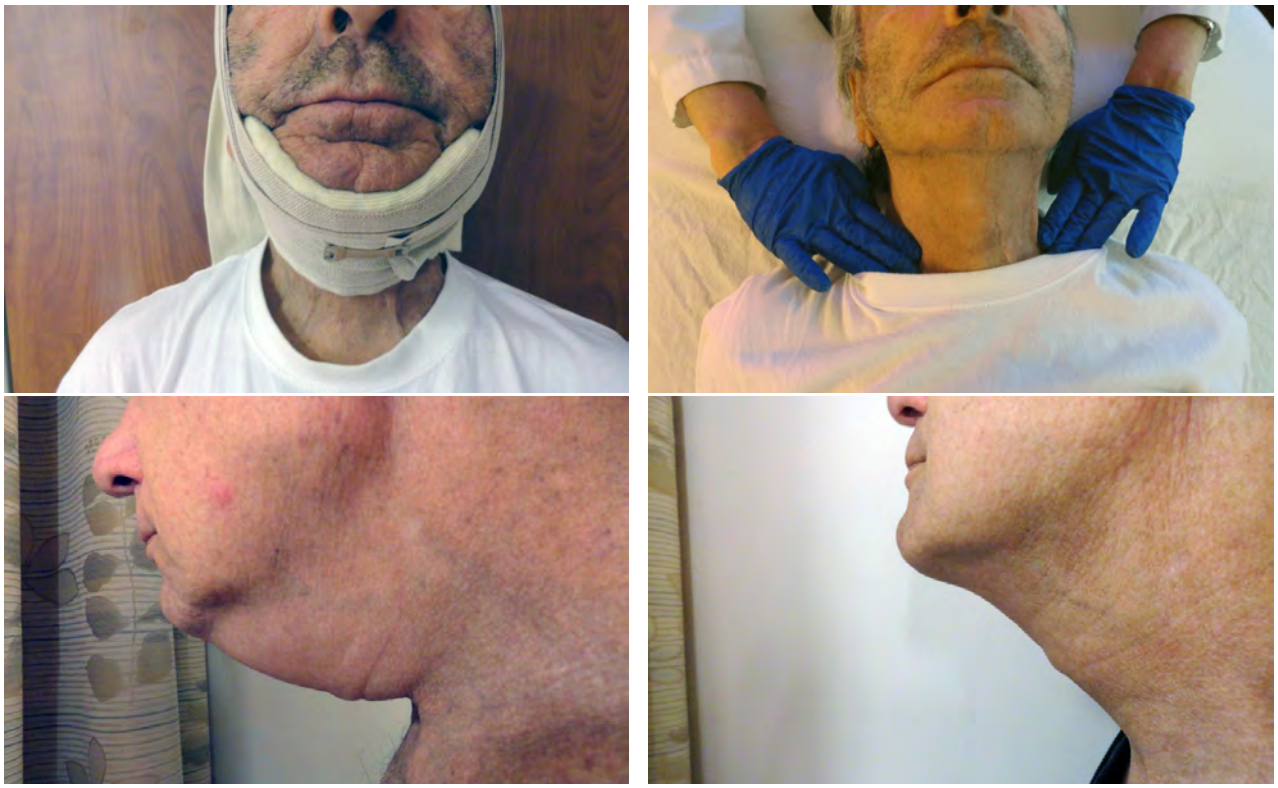

**FIGURE** Compression and manual lymph drainage in head and neck cancer. **A**, Compressive bandages and garments are designed to reduce fluid content of tissues. **B,** Specialized light manual techniques improve lymph flow and reduce lymphedema. **C,** A patient who developed lymphedema after tonsillectomy for right tonsillar cancer, before complete decongestive therapy. **D,** The same patient at discharge, after 11 visits for CDT over 4 months.

radiology, pathology, radiation oncology, medical oncology, reconstructive surgery, oncology rehabilitation (physical/occupational therapist), dietary services, speech pathology, social services and clinical research. This regular contact allows for earlier awareness about which patients are at greater risk for developing lymphedema, thus enabling early intervention (and patient education) in a timely manner.

Education of the patient, before cancer therapy, of the risks of lymphedema is very important. Before the implementation of the prehabilitation program, some patients did not fully comprehend what a painful and debilitating consequence of cancer treatment lymphedema could be.

## Discussion

We introduced a prehabilitation program to detect and treat lymphedema in head and neck cancer patients in January 2012 part way through following an observation cohort from June2008 through June2015. Central to this, in our center, was the appointment of a nurse navigator whose primary focus was on head and neck cancer patients. We placed a high priority on the early detection and treatment of lymphedema because do so has been associated with better outcomes in other centers.

One immediate consequence of the inception of our program was the identification of more patients with external lymphedema. Our detected incidence rose significantly ($P$ = .0002), from 27% in the period June 2008-December 20112010, before the program, to 48% during the January 2012-June 2015 period, after the inception of the program. This later incidence rate is in line with published incidence rates in most centers. However, it is still somewhat short of the 75% suggested in one center,[9] which suggests we are either we are underdetecting lymphedema or there are differences in definition criteria or sensitivity levels for defining lymphedema.

There are currently no specific objective measures of lymphedema, so there is bound to be some variation in diagnosis rates. In our program, we rely heavily on the patient-reported outcome measures, the NDI instrument, and digital photography to detect and monitor lymphedema, starting with the pretreatment baseline values that are established for each patient.

The use of digital photography in our community hospital setting, which includes taking photographs before and after treatment and at each visit, motivates and encourages patients and provides a tool for clinical lymphedema thera-

pists to visually document benefits of treatment. Patients' motivation and compliance with their established home program for head and neck lymphedema self-management are essential. The elements of the home program may include self-manual lymph drainage, home-modified compression bandaging and garment wear, therapeutic exercises, and skin care. Patients with lymphedema who adhered closely with their therapy program were more than 8 times more likely to improve compared with noncompliant patients.[17]

Some groups of patients have a greater risk of developing lymphedema than others,[5] so the development of an algorithm to predict lymphedema seemed possible. However, in our cohort of patients, only neck dissection, with its disruption of the lymphatic system of the neck, was strongly associated with external lymphedema (Table 3). It is important to note that some patients who did not undergo surgery developed lymphedema. In our patients, high doses of radiation alone did not seem to predispose to lymphedema. That suggests that no group of head and neck cancer patients should be ignored, which is why we did routine screening of all patients before, during, and after treatment.

Our protocol falls short in the detection of internal lymphedema. For example, information on swallowing gathered by our speech pathologists (in a different department) has not, so far, been included in our assessment. This is one opportunity to improve on our approach, especially because speech difficulties may be associated with internal lymphedema. In addition, we are not equipped for the requisite internal examinations. Unfortunately, there are no practical and successful treatments for patients suffering from internal swelling. This represents a challenge for the medical community to better meet this need. Therefore, although we are missing some assessments of internal lymphedema, this is of little therapeutic consequence at this time.

The increase in the detected incidence of external lymphedema points to a practice gap that has been resolved by the appointment of a dedicated nurse navigator who attends oncology reviews to share knowledge and information. Another educational effort has been made with the patients themselves to increase compliance and improve continuous care at home.

There is always room for improvement, however, either by feedback acquired from other institutions and hospitals or through the future introduction of more objective assessment techniques.

## Conclusions

The introduction of the prehabilitation program at our center has coincided with a significantly improved detection rate for external lymphedema in head and neck cancer patients. It may be because the program emphasizes education about lymphedema that awareness of the condition has increased throughout the center. It is now widely recognized that all patients are at risk of lymphedema regardless of whether they fall into an acknowledged high-risk group. Our experience shows that there is no significant difference between treatment modalities apart from neck dissection. In our population, the use of this procedure is decreasing. External lymphedema can develop even in patients who do not have surgery. Therefore, there is no sound way to predict which patients are most likely to suffer from the accumulation of fluid in their head and neck after treatment for head and neck cancer. Thus, an assessment as described here, during and after treatment for all patients, is warranted. Patients are now being seen earlier as a part of the prehabilitation program, which facilitates access to complete decongestive treatment at an earlier stage, improves patient outcomes, and increases patient satisfaction with their treatment. Our prehabilitation program could serve as a model for other community hospital centers in achieving outcomes that are as good as those in academic centers.

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# Pancreatitis associated with newer classes of antineoplastic therapies

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Newer anticancer therapies including tyrosine kinase inhibitors, immune modulators, immunotherapies, and chemotherapies have been reported to cause acute pancreatitis. This review gathers data from multiple case reports and small case series that associate these agents with pancreatitis. The mechanism of the pancreatitis may be direct toxicity, elevated triglycerides, immune mediated, or injury with direct injection into the liver, pancreas, or its blood supply. As abdominal pain, nausea, vomiting are associated with cancer chemotherapy itself, the diagnosis of acute pancreatitis might be missed.

Patients with advanced malignancies may develop pancreatitis during therapy for their cancer. Acute pancreatitis is inflammation of the pancreas. Common symptoms include abdominal pain, nausea, vomiting, shortness of breath, dehydration. Laboratory evidence of acute pancreatitis includes elevations of the amylase and lipase. Mild pancreatitis occurs when there is no organ dysfunction, moderate pancreatitis is associated with one organ dysfunction, and severe pancreatitis is complicated by multiple organ dysfunction. Hypotension, hypocalcemia, or anemia suggest a more severe course of the pancreatitis. In some instances, the pancreatitis may be an adverse reaction to the therapy being given. However, other causes such as hypercalcemia, hypertriglyceridemia, cholelithiasis, and underlying malignancy must be ruled out before ascribing pancreatitis to a specific drug. To date, two classifications systems have been proposed by Trivedi[1] and Badalov[2] to evaluate the degree to which a drug is responsible for pancreatitis (Table 1). Furthermore, Naranjo and colleagues have proposed a more general method of assessing the causal relationship between drugs and adverse events.[3] The Naranjo algorithm is not specific for pancreatitis. Jones and colleagues[4] reported that 0.1%-2% of acute pancreatitis cases were owing to drugs. In 2015, they listed the older chemotherapy agents associated with pancreatitis. However, more recently, many new agents have been approved for the management of cancers. The newer classes of antineoplastic agents including proteasome inhibitors, immune-modulating agents, tyrosine kinase inhibitors, monoclonal antibodies against programmed cell death-1 (PD-1) and its ligand PD-L1 and antibody-toxin conjugates are now associated with acute pancreatitis.

## Methods

We conducted a search in PubMed, Google Scholar, and Micromedex for pancreatitis related to antineoplastic agents, including proteasome inhibitors, immune checkpoint inhibitors, monoclonal antibodies, immune-modulating agents, drug-induced pancreatitis. Terms used for the searches included each specific agent and *pancreatitis*, *immunotherapy and pancreatitis*, *tyrosine kinase inhibitors and pancreatitis*, *auto immune pancreatitis*, and *toxicities of molecular target therapies*. Reference lists from the identified manuscripts were reviewed for further studies of pancreatitis as a result of antineoplastic therapy. The most recent search date was February 15, 2017.

The degree to which each agent was associated with inducing pancreatitis was evaluated using the Badalov classification system[2] in addition to the Naranjo Adverse Drug Reaction (ADR) Probability Scale.[3] The Naranjo scale consists of 10 questions with values assigned to each answer. Total scores range from -4 to 13, where 13-9 indicates the reaction is considered definitely attributable to the drug; 8-5, probably attributable; 4-1, possibly attributable; and ≤0, doubtful if attributable.

A total of 67 manuscripts and abstracts were identified. Four manuscripts and 3 abstracts were excluded because they had insufficient information about possible pancreatitis or there was a presence of

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**TABLE 1** Classification systems for drug-induced pancreatitis

| Trivedi[1] | Badalov[2] |
|---|---|
| Class 1 | Class Ia |
| At least 20 reported cases of acute pancreatitis<br>At least 1 case with positive rechallenge | At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs |
| | Class Ib |
| | At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out |
| Class II | Class II |
| >10 but <20 reported cases of acute pancreatitis with or without positive rechallenge | As least 2 cases in the literature<br>Consistent latency (≥75% of cases) |
| Class III | Class III |
| All medications implicated in pancreatitis, ie, Class I, Class II, and those with ≤10 reported cases or unpublished reports in pharmaceutical or FDA files | At least 2 cases in the literature<br>No consistent latency among cases<br>No rechallenge |
| | Class IV |
| | Drugs not fitting into the previously described classes, single case report published in medical literature, without rechallenge |

FDA, US Food and Drug Administration;

multiple other agents or conditions that might have caused pancreatitis. In total, 60 publications met inclusion criteria and were evaluated.

## Results

### Immune checkpoint inhibitors

In a review of toxicities of anti-programmed cell death-1 (PD-1) therapy, pancreatitis was reported to occur in about 1.8% of patients who received nivolumab or pembrolizumab.[5] The 9 patients with pancreatitis attributed to an immune etiology were treated with corticosteroids. Pancreatitis was grade 2 in 3 patients (1.5-2 times upper limit of normal [ULN]), grade 3 in 4 patients (>2-5 ULN), and grade 4 ( >5 ULN) in 2 patients.

In asymptomatic individuals, pancreatitis has been detected on a positron-emission tomography–computed tomography (CT) scan after anti-PD-1 therapy.[5] By contrast, there was a case report of a patient treated with nivolumab for lung cancer who developed anorexia, vomiting, and back pain on day 18 of therapy with an elevation of the amylase and lipase levels, but a negative CT.[6] Later the patient developed a swollen pancreas on CT. Autoimmune pancreatitis comes in two forms. The most common relates to elevated levels of immunoglobulin G4 (IgG4; normal, 135 mg/dL ULN)[7] The mechanism of immune pancreatitis associated with anti-PD-1 therapy is unknown.

Ipilimumab (an anti-CTLA4 antibody) has been approved by the US Food and Drug Administration (FDA) for the treatment of melanoma. Pancreatitis occurred in 1 patient in a phase 1 trial in pediatric patients.[9] In a summary of 14 phase 1-3 trials of ipilimumab in advanced melanoma, pancreatitis was reported in fewer than 1% of the patients.[10] In management guidelines for therapy with ipilimumab, pancreatitis may present as an asymptomatic increase in the levels of amylase and lipase, or with fevers, malaise, or abdominal pain. Oral prednisone or dexamethasone were given for the immune pancreatitis, but the decline in enzymes was slow, often taking months.[11] In a preclinical model of autoimmune pancreatitis due to the blocking of CTLA4, there was suppression of regulatory T-cell function. The autoimmune pancreatitis responded to cyclosporin or rapamycin but there are no clinical data for these agents.[12] The anti-PD-L1 agent atezolizumab has been associated with acute pancreatitis in 2 of 1,978 patients (0.1%).[13] A review by Champiat and colleagues on dysimmune toxcities related to immune checkpoint inhibitors includes pancreatitis as an autoimmune complication of such therapies.[14]

Blinatumomab is an anti-CD19–directed CD3 T-cell engager that has been approved by the FDA for refractory B-cell acute lymphoblastic leukemia. In August 2016, the maker of the drug, Amgen, advised hematologists and oncologists that since February 2016, 10 patients out of more than 2,000 treated with blinatumomab had developed pancreatitis.[15] Other medications the patients were receiving such as high-dose steroids might have caused or contributed to the pancreatitis. In one case, the pancreatitis improved with stopping blinatumomab but worsened with re-challenge. It is possible that the mechanism of the associated pancreatitis relates to a change in immune checkpoint inhibition. CD19-positive, CD24-high, CD27-positive regulatory B cells are decreased in autoimmune pancreatitis.[16] Treatment with blinatumomab may decrease the CD19-positive cells.

### Molecularly targeted agents, including TKIs

Molecularly targeted agents such as tyrosine kinase inhibitors (TKIs) or other kinase inhibitors have been associated with pancreatitis.[17, 18] In a retrospective study by Tiruman and colleagues,[19] the investigators found 91 patients with pancreatitis on imaging, of whom 15 were receiving molecularly target drugs. The pancreatitis was asymptomatic in 2 patients, but 13 had abdominal pain, many with nausea. Four of the patients also had gallstones, but the drug was deemed to be the cause of the pancreatitis. In 4 of the 9 patients in whom a rechallenge was done with the TKI, the pancreatitis relapsed. The pancreatitis resolved in 14 of the

15 patients; 1 patient died because of progressive cancer before the pancreatitis resolved. The pancreatitis was mild, 7 of the 15 patients had normal pancreatic enzymes and the pancreatitis was diagnosed by radiology.

Ghatlia and colleagues[17] performed a meta-analysis of trials of TKI. They found 9 cases of pancreatitis in patients on sunitinib therapy. Of those, 4 patients were on sunitinib alone, and 5 were on other chemotherapy agents in combination with sunitinib. Eight cases of pancreatitis due to sorafenib were found. Three of the patients were on sorafenib alone, and 5 were on other chemotherapy including 1 on transcatheter embolization (TACE). Three cases of pancreatitis were associated with vandetanib; 2 of those patients had other concurrent chemotherapy. One case of axitinib induced pancreatitis was described.

Pancreatitis was reported in the phase 1 trials of sorafenib and sunitinib. In all, 3 of 69 patients treated with sorafenib had grade 3 pancreatitis and asymptomatic elevations of amylase and lipase levels were present in about 5% of patients receiving sunitinib.[18,19]

Other TKIs associated with pancreatitis include pazopanib,[20,21] axitinib,[22] and nilotinib.[23] Pezzilli and coleagues[24] described 5 patients with pancreatitis on sorafenib, 3 on sunitinib, 6 on nilotinib. It is possible that some of these cases appeared in other reviews. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, caused a single case of pancreatitis in 9 patients.[25]

Vemurafenib, a BRAF kinase inhibitor, was associated with pancreatitis in one case. In this case, the pancreatitis resolved on stopping the medication but recurred when vemurafenib rechallenge was attempted.[26] There is a report of dabrafenib being associated with pancreatitis in 1 patient.[27]

Agents that inhibit the TKIs associated with BCR-ABL in chronic myelogenous leukemia are associated with acute pancreatitis. Imatinib-induced pancreatitis was reported in a small number of cases.[28] Nilotinib has caused amylase/lipase elevations with and without symptomatic pancreatitis.[29,30] Ponatinib, an inhibitor of BCR-ABL tyrosine kinase, is associated with pancreatitis.[31] Pancreatitis occurred in 11 of 81 patients treated with ponatinib, and in 8 patients it was described as serious. Further elevation of amylase or lipase levels without clinical pancreatitis was noted in 7 other patients.

**Proteosome inhibitors**

In 2010, Elouni and colleagues[32] reported a case of IV bortezomib-induced pancreatitis, which recurred on rechallenge with bortezomib. This same patient was also reported in an abstract in 2009.[33] In 2009, there was an editorial comment which was added to the end of the abstract that the World Health Organization Adverse Drug Reaction database had 11 reports of bortezomib associated pancreatitis. Talamo and colleagues[34] reported a case of bortezomib-induced pancreatitis due to bortezomib that had been administered subcutaneously. At that time, they also summarized 7 previous reports of bortezomib-associated pancreatitis. The mechanism of bortezomib-induced pancreatitis is not known.[35-37]

Fotoh and colleagues reported a patient with myeloma who had elevated triglyceride levels after bortezomib therapy.[38] In one case of bortezomib-associated pancreatitis, the patient had an elevated triglyceride level, but it was not extremely high.[39] Multiple myeloma itself may be associated with hyperlipidemia but only rarely.[40] Gozetti and colleagues reported a patient who developed hyperlipidemia after two courses of bortezomib;[41] stopping bisphosphonates may be associated with a rise in triglycerides. There was one case of carfilzomib causing pancreatitis during a phase 1 trial.[42]

**Older chemotherapy agents**

Reviews of drug-induced pancreatitis have listed many chemotherapy agents which may cause pancreatitis.[1,43] The agent most frequently associated with acute pancreatitis has been asparaginase,[44] with 2%-16% of patients undergoing asparaginase therapy developing pancreatitis. Asparaginase-related pancreatitis is grade 3 or 4 in 5%-10% of patients, and recurs in 63% of patients on rechallenge. Other chemotherapy agents associated with pancreatitis include: mercaptopurine, cytosine arabinoside, cisplatin, interferon alfa-2b, doxorubicin, tamoxifen, gefitinib, vinorelbine, oxaliplatin, levamisole, methotrexate, azathioprine, 5-fluorouracil, capecitabine, ifosfamide, paclitaxel, and all-trans retinoic acid.

Oxaliplatin carries a 0.1%-2% incidence of drug-induced pancreatitis. In one series of 6 patients, cessation of the agent allowed for resolution of symptoms and decrease in serum lipase and amylase levels.[45] With capecitabine there are 2 case reports of pancreatitis.[46] Cases of pancreatitis associated with trifluridine or tipiracil were not present in the literature.

Thalidomide caused severe pancreatitis in a patient when it was used to treat chronic graft-versus-host disease.[47] This patient suffered recurrent pancreatitis on retreatment with the thalidomide. The authors further referenced two other suspected cases of thalidomide-induced, acute pancreatitis. However, in view of the extensive use of thalidomide for multiple myeloma before the development of lenalidomide, thalidomide-associated pancreatitis would be <1% of patients.

Agents that cause hypertriglyceridemia may cause pancreatitis. This mechanism has been reported as the cause of pancreatitis for everolimus[48] and tamoxifen.[49,50-52] Everolimus causes elevated triglycerides in 30%-50% of patients. There are case reports and a review of tamoxifen-associated pancreatitis caused by elevated triglycerides.[52] There has also been a case of temsirolimus-associated pancreatitis,[53] another agent that elevates triglycerides.

**Pancreatitis associated with hepatic embolization or hyperthermic intraperitoneal chemotherapy**

TACE leads to symptomatic acute pancreatitis in 0.4%-2%

of patients, but nonselective TACE (into the hepatic artery and not just feeder vessels), may lead to elevated amylase levels in 15%-40% of patients.[54-56] The risk of pancreatitis would depend on which chemotherapy drug is being infused into the liver. It would also be greater if the chemotherapy has to be infused into a larger part of the liver than into a small portion of the liver. In one patient, severe pancreatitis secondary to TACE occurred after two previous embolizations; prior embolization may have led to occlusion of the previously infused vessels.[57] Radioembolization with 90Y microspheres was associated with one case of pancreatitis in 112 consecutive patients.[58] The postembolization syndrome in the first 24 hours after the procedure may involve fever, abdominal pain, nausea, and vomiting due to acute pancreatitis in some instances.

Acute pancreatitis has also been described as a complication of hyperthermic intraperitoneal chemotherapy (HIPEC).[59,60] Two of 13 patients receiving HIPEC for gastric cancer developed pancreatitis.[59] In 25 patients with colon cancer who were treated with HIPEC, 1 patient had pancreatitis.[60]

**Antibody-drug conjugates**

Muzaffar and colleagues reported a patient with acute pancreatitis 3 days after starting therapy with ado-trastuzumab emtansine.[61] Urru and colleagues[62] reported a patient who developed acute pancreatitis after brentuximab vedotin therapy. Ghandi and colleagues[63] identified 2 cases of fatal acute pancreatitis with brentuximab vedotin and 6 cases of nonfatal pancreatitis. Two of the nonfatal patients were rechallenged, and 1 developed recurrent pancreatitis. Because abdominal pain may occur in up to 18% of patients receiving brentuximab vedotin, the incidence of pancreatitis may be underestimated with this agent.[64]

In Table 2, ado-trastuzumab emtansine and brentuximab vedotin are listed with incidence and level of association given by the Baldavo[2] and Naranjo.[3] With greater awareness, the incidence of pancreatitis associated with these agents may rise or fall as more data is accumulated. In many instances, there are insufficient numbers of reported cases or insufficient information in single-case reports to complete the entire table.

## Discussion

Acute pancreatitis is an uncommon complication of tyrosine kinase inhibitors, other kinase inhibitors, proteasome inhibitors, monoclonal antibody-drug conjugates and anti-PD-1 immunotherapies. As nausea, abdominal pain, emesis are common in patients with cancer on antineoplastic therapy, some patients may have acute pancreatitis which is undiagnosed. It is not clear whether a patient with pancreatitis secondary to a TKI can be safely switched to a different TKI. As more molecularly targeted agents and more monoclonal antibodies targeting PD-L1 and PD-1 are under development, screening for amylase and lipase levels during phase 1/2 testing may prove helpful.

The natural history of cancer-drug–associated pancreatitis may depend on which agent is the cause. Although there are descriptions of the course of autoimmune pancreatitis, these studies have not included pancreatitis associated with anti-PD-L1 or -PD-1 therapies.[65] It is possible that once an autoimmune pancreatitis has developed, simply stopping the inciting anti-PD-L1 or -PD-1 antibody may not lead to immediate resolution. Therapy with combined immune checkpoint blockade agents (eg, nivolumab and ipilimumab) may cause a higher incidence of pancreatitis than therapy with a single agent.[66]

In a report of 119 patients with melanoma who were treated with nivolumab and ipilimumab, there were 2 cases of acute pancreatitis, though 20% of patients had a grade 3 or higher amylase level, and just over 6% had a grade 3 or higher lipase.[67] Stopping this type of immunotherapy early for grade 1,2, or 3 rises in pancreatic enzymes might prevent symptomatic pancreatitis from developing, but would stop potentially curative therapy for many patients who would have never developed clinically serious pancreatitis. Patients who suffer immune toxicities with anti-PD-1 therapies may be more apt to obtain some clinical benefit. The development of immune-related toxicities in patients treated with ipilimumab ( an anti CTLA4 antibody) seemed to correlate the tumor regression.[68] This has also been suggested by the fact that the development of vitiligo correlates with clinical response in melanoma patients treated with nivolumab.[69] Although clinically significant pancreatitis might be averted by stopping immune therapies earlier, stopping before it is deemed necessary might prevent cancer patients from receiving life-prolonging therapy.

Acute pancreatitis in general is severe in about 25% of cases and is associated with a significant risk of death. Scoring systems such as Ranson criteria and Apache 2 are used to assess the severity of pancreatitis although their utility is debated.[70] Asparaginase is the chemotherapy agent most frequently associated with pancreatitis. It has been used to treat acute lymphoblastic leukemia for more than 30 years. This allowed for a study of 5,185 children and young adults who received asparaginase to determine what clinical factors and genomic factors were associated with the development of acute pancreatitis in 117 individuals.[71] Further information gathered from programs such as the FDA and the adverse drug reaction program at Northwestern University in Chicago, coupled with the publication of other cases of pancreatitis associated with newer cancer agents may provide more insight into the mechanism causing pancreatitis due to a specific agent. With more cases being published, it may also become possible to determine if there are specific predisposing factors based on the clearance or metabolism of the offending agent or any genetic predisposition for drug-related pancreatitis.

**TABLE 2** Pancreatitis secondary to new anticancer therapy using Badalov criteria and Naranjo algorithm

| Agent | Incidence | Level of evidence | | Notes |
|---|---|---|---|---|
| | | Badalov | Naranjo score (n) | |
| Immunotherapy | | | | |
| Nivolumab | cases/total patients (<1%) | Class 2 | Probable (1) | |
| Ipilimumab/nivolumab | cases/total patients (6%) | Class 2 | ID | |
| Pembrolizumab | cases/total patients (<1%) | Class 2 | ID | |
| Ipilimumab | cases/total patients (1.3%) | Class 2 | ID | |
| Blinatumomab | 10/>2,000 | Class 3 | ID | |
| Atezolizumab | 2/1,978 (<1%) | Class 4 | ID | |
| Tyrosine kinase inhibitors | | | | |
| Sunitinib | cases/total patients (4.3%) | Class 2 | ID | No rechallenges reported |
| Sorafenib | cases/total patients (<1%) | Class 1 | ID | |
| Pazopanib | cases/total patients (<1%) | Class 1 | Probable (4) | |
| Nilotinib | 8 case reports | Class 1 | Probable (1) | |
| Axitinib | ND | Class 4 | Probable (1) | |
| Ibrutinib | ND | Class 4 | ID | |
| Vemurafinib | cases/total patients (<1%) | Class 1 | Definite (1) | 1 case with rechallenge |
| Dabrafenib | cases/total patients (<10%) | Class 4 | ID | |
| Ponatinib | 11/81 (14%) | Class 2 | ID | |
| Proteosome inhibitors | | | | |
| Bortezomib | cases/total patients (<1%) | Class 1 | Possible (2)<br>Probable (4) | 3/6 rechallenge |
| Carfilzomib | 1 case report | Class 4 | ID | |
| Other | | | | |
| Oxaliplatin | cases/total patients (<1%) | Class 2 | Probable (2) | No rechallenge |
| Thalidomide | 1 case report | Class 1 | Probable (1) | |
| Everolimus | ND | Class 4 | Probable (1) | |
| Tamoxifen | 5 case reports | Class 4 | Probable (1) | |
| Temsirolimus | | Class 4 | Possible (1) | |
| TACE | | Class 2 | ID | |
| Radioembolization | 3/193 (2%) | Class 3 | ID | |
| HIPEC | 2 case reports | Class 4 | ID | |
| Ado-trastuzumab emtansine | 1 case report | Class 4 | Probable (1) | |
| Brentuzimab vendotin | 8 case reports | Class 1 | | 2 rechallenge; 1 recurrence |

HIPEC, hyperthermic intraperitoneal chemotherapy; ID, insufficient data; ND, not documented; TACE, transcatheter arterial chemoembolization

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# Prescriber adherence to antiemetic guidelines with the new agent trifluridine-tipiracil

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**Background** In 2015 alone, the US Food and Drug Administration approved 18 cancer drugs, but to our knowledge, few studies, if any, have examined prescribers' adherence to antiemetic guidelines as new chemotherapy agents become available. This issue is important because poor adherence to antiemetic guidelines has been shown in previous studies to have a negative impact on the control of nausea and vomiting. Here we report on antiemetic practices and outcomes for trifluridine-tipiracil, a drug newly approved in 2015.

**Objective** To test the hypothesis that patients prescribed a newly available chemotherapy agent, trifluridine-tipiracil, are at risk for chemotherapy-induced nausea and vomiting because of providers' poor adherence to antiemetic guidelines.

**Methods** All patients who received their first dose of trifluradine-tipiracil for metastatic colon cancer in 2015 were included in this retrospective, single-institution study of pretreated patients. The study time frame was the 2015 calendar year: 9 months before the drug was approved in September 2015, when patients received the medication through a compassionate-use program, and the 3 months immediately after drug approval. First-cycle antiemetic prescribing was examined for adherence to National Comprehensive Cancer Network Guidelines (v1.2015) and categorized as guideline adherent, non–guideline-adherent/aggressive (received more prophylaxis than called for), and non–guideline-adherent/less aggressive (including no antiemetics).

**Results** Of the 44 patients in this study, 28 (64%) had had nausea and vomiting with previous chemotherapy. With the first cycle of trifluridine-tipiracil, 25 patients (57%; 95% confidence interval [CI]: 42%, 70%) were prescribed prophylactic antiemetics in a guideline-adherent manner; 15 (34%; 95% CI: 22%, 49%) in a non–guideline-adherent/aggressive manner; and 4 (9%; 95% CI: 4%, 21%) in a non–guideline-adherent/less aggressive manner. In guideline-adherent patients, rates of nausea and vomiting were 52% and 24%, respectively. In non–guideline-adherent/aggressive patients, those rates were 33% and 27%, respectively. In both the aforementioned groups, a total of 2 patients received interim care for nausea and vomiting. No nausea or vomiting was reported among non–guideline-adherent/less aggressively managed patients.

**Limitations** Single-institution, retrospective study of a small group of patients

**Conclusions** Poor adherence to antiemetic guidelines was common. However, because adherence was not consistently associated with better control of nausea and vomiting, clinical judgment should complement guideline adherence when prescribing trifluridine-tipiracil and other newly approved cancer drugs.

Cancer drugs are becoming available at an unprecedented rate. In 2015 alone, the US Food and Drug Administration (FDA) approved 18 new agents.[1] Although many of those agents have adverse event profiles that are more favorable than those seen with conventional chemotherapy, nausea and vomiting still occur. In fact, nausea and vomiting continue to be ranked as among the most common and distressing of cancer symptoms.[2,3] In a 2004 study, Grunberg and colleagues reported that as many as 75% of health care providers misjudge the risk for chemotherapy-induced nausea and vomiting (CINV), even when prescribing cancer drugs that have been available for years,[4] thus amplifying concerns that such risk assessment might be even worse when new cancer agents are prescribed for the first time.

In this study, we hypothesized that patients prescribed a new cancer drug, trifluridine-tipiracil, would be at risk for CINV because of poor guideline adherence on the part of health care providers. The correct matching of antiemetics to chemotherapy is important. Inadequate antiemetic prophylaxis predisposes to nausea and vomiting with dehydration and met-

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abolic and electrolyte derangements – complications that can occur in up to one-third of patients who receive moderately or highly emetogenic chemotherapy and who have been reported to achieve poor symptom control.[4] Overprophylaxis also has drawbacks. For example, antiemetics are expensive and, at times, they can induce their own adverse events, such as lethargy, dyskinesia, constipation, headaches, hiccups, fatigue, and even cardiac arrhythmias.[5] The best approach is to appropriately match the antiemetic to the chemotherapy. Indeed, adherence to evidence-based guidelines has yielded success in symptom control, but the guidelines work on the assumption that the emetogenic potential of new chemotherapy agents has been accurately determined and then disseminated to and acted upon by health care providers.[6,7] To our knowledge, no previous studies have tested that assumption, as we do in the present study.

Trifluridine-tipiracil was selected as the focus of this project and as illustrative of other newly approved chemotherapy agents for two reasons. First, it became available for routine prescribing in pretreated patients with metastatic colorectal cancer in the United States in September 2015.[1] That timing allowed us to analyze much of the early prescribing period, both during the 9 months before approval, when the drug was available on a compassionate-use basis at our institution, and the 3 months after approval. Second, trifluridine-tipiracil has classifiably low emetogenic potential, and mismatching of antiemetics tends to occur more often with low emetogenic chemotherapy.[9] Trifluridine-tipiracil and placebo patients manifest rates of nausea at 48% and 24%, respectively, and rates of vomiting at 28% and 14%, respectively.[8]

Hence, the goal of this study was to explore whether a guideline-based prophylactic antiemetic regimen was appropriately matched to the new chemotherapy agent, trifluridine-tipiracil, to report whether such symptoms of nausea and vomiting are kept at bay, and to identify a potentially vulnerable interval – immediately after drug approval – when cancer patients may be at risk for CINV because of poor adherence to antiemetic guideline prescribing practices by health care providers.

## Methods

### Overview

The Mayo Clinic Institutional Review Board approved this study. We obtained the identifying information of all patients treated with trifluridine-tipiracil at our institution from the Mayo Clinic Specialty Pharmacy, which uses an electronic prescribing system that contributed to the comprehensiveness of the data set. Patients included those who had participated in a colorectal cancer compassionate-use program before the September 2015 approval of the drug and those who received the drug shortly after its approval. In essence, this retrospective, single-institution study included every patient who received trifluridine-tipiracil for metastatic colorectal cancer in 2015 (January through December); this approach enabled us to systematically report on early first-cycle prescribing practices 9 months before and 3 months after the drug's approval in September of 2015.

### Determination of guideline adherence

This project relied on the National Comprehensive Cancer Network (NCCN) Guidelines (v1.2015, behind paywall) because they had been updated in 2015 (and hence coincided with this project's study dates) to incorporate recommendations specific to oral chemotherapy and because they seemed concordant with other guidelines.[10,11]

Antiemetic prophylaxis for a specific patient was deemed guideline adherent if a version of the recommended NCCN antiemetic regimen had been prescribed during the first cycle of chemotherapy. This regimen consisted of metoclopramide, prochlorperazine, haloperidol, or a 5-hydroxytryptamine receptor antagonist. In contrast, if a patient had been prescribed a more aggressive or less aggressive regimen, such prescribing practices were deemed non–guideline adherent/aggressive (received more prophylaxis than called for) or non–guideline adherent/less aggressive (including no antiemetics), respectively. Again, medical record prescribing determined adherence.

### Data reporting

The primary goal of this study was to report the percentage of patients who had been prescribed a first-cycle antiemetic prophylaxis regimen concordant with NCCN guidelines. Secondary goals included reporting the incidence of nausea and vomiting, the use of rescue antiemetics other than those prescribed up front, the need for an unplanned medical encounter to address nausea and vomiting, and change in antiemetic prescribing before the second chemotherapy cycle. Confidence intervals were calculated with JMP® Pro 10.0.0. This study was too limited in sample size to assess sex-based differences in outcomes.

## Results

### Demographics

This report focuses on 44 patients who received first-cycle trifluridine-tipiracil during the first calendar year of the drug's FDA approval. All patients had metastatic colorectal cancer and had previous exposures to other chemotherapy agents (Table 1). Of note, 28 patients (64%) had experienced CINV before starting trifluridine-tipiracil and all these patients had been heavily pretreated with multiple lines of chemotherapy.

### Guideline adherence

Patients were most commonly prescribed prochlorperazine and ondansetron prophylaxis for CINV before the first chemotherapy cycle of trifluridine-tipiracil (Table 2): 15 patients were prescribed combination antiemetic ther-

apy, typically two of the most commonly prescribed single agents with different mechanisms of action. Twenty-five patients (57%; 95% confidence interval (CI): 42%, 70%) were prescribed antiemetics in a manner consistent with guidelines; 15 (34%; 95% CI: 22%, 49%) were prescribed antiemetics in a non–guideline-adherent/more aggressive manner (received more prophylaxis than called for); and 4 (9%; 95% CI: 4%, 21%) were prescribed them in a non–guideline-adherent/less aggressive manner.

### Clinical outcomes based on guideline adherence

In guideline-adherent patients, first-cycle nausea and vomiting occurred in 13 patients (52%) and 6 patients (24%), respectively, with 1 patient requiring an unscheduled clinic visit and another an emergency department visit and hospital admission – all for nausea and vomiting (Table 3). In non–guideline-adherent/more aggressive patients, those symptoms occurred in 5 patients (33%, nausea) and 4 patients (27%, vomiting), with 1 patient requiring a clinic visit and emergency department visit and another an emergency department visit – again, all for nausea and vomiting. In non–guideline-adherent/less aggressive patients, no nausea or vomiting was reported.

## Discussion

This study examined adherence to antiemetic guidelines in the setting of a soon-to-be-approved or newly approved antineoplastic agent. As hypothesized, a substantial proportion of patients (43% in this study) were prescribed antiemetics in a nonadherent manner with respect to guidelines, thus identifying the period shortly before and after FDA approval as a particularly vulnerable interval with respect to antiemetic guideline adherence. It is possible that our institution's practice of testing novel chemotherapy agents for the treatment of colorectal cancer prompted a heightened awareness of potential adverse events, leading to greater guideline adherence than might have occurred in other settings and resulting in judicious straying from guideline adherence only when appropriate.[12-14] Thus, these high rates of poor adherence may in fact represent an underestimate of what one might see in other clinical practices; and, similarly, these rates of symptom control might also be more favorable than those one might see in other clinical practices. To our knowledge, antiemetic prescribing practices with newer chemotherapy agents have not been explored before now, and our data underscore a clear need to do so – particularly during this limited interval when health care providers begin to prescribe new chemotherapy agents for the first time.

It is worth noting that despite the high rates of guideline nonadherence, rates of nausea and vomiting seemed to be comparable in patients prescribed antiemetics in a guideline-adherent manner and those prescribed antiemetics in a non–guideline-adherent/aggressive manner.A small number of patients in both the guideline-adherent and non–guideline-adherent/aggressive groups required rescue medications, unscheduled medical visits for nausea and vomiting, and additional antiemetics during the second cycle of chemotherapy. Of note,none of those interventions occurred in patients who were prescribed antiemetics in a non–guideline-adherent/less aggressive manner. These findings might reflect the fact that the patients had proven themselves to be at risk for nausea and vomiting with previous chemotherapy. Before they became candidates for trifluridine-tipiracil, patients had been heavily pretreated

**TABLE 1** Patient characteristics (N = 44)

| Characteristic | No. of patients (%) |
|---|---|
| Mean age at Trifluridine/tipiracil initiation: 60 y (SD, 12) | — |
| Sex | |
| Men | 23 (48) |
| Women | 21 (52) |
| Trifluridine-tipiracil dose | |
| 35 mg/m$^2$ | 43 (98) |
| Other | 1 (2) |
| Concurrent bevacizumab? | |
| No | 43 (98) |
| Yes | 1 (2) |
| History of CINV? | |
| No | 5 (11) |
| Yes | 28 (64) |
| Unable to determine | 11 (25) |

CINV, chemotherapy-induced nausea and vomiting

**TABLE 2** Prescribed first-cycle antiemetics[a]

| Drug | n (%) |
|---|---|
| Ondansetron | 16 (36) |
| Granisetron | 1 (2) |
| Dexamethasone | 1 (2) |
| Metoclopramide | 1 (2) |
| Prochlorperazine | 34 (77) |
| Promethazine | 3 (7) |
| Lorazepam | 10 (23) |
| Olanzapine | 1 (2) |

[a]15 patients were prescribed a combination of these listed agents, with the combination often including 2 agents with different mechanisms of action.

**TABLE 3** Outcomes based on first-cycle guideline adherence

| | Total, n (%) [N = 44] | Guideline-adherent, n (%) [n = 25] | Non-guideline-adherent/ aggressive, n (%) [n = 15] | Non-guideline adherent/ less aggressive, n (%) [n = 4] |
|---|---|---|---|---|
| Nausea | 18 (41) | 13 (52) | 5 (33) | 0 (0) |
| Vomiting | 10 (23) | 6 (24) | 4 (27) | 0 (0) |
| Rescue antiemetics | 2 (5) | 1 (4) | 1 (7) | 0 (0) |
| Unscheduled clinic visit* | 2 (4.5) | 1 (4) | 1 (7) | 0 (0) |
| ED visit* | 3 (7) | 1 (4) | 2 (13) | 0 (0) |
| Hospital admission* | 1 (2) | 1 (4) | 0 (0) | 0 (0) |
| Additional antiemetics for C2 | 2 (5) | 1 (4) | 1 (7) | 0 (0) |

C2, Cycle2; ED, emergency department
*Clinic visits, emergency department visits, and hospital admissions were all for nausea and vomiting.

with other chemotherapy agents, most had experienced CINV, and many were therefore highly predisposed to nausea and vomiting. These observations underscore the fact that guidelines – even those that are well accepted and widely used – should be implemented in concert with good clinical judgment.[10,11]

This study has shortcomings, most notably its small sample size. However, had we extended our study beyond 3 months of the FDA approval to include more patients, our findings would have reflected more experienced prescribing practices and we thereby would have deviated from our primary goal of assessing antiemetic prescribing practices with only recently-approved and available chemotherapy agents. In this context, this limited sample size aptly serves a primary role of capturing outcomes within a fleeting but critical interval of new drug availability.

In summary, this study found a notable rate of poor guideline adherence when prescribing antiemetics for trifluridine-tipiracil, a new chemotherapy agent of low emetogenic potential. Although the resultant rates of nausea and vomiting suggest that good clinical judgment might have influenced whether or not guidelines were adhered to, these findings nonetheless underscore the need to assess adherence to antiemetic guidelines when new chemotherapy drugs become available and potentially to put in place institutional infrastructure rapidly to promote improved adherence. Such an assessment should be deliberate, formalized, and prompt within individual oncology clinics and cancer centers after a new cancer drug becomes available. In conjunction with clinical judgment, such measures might lead to improved symptom control.

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# Physician attitudes and prevalence of molecular testing in lung cancer

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**Background** EGFR mutations and EML4-ALK rearrangements are key therapeutic targets in nonsquamous non–small-cell lung carcinoma (nsNSCLC). Current guidelines recommend testing all patients with advanced nsNSCLC (stages IIIB and IV).
**Objective** To evaluate physician attitudes about molecular testing for nsNSCLC and to determine the rate of testing, the effect of biopsy sample size, and prevalence of driver mutations .
**Materials and methods** In this retrospective study, 206 cases of advanced nsNSCLC were identified from the tumor registry from 3 hospitals within a health network (February 2011-February 2013). EGFR and ALK testing was performed using commercial laboratories and mutation prevalence was determined. A survey was sent to practitioners who care for patients with lung cancer to evaluate their attitudes toward molecular testing.
**Results** The prevalence of EGFR mutation (7.8%) and ALK rearrangement (2%) was lower than reported in the literature. Large biopsy samples were more likely to be analyzed for EGFR mutations and ALK rearrangements ($P$ = .023 and $P$ = .007, respectively) than were smaller samples. There was a high level of agreement among survey respondents that mutation testing was essential. Nevertheless, we found that fewer than half of the eligible patients had been tested for these critical driver mutations.
**Limitations** Small sample size
**Conclusion** Despite current recommendations to test patients with advanced nsNSCLC for EGFR mutations and ALK rearrangements and physician assertions that they deemed mutation testing essential, fewer than 50% of the patients at the 3 hospitals had been assayed. Our findings imply that large biopsy samples, such as those from surgical or core biopsies, are better than small samples, such as those from needle aspiration for the purpose of molecular testing. In addition, the prevalence of driver mutations among patients who were treated at the cancer center is lower than that published in the literature.

Lung cancer is the leading cause of cancer death in the United States. It is estimated that there will be 222,500 new cases of lung cancer and 155,870 deaths from lung cancer in 2017. Non–small-cell lung carcinoma (NSCLC) accounts for 80%-85% of lung cancers, with adenocarcinoma being the most common histologic subtype. Other less common subtypes include squamous-cell carcinoma, large-cell carcinoma, and NSCLC that cannot be further classified.[1] Nearly 70% of patients present with locally advanced or metastatic disease at the time of diagnosis and are not candidates for surgical resection.[2] For that group of patients, the mainstay of treatment is platinum-based chemotherapy with or without radiation therapy. Patients who are chemotherapy naive often experience a modest response, however; durable remission is short lived, and the 5-year survival rate remains staggeringly low.[3] Improved understanding of the molecular pathways that drive malignancy in NSCLC has led to the development of drugs that target specific molecular pathways.[4] By definition, these driver mutations facilitate oncogenesis by conferring a selective advantage during clonal evolution.[5] Moreover, agents targeting these pathways are extremely active and induce durable responses in many patients.[6,7,8]

Predictive biomarkers in NSCLC include anaplastic lymphoma kinase (ALK) fusion oncogene and sensitizing epidermal growth factor receptor (EGFR) mutations. Mutations in the EGFR tyrosine kinase are observed in about 15%-20% of NSCLC adenocarcinomas in the United States and upward of 60% in Asian populations. They are also found more frequently in nonsmokers and women.[6] The two most prevalent mutations in the EGFR tyrosine kinase domain are in-frame deletions of exon 19 and L858R substitution in exon 21, representing about 45% and 40% of mutations, respectively.[9] Both mutations result in activation of the tyrosine kinase domain, and both are associated with sensitivity to the small-molecule tyrosine

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kinase inhibitors (TKIs), such as erlotinib, gefitinib, and afatinib.[10] Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).[11] Targeted therapy produces durable responses in the majority of patients.[12,13,14] Unfortunately, most patients develop acquired resistance to these therapies, which leads to disease progression.[4,15-17]

ALK gene rearrangements, although less prevalent, are another important molecular target in NSCLC and are seen in 2%-7% of cases in the United States.[7] As with EGFR mutations, these mutations are more prevalent in nonsmokers, and they are found more commonly in younger patients and in men.[8]

Identification of driver mutations early in the course of disease and acquired resistance mutations later are crucial for the optimal management of advanced NSCLC. DNA analysis using polymerase chain reaction (PCR) and next-generation sequencing is the preferred method for testing for EGFR mutations, and ALK rearrangements are generally tested either by flourescence in situ hybridization (FISH) or immunohistochemistry.[18,19] Newer blood-based assays have shown great promise, and clinicians may soon have the ability to monitor subtle genetic changes, identify resistance patterns, and change therapy when acquired resistance occurs.[20]

The American College of Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology have proposed guidelines for molecular testing in lung cancer. It is recommended that all advanced squamous and nonsquamous cell lung cancers with an adenocarcinoma component should be tested for EGFR and ALK mutations independent of age, sex, ethnicity, or smoking history. In the setting of smaller lung cancer specimens (eg, from biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (eg, young age, lack of smoking history) may be useful in selecting a subset of these samples for testing. Samples obtained through surgical resection, open biopsy, endoscopy, transthoracic needle biopsy, fine-needle aspiration, and thoracentesis are all considered suitable for testing, but large biopsy samples are generally preferred over small biopsy samples, cell-blocks, and cytology samples.[21] Despite this recommendation, not all patients who are eligible for mutation analysis are tested. At our institution, preliminary observations suggested that the percentage of patients being tested and the prevalence of driver mutations were significantly lower compared with published data. The purpose of this study was to evaluate physician attitudes about molecular testing, and to determine the rate of testing, the effect of biopsy sample size on rate of testing, and the prevalence of driver mutations at our institution.

## Methods

In this retrospective clinical study, we identified 206 cases of advanced nsNSCLC from the tumor registry (February 2011-February 2013). Registry data was obtained from three hospitals within our health network – two academic tertiary care centers, and one community-based hospital. The other hospitals in the network were excluded because their EHR systems were not integrated with the rest of the hospitals and/or there was a lack of registry data. The testing rates for driver mutations, prevalence of driver mutations, and the tissue procurement techniques were obtained from individual chart review. Surgical specimens, core biopsy samples, and large volume thoracentesis specimens were categorized as large biopsy samples, and samples obtained by fine-needle aspiration, bronchial washing, and bronchial brushing were considered small biopsy samples. We used a chi-square analysis to compare mutation testing rates between the large and small biopsy sample groups. The prevalence of driver mutations was determined, excluding unknown or inadequate samples.

EGFR analysis had been conducted at Integrated Oncology, using formalin-fixed, paraffin-embedded tissue. Genomic DNA was isolated, and EGFR mutation analysis was performed using SNaPShot multiplex PCR, primer extension assay for exons 18-21; samples with >4mm$^2$ and ≥50% tumor content were preferred. Macrodissection was used to enrich for tumor cells when samples had lower tumor cellularity and content. ALK rearrangements were tested in the hospital using the Vysis ALK Break Apart FISH probe kit (Abott Molecular Inc, Des Plaines, IL).

We conducted a web-based, 20-question survey about molecular profiling among 110 practitioners to gauge their knowledge and opinions about molecular testing. The practitioners included medical oncologists, thoracic surgeons, pulmonologists, and interventional radiologists. Each received an initial e-mail informing them of the study, inviting them to complete survey, and providing a link to it, and two reminder e-mails at biweekly intervals to maximize survey participation and responses. The questions were aimed at understanding the challenges surrounding molecular testing within our network. Apart from the questions gathering demographic information about the respondents, the questions were intended to highlight the disparities between guideline recommendations and physician practices; to gauge the perceived importance of molecular evaluation; to identify individual, subspecialty, and hospital-based challenges; and to assess physician attitudes toward alternatives to traditional tissue-based testing (Table 1, p. e150). Nineteen of the questions were structured as single or best answer, whereas Question 9, which was

aimed at identifying system-based challenges, allowed for multiple answer selections.

## Results

There were a total of 206 cases of advanced stage IIIb or IV nsNSCLC identified at three hospitals during 2011-2013. Of those 206 cases, 161 (78.2%) were recorded at the two large academic medical centers, and 45 (21.9%) were recorded at the smaller community-based hospital. Of the total, there were 145 (70.4%) large biopsy specimens and 61 (29.6%) small biopsy specimens. We found that 89 of the 206 cases (43.2 %) had been tested for EGFR mutations, and 49 (23.8%) had been tested for ALK rearrangements (Figure, A and C). In all, 70 (48.3%) large-sample biopsies and 19 (31.1%) small-sample biopsies were submitted for EGFR analysis (Figure, B), and 42 (29%) large-sample biopsies and 7 (11.5%) small-sample biopsies were tested for ALK rearrangements (Figure, D). Large-sample biopsies were more likely to be analyzed for EGFR mutations and ALK rearrangements, with the results reaching statistical significance ($P$ = .023 and $P$ = .007, respectively). Across all samples, a total of 7 EGFR mutations and 1 ALK rearrangement were identified, yielding a prevalence of 7.9% and 2% respectively (Figure, A and C). Table 2 shows the demographics, smoking status and type of driver mutation identified. Core biopsies were obtained in 45.6% of the cases and fine-needle aspiration biopsies were obtained in 25.2% of the cases with surgical resections, with thoracentesis and bronchial washings comprising the rest of the biopsies (Table 3).

The average age at diagnosis of the patients in the cases that were analyzed was 69.3 years. Most of the patients (83.9%) identified as white, 3.8% were African American, and 12.6% were in the Unknown category. Of the total number of patients, 11 were identified as never-smokers (5.3%), 50 (24.3%) had a 1-15 pack-year smoking history, 104 (50.5%) had a 16-45 pack-year smoking history, and 41 (19.9%) had a >45 pack-year smoking history.

In regard to the survey, 46 of the 110 physicians asked to participate in the survey responded, representing a response rate of 41.8% (range across medical specialties, 26%-45%, Table 4). Of those respondents, 38 (82.6%) indicated they believed molecular evaluation was a very important aspect of NSCLC care, with the remainder indicating it was somewhat important. 91.4% of the respondents who routinely ordered molecular testing agreed that stage IIIb or IV nsNSCLC should undergo molecular evaluation.

The top barriers to molecular evaluation identified through this survey were the availability of sufficient tissue to complete molecular testing and the Center for Medicare and Medicaid Services's (CMS's) 14-day rule that requires hospitals to wait 14 days after the patient is discharged for the lab to receive reimbursement for molecular testing (Table 5).

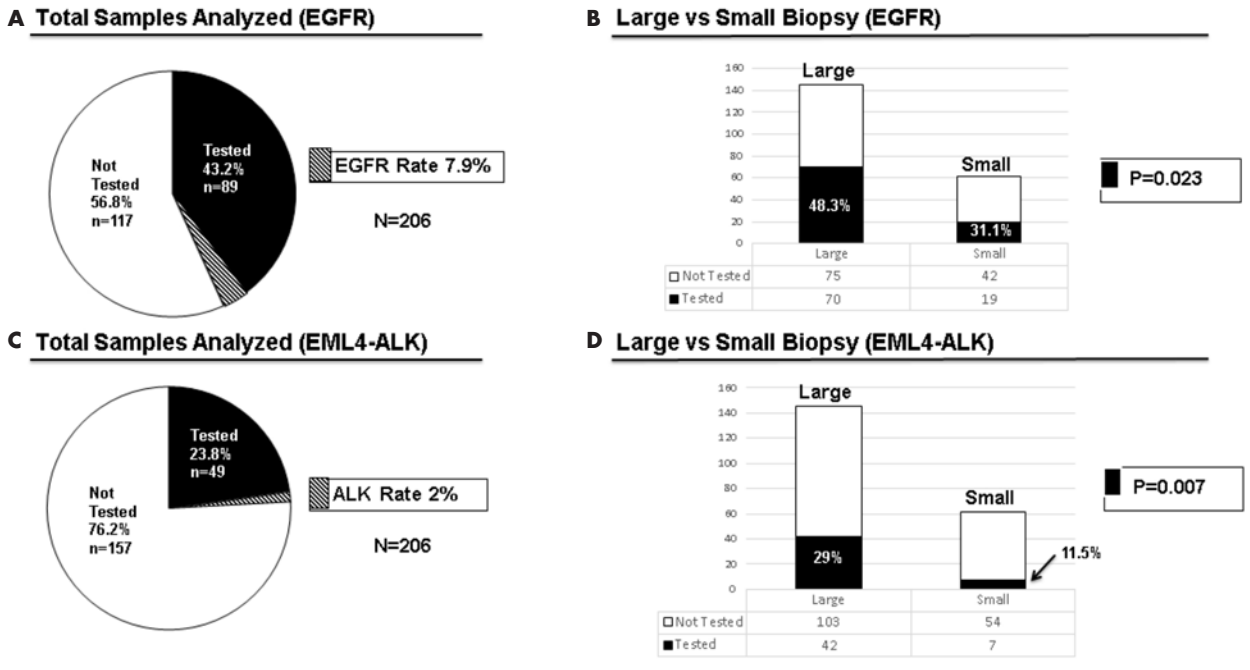


**FIGURE** Study results. **A,** Total samples tested for EGFR 43.2%, EGFR rate 7.9%. **B,** Large biopsies more likely to be tested for EGFR mutations, $P$ = .023. **C,** Total samples tested for EML4-ALK rearrangement 23.8%, EML4-ALK rate 2%. **D,** Large biopsies more likely to be tested for EML4-ALK, $P$ = .007

## Discussion

The treatment of advanced nsNSCLC has evolved significantly over the past decade. Molecular profiling is now an essential part of initial evaluation, and larger-sample biopsies are needed to ensure accurate evaluation and appropriate treatment. The detection of EGFR and EML4-ALK driver mutations are associated with increased response to tyrosine kinase inhibitors and are associated with improvement in progression-free survival, patient quality of life, and even overall survival in some studies.[12,22,23,24] Early identification of these driver mutations is crucial, however, preliminary observation in our network suggested that a large percentage of patients with advanced nsNSCLC in were not being appropriately evaluated for those mutations. To evaluate our molecular profiling rates, we conducted a retrospective study and reviewed 3 years of registry data at 3 hospitals within our health system. Two of the hospitals included in our analysis were large tertiary academic centers, and one was a community hospital. Our findings confirmed that a large percentage of our patients who are eligible for molecular evaluation are not tested: 56.7% of cases were not tested for EGFR mutations, and 76.2% of cases were not tested for ALK rearrangements.

In a similar study, the Association for Community Cancer Centers conducted a project aimed at understanding the landscape and current challenges for molecular profiling in NSCLC. Eight institutions participated in the study, and baseline testing rates were analyzed. The findings demonstrated that high-volume institutions (treating >100 lung cancer patients a year tested 62% and 60% of advanced lung cancer patients for EGFR and EML4-ALK, respectively, and low-volume institutions (treating <100 lung cancer patients a year tested 52% and 47% for EGFR and EML4-ALK, respectively.[25,26] In a recent

**TABLE 1** Survey questions in detail

1. Approximately how many members of your cancer center staff are formally trained or certified in process improvement (Lean, Lean Six Sigma, etc)?
2. Do you have any ongoing quality improvement projects focused on NSCLC?
3. Approximately what percent of all your patients with NSCLC are diagnosed as inpatients vs outpatients?
4. Rate the importance of molecular testing in advanced NSCLC?
5. Who typically makes the decision on the best way to obtain tissue in advanced stage lung cancer?
6. How likely are you to send molecular testing (EGFR or ALK) on a stage I, II, or IIIA nonsquamous NSCLC?
7. How likely are you to send molecular testing (EGFR or ALK) on a stage IIIB/IV nonsquamous NSCLC?
8. How likely are you to send molecular testing on stage IIIB/IV squamous cell lung cancer patient?
9. What challenges/barriers has your practice/organization has faced with molecular testing in advanced NSCLC. (check all that apply)
   - A. Availability of sufficient tissue to complete molecular testing
   - B. Poor performance status
   - C. Poor pulmonary function
   - D. Risk of pneumothorax
   - E. Risk of bleeding
   - F. Location of tumor (central versus peripheral)
   - G. Comorbid conditions (eg. chronic anticoagulation therapy etc.)
   - H. Level of patient commitment
   - I. Level of physician commitment
   - J. Current or prior smoking history
   - K. 14 day rule
   - L. Other _____
10. How likely are you to send a molecular testing order for a patient with a smoking history?
11. How likely are you to send a molecular testing order for a patient with poor performance status?
12. How often does lack of tissue effect your decision to order molecular testing?
13. How likely are you to repeat a biopsy if there is inadequate tissue for molecular testing?
14. How does your organization select a molecular testing lab for NSCLC biopsy specimens?
    - A. Molecular testing is done internally
    - B. The pathology department selects the lab
    - C. The medical oncology department selects the lab
    - D. The pathology and medical oncology departments work together to select the lab
    - E. Other (Please specify)
15. How likely would you be to do molecular testing if it was delayed by the 14-day rule?
16. How likely is it that molecular profiling influences your first line treatment decision?
17. Although the rate of cancer growth varies among patients, generally how long would you be willing to wait for molecular testing results prior to instituting first-line therapy?
18. If you had the ability to order a blood test for molecular testing with turnaround time of 2 weeks how likely would you order this blood test?
19. If you were confident that the concordance between mutations detected in the tissue and the mutations detected in the blood was greater than 95% would you be willing to forgo an additional tissue biopsy and substitute blood based test (liquid biopsy)
20. What concordance rate would convince you to forgo subsequent biopsies and use a liquid biopsy?
    - A. 80%
    - B. 85%
    - C. 90%
    - D. 95%
    - E. Don't know/unsure
    - F. Would never use a liquid biopsy

international physician self-reported survey, Spicer and colleagues found that EGFR testing was requested before first-line therapy in patients with stage IIIB or IV disease in 81% of cases, and mutation results were available before start of therapy in 77% of the cases.[27] Those percentages are relatively low, given that current guidelines recommend that molecular testing should be done for all patients with stage IIIB or IV nsNSCLC. This highlights the need for objective performance feedback so oncologists can make the necessary practice changes so that molecular testing is done before the start of therapy to ensure high-quality cancer care that will translate into better, cost-effective outcomes and improved patient quality of life.

Our study findings showed that the prevalence of EGFR and ALK mutations is substantially lower among the patients we treat in our network compared with other published data on prevalence. The reason for those low rates is not clear, but it is likely multifactorial. First, Western Pennsylvania, the region our network serves, has a large proportion of older adults – 17.3% of the population is older than 65 years (national average, 14.5%) and advanced age might have contributed to the lower EGFR and ALK rates measured in our study.[28] Second, the smoking rate in Pennsylvania is higher than the national average, 20%-24% compared with 18%, respectively.[29] Third, the air quality in Western Pennsylvania has historically been very poor as a result of the large steel and coal mining industries. Even though the air quality has improved in recent decades, the American Lung Association's 2017 State of the Air report ranked Pittsburgh and surrounding areas in Western Pennsylvania among the top 25 most air polluted areas in the United States.[30] It is not certain whether air pollution and air quality have any impact on driver mutation rates, but the correlation with smoking, ethnicity, and geographic distribution highlight the need for further epidemiologic studies.

Biopsy sufficiency – getting an adequate amount of sample tissue during biopsy – is a known challenge to molecular profiling, and we found that biopsy sample size had an impact on the testing rates in a large percentage of our cases. To fully understand the impact of biopsy sufficiency, we conducted a subset analysis and compared the testing rates between our large and small biopsy samples. Our analysis showed that larger-sample biopsies were more likely to be tested for mutations than were smaller-sample biopsies (EGFR: $P = .023$; ALK: $P = .007$).

Those results suggest that larger-sample biopsies should be encouraged, but procedural risks, tumor location, and patient age and wishes need to be considered before tissue acquisition.[21] Furthermore, clinicians who are responsible for tissue procurement need to be properly educated on the tissue sample requirements and the impact these results have on treatment decisions.[31] Our institution, like many others, has adopted rapid onsite evaluation (ROSE) of biopsy samples, whereby a trained cytopathologist reviews sample adequacy at the time of tissue procurement. Although there is scant data directly comparing molecular testing success rates with and without the ROSE protocol, a meta-analysis conducted by Schmidt and colleagues concluded that ROSE improved the adequacy rate of fine-needle aspiration cytology by 12%.[32,33] Given that molecular profiling depends on both the absolute and relative amount of tumor cells present in the sample, the ROSE protocol likely enhances the procedural success rate and reduces the need for repeat and subsequent biopsies.

It is interesting to note that our data also demonstrated that we are obtaining large-sample biopsies in most of our patients (about 70%). However, we are still failing to test more than half of our cases for driver mutations (Figure, A and C). This strongly suggests there are additional factors beyond tissue adequacy that are contributing to our high failure rate. It is essential to understand the dynamics and system practices that influence testing rates if we are to improve the care and outcomes of our cancer patients. To better understand those barriers, we surveyed 110 practitioners (including medical oncologists, pulmonologists, thoracic surgeons, and interventional radiologists) about the molecular profiling process and their responses high-

**TABLE 2** Driver mutation present: patient demographics, smoking status, and mutation type

| Patient | Age, y/Race | Smoking status | Driver mutation |
|---|---|---|---|
| 1 | 75/WM[1] | Nonsmoker | Exon 19 deletion |
| 2 | 62/WF[2] | Nonsmoker | Exon 19 deletion |
| 3 | 58/WM[1] | Nonsmoker | Exon 20 insertion |
| 4 | 73/WF[2] | Nonsmoker | Exon 19 deletion |
| 5 | 86/WM[1] | 40-pack year | L858R |
| 6 | 87/AAM[3] | 30-pack year | L858R |
| 7 | 78/WM[1] | 20-pack year | L858R |
| 8 | 24/WF[2] | Nonsmoker | EML4-ALK rearrangement |

WM, Caucasian male; WF, Caucasian female; AAM, African American male

**TABLE 3** Biopsy type: number and percentage of cases (N = 206)

| Biopsy type | n (%) |
|---|---|
| Core biopsies | 94 (45.6) |
| Fine-needle aspirates | 52 (25.2) |
| Surgical resection | 34 (16.5) |
| Thoracentesis | 17 (8.3) |
| Bronchial brushing, washings | 9 (4.4) |

**TABLE 4** Survey response rate by medical specialty: number and percentage

| Specialty | Respondents | Response rate, % |
|---|---|---|
| Thoracic surgery | 2/3 | 33 |
| Oncology | 17/38 | 45 |
| Pathology | 9/23 | 39 |
| Pulmonology | 7/27 | 26 |
| Radiology | 7/16 | 44 |
| Other | 4 | - |
| Total | 46/110 | 42 |

**TABLE 5** Survey identified barriers to molecular evaluation

| Barrier | No. of respondents |
|---|---|
| Availability of sufficient tissue to complete molecular testing | 27 |
| 14-day rule | 22 |
| Risk of pneumothorax | 8 |
| Location of tumor (central vs peripheral) | 8 |
| Level of physician commitment | 8 |
| Comorbid conditions (eg, chronic anticoagulation therapy, etc) | 7 |
| Poor pulmonary function | 5 |
| Level of patient commitment | 4 |
| Poor performance status | 3 |
| Risk of bleeding | 2 |
| Current or prior smoking history | 1 |

lighted several important areas that deserve special attention (Tables 1, 4, 5).

In our institution, testing initiation is primarily the responsibility of the treating medical oncologist. This presents a challenge because there is often a significant delay between tissue acquisition, histologic confirmation, and oncologic review. Many institutions have adopted pathology-driven reflex testing to help overcome such delays. Automatic testing after pathologic confirmation streamlines the process, increases testing rates, and eliminates unnecessary delay between the time of diagnosis and the time of test ordering.[34] It also allows for the molecular and histologic diagnosis to be integrated into a single pathology report before therapy is initiated.

Another barrier to timely testing according to the respondents, was the CMS's 14-day rule. The 14-day rule requires hospitals to wait 14 days after the patient is discharged for the lab to receive reimbursement for molecular testing and was frequently identified as a cause for significant delay in testing and having an impact on first-line treatment decisions.[35,36]

Often clinicians will choose to defer testing until this time has elapsed to reduce the financial burden placed on the hospital but by that time, they might well have initiated treatment without knowing if the patient has a mutation. This is a significant challenge identified by many of our oncologists, and is a limitation to our analysis above as it is unclear what percentage of patients received follow up testing once care was established at an outside facility and once the 14-day time period had elapsed.

The data from our institution suggests there is discordance between physician attitudes and molecular testing practices. However, there are several limitations in our study. First, most of the survey respondents agreed that molecular testing is an important aspect of treating advanced lung cancer patients, but the retrospective nature of the study made it difficult to identify why testing was deferred or never conducted. Second, the absence of a centralized reporting system for molecular testing results at our institution, may have resulted in an overestimation of our testing failure rate in cases where results were not integrated our electronic medical record.

Third, the low survey response rate only allowed us to make generalizations regarding the conclusions, although it does provide a framework for future process improvements.

We believe the poor testing rates observed in our study are not isolated to our institution and reflect a significant challenge within the broader oncology community.[27] A system of best practices is essential for capturing this subset of patients who are never tested. There is agreement among oncologists that improving our current testing rates will require a multidisciplinary approach, a refined process for molecular evaluation, a push toward reflex testing, and standardization of biopsy techniques and tissue handling procedures. In our institution, we have initiated a Lean Six Sigma and PDSA (plan, do, study, act) initiative to improve our current molecular testing process. In addition, because obtaining larger-sample biopsies or additional biopsies is often not feasible for many of our advanced cancer patients, we have started using whole blood circulating tumor cells (CTC) and plasma ctDNA (cell-free circulating DNA) for molecular testing. Recent studies have shown high concordance (89%) between tissue biopsies and blood-based mutation testing, which will likely have a positive impact on the cancer care of our patients and help to capture a subset of patients who are not candidates for traditional biopsies.[37]

## Conclusions

Despite current guidelines for testing driver mutations in advanced nsNSCLC, a large segment of our patients are not being tested for those genetic aberrations. There are several barriers that continue to thwart the recommendation, including failure to integrate driver mutation testing into routine pathology practice (ie, reflex testing), insufficient tissue obtained from biopsy, and difficulty in obtaining tissue because of tumor location or risk of complications from the biopsy procedure. More important, these trends are not isolated to our institution and reflect a significant challenge within the oncology community. Our data show that for the purpose of driver mutation testing, larger-sample biopsies, such as surgical/core biopsies, are better than small-sample biopsies, such as needle aspiration. We have also demonstrated that the prevalence of driver mutations is lower in Western Pennsylvania, which is served by our network, than elsewhere in the United States.

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# Comprehensive assessment of cancer survivors' concerns to inform program development

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**Background** Health care professionals are caring for a growing number of diverse cancer survivors, often in an environment in which resources are limited. The identification of the most salient concerns of survivors is essential for targeted program planning and for providing quality care.
**Objective** To prioritize survivors' physical, social, emotional, and spiritual concerns, and to assess the perceived importance of those needs and the extent to which staff were attentive to them. To demonstrate the usefulness of a broad survey approach.
**Methods** Surveys that used a quality-of-life framework to assess concerns were mailed to a convenience sample of 2,750 cancer survivors. Logistic regression models were used to identify associations with the 12 most highly rated moderate or high concerns.
**Results** A total of 1,005 surveys were returned for a 37% response rate. Fears of the cancer recurring (n = 486, 51%) and developing a new cancer (n = 459; 47.5%) were the 2 most prevalent concerns among respondents. Young age, unemployment, race other than white, and female sex were associated with greater moderate- or high-level concerns throughout the cancer trajectory. Spiritual and social concerns were least often attended to by staff.
**Limitations** Use of a nonvalidated survey and cross-sectional approach limited our ability to explore how concerns may change over the cancer trajectory.
**Conclusion** A comprehensive needs assessment is a valuable tool to inform survivorship and supportive care program development by highlighting common concerns, demographic and medical factors associated with specific concerns, and timing of moderate- or high-level concerns along the cancer trajectory.
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Complex cancer treatments, limited personnel resources, and a growing number of cancer survivors are challenging cancer health care professionals' abilities to provide comprehensive care. Cancer survivors have a range of needs that extend over the cancer care trajectory and that represent physical, psychological, social, and spiritual domains. Numerous studies have explored supportive care needs and recent systematic reviews have highlighted the supportive care needs related to cancer[1] and to specific cancer types, including prostate cancer,[2] breast cancer,[3] gynecologic cancer,[4] hematological cancer,[5] and lung cancer.[6] However, reviews are limited in that they do not always assess needs across the cancer trajectory or identify demographic or clinical variables that are associated with needs. These data are needed to focus survivorship program development in cancer centers in order to target populations most likely at risk for unmet needs, identify what salient concerns to address, and to appropriately schedule supportive care programs.

The importance of assessing the patient's subjective view of his/her needs or concerns is well acknowledged as being fundamental to patient-centered care.[7] Clinicians routinely assess needs in practice using a variety of screening tools. However, there needs to be a broader assessment of concerns and needs in a population of survivors with mixed cancer diagnoses, along with their appraisal of how well their needs were addressed by their health care team, to provide an overall identification of gaps in supportive care. The primary purpose of the present study was to prioritize survivors' most salient physical, social, emotional, and spiritual concerns or needs; ascertain survivors' perceived importance of those needs and the extent to which our institution, the University Hospitals Seidman Cancer Center, was attentive to those needs; and to identify who

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might be at risk for having greater concerns. The overall goal was to use the data to inform survivorship and supportive care program development.

## Methods

### Design, sample and setting

We used a cross-sectional design. Surveys were mailed once to a convenience sample of 2,750 adult patients who had been seen in follow-up during the previous 2 years (2010-2011) at all clinical sites of University Hospitals Seidman Cancer Center, a Midwestern National Cancer Institute-designated Comprehensive Cancer Center. Patients who had a noncancer diagnosis were excluded. The distribution list was screened for deceased individuals and those patients who had multiple visits during the time period. The project was reviewed and approved as nonresearch by the Case Western Reserve University Cancer Institutional Review Board.

### Survey

An interdisciplinary team of clinicians, administrators, and researchers adapted the Mayo Clinic Cancer Center's Cancer Survivors Survey of Needs[8] to create a comprehensive survey for the cancer center. Input regarding the scope of the survey was sought from the Patient and Family Advisory Council of the cancer center. The survey, which was formatted for scanning purposes, consisted of 33 questions that were compiled into 4 sections. Sections 1 and 2 focused on demographic and treatment-related information, including use of community and hospital support services and preferences for follow-up care. In section 3, a quality-of-life framework was used to assess physical, social, emotional, and spiritual needs. Respondents were asked to rate their current level of concern for 19 physical effects, 10 social effects, 10 emotional effects, and 5 spiritual effects on a scale ranging from 0 (no concern) to 5 (extreme concern). In section 4, respondents were asked to indicate the importance of the cancer team addressing their physical, social, emotional, and spiritual needs. This was followed by their rating of the cancer team's attention to their needs as Poor, Fair, Good, Excellent, or They did not ask about my needs. Respondents were asked about preferences for learning about physical, social, emotional, and spiritual effects. In addition to the 33 questions, there were 6 open-ended questions in which respondents were encouraged to share additional information about their needs, sources of support, and other concerns.

### Procedures

Eligible respondents were mailed a cover letter explaining the survey from both the director and president of the cancer center, a survey, and a postage-paid return envelope. The option to respond to the survey by a telephone call to the director of the Office of Cancer Survivorship was offered in the cover letter.

### Data analysis

Returned surveys were scanned into a Teleform database, verified, and exported into an SPSS data file. Data quality was checked by running frequency analyses and summarizing variables. Time-since-treatment responses were collapsed into 4 categories: on treatment, up to 2 years posttreatment, 2-5 years posttreatment, and more than 5 years posttreatment. Descriptive statistics were used to summarize demographic and medical characteristics of the respondents and to calculate the mean score for each concern for the total sample and then for each category of time since treatment. Because of the large number of respondents with breast cancer, the respondents were stratified into two groups, one of breast cancer the other of nonbreast cancer respondents. Then, the Mann-Whitney test was performed for each concern to examine differences between respondents with and without breast cancer.

To identify the most prevalent concerns, ratings for concerns were recoded into no concern (rated as 0), low concern (1 or 2), and moderate/high concern (3, 4, or 5). Since our interest was in the moderate and high concerns, the responses were dichotomized into moderate/high concerns and all other levels. Logistic regression models were then used to identify associations between a set of survivor characteristics or covariates (age, sex, living status, marital status, employment status, cancer type, and time since treatment) with the 12 most highly rated moderate/high concerns. All the analyses were performed using statistical software SPSS 20 and Stata 13.0

## Results

### Respondents

A total of 1,005 surveys were returned for a 37% response rate. Forty-two patients responded by telephone. The mean age of respondents was 64.9 years (range, 22-98; SD, 12.8). The typical respondent was female, white, and married (Table 1). Twenty-four percent of the respondents (n = 240) reported living alone. Although about 47% of respondents (n = 473) reported a breast cancer diagnosis, more than 17 cancers were identified, and 14% of respondents (n = 145) listed multiple diagnoses. About a third of respondents were receiving treatment when they completed the survey.

Just under half of the respondents (n = 498) reported using community resources for support and information about cancer, and 29.5% (n = 296) sought information on the internet during their cancer experience. The most commonly used community resources were The Gathering Place, a local organization offering free supportive programs and services to individuals with cancer and their families (n = 167), and the American Cancer Society (n = 138). Of the 496 respondents who reported accessing hospital resources, most (n = 322) said they used information that their health care team recommended. Other sup-

**TABLE 1** Participant characteristics (N = 1,005)

| Characteristic | n (%) |
|---|---|
| Sex (n = 1,001)[a] | |
| Female | 719 (71.8) |
| Male | 282 (28.2) |
| Race (n = 1,007)[b] | |
| White | 835 (82.9) |
| Black | 145 (14.4) |
| Asian | 7 (.7) |
| American Indian/Alaskan Native | 3 (.3) |
| Other | 17 (1.7) |
| Marital status (n =997)[c] | |
| Married | 634 (63.6) |
| Single | 105 (10.5) |
| Divorced | 108 (10.8) |
| Widowed | 138 (13.8) |
| Lives with significant other | 12 (1.2) |
| Employment status (n = 980)[d] | |
| Employed | 347 (35.4) |
| Unemployed | 98 (10.0) |
| Retired | 535 (54.6) |
| Type of cancer | |
| Breast | 473 (47.1) |
| Non-breast solid tumor | 242 (24.1) |
| Hematological | 145 (14.4) |
| Multiple types listed | 145 (14.4) |
| Treatment status | |
| On treatment | 312 (31.0) |
| <2 years posttreatment | 151 (15.0) |
| 2-5 years posttreatment | 267 (26.6) |
| >5 years posttreatment | 275 (27.4) |
| Type of treatment[e] | |
| Surgery | 647 (64.4) |
| Chemotherapy | 630 (62.7) |
| Radiation therapy | 575 (57.2) |
| Hormone therapy | 176 (17.5) |
| Bone marrow transplant | 42 (4.2) |
| Other | 80 (8.0) |

[a]4 respondents did not answer question. [b]2 respondents identified with more than 1 group. [c]8 respondents did not answer question. [d]25 respondents did not answer question. [e]Total is greater than N = 1,005 because some patients had combinations of listed therapies.

portive options were used to a lesser degree: support groups (n = 92), chemotherapy and radiation therapy classes (n = 129), and supportive/educational programs offered by the cancer center (n = 27). Most of the respondents (n = 822, 88.6%) preferred to have their follow-up care remain with their cancer care team 1 year after treatments are completed. Almost two-thirds of respondents (n = 601, 64%) cited being seen at the cancer center for follow-up care as the most important factor in considering follow-up care.

Concerns In determining whether the large proportion of respondents with breast cancer skewed the study results, it was determined that median scores differed significantly in only four concerns. Compared with respondents without breast cancer, respondents with breast cancer were more likely to have significantly lower scores for concerns related to fatigue ($P$ <.001) and sexual issues/intimacy ($P$ = .001). Respondents with breast cancer were more likely to have significantly higher scores than respondents without breast cancer for concerns related to genetic counseling ($P$ = .001) and fear of developing a new cancer ($P$ = .010).

Fears of the cancer returning and developing a new cancer were the two most prevalent concerns, identified by 51% (n = 486) and 47.5% (n = 459), respectively (Table 2). Physical concerns, rated as moderate/high concerns by at least 25% of the sample, were fatigue (n = 336, 34.8%), changes in [the] body after cancer (n = 323, 33.7%), trouble sleeping (n = 302, 31.0%), sexual issues/intimacy (n = 263, 28.0%), memory and concentration (n = 261, 26.7%), and weight changes (n = 248, 25.5%). The most prevalent moderate/high social concerns were related to finances (n = 265, 27.5%) and debt from medical bills (n = 232, 25.1%). Managing stress (n = 279, 29.2%) and difficult emotions (n = 244, 25.1%) were prevalent moderate/high emotional concerns. Spiritual concerns were less often rated as moderate/high concerns. Having a breast cancer diagnosis was not significantly related to the number of reported moderate to high concerns ($P$ = 1.00).

Variables associated with the 12 most frequent moderate/high concerns are shown in Tables 3 and 4. Age was associated with the most moderate/high concerns. With every decade of age, the odds of having the following moderate/high concerns decreased: bodily changes after cancer (odds ratio [OR], 0.75), sexual intimacy (OR, 0.81), memory and concentration (OR, 0.83), weight changes (OR, 0.77), financial (OR, 0.75), debt (OR, 0.71), cancer returning (OR, 0.66), developing a new cancer (OR, 0.67), managing stress (OR, 0.67), and managing difficult emotions (OR, 0.67).

Female sex was associated with lower odds of having a concern about sexual intimacy (OR, 0.30) and increased odds of having concerns related to memory and concentration (OR, 1.78), managing stress (OR, 2.35), and managing difficult emotions (OR, 1.77). Race was another demographic characteristic statistically associated with numerous moderate/high concerns. Survivors who identified white, were more likely than other people of other races to have fewer moderate/high concerns regarding bodily changes after cancer (OR, 0.46), weight change (OR, 0.46), finances (OR, 0.46),

**TABLE 2** Prevalence of all concerns

| Concern | N | Level of concern, n (%) | | |
|---|---|---|---|---|
| | | None | Low | Moderate/High |
| *Physical effects* | | | | |
| Fatigue | 967 | 312 (32.3) | 319 (33.0) | 336 (34.8) |
| Changes in my body after cancer | 960 | 323 (33.7) | 326 (34.0) | 323 (33.7) |
| Trouble sleeping | 974 | 400 (41.1) | 272 (27.9) | 302 (31.0) |
| Sexual issues/intimacy | 940 | 512 (54.8) | 162 (17.2) | 263 (28.0) |
| Memory and concentration | 976 | 391 (40.1) | 324 (33.2) | 261 (26.7) |
| Weight changes | 972 | 473 (48.7) | 251 (25.8) | 248 (25.5) |
| Balance/walking/mobility | 973 | 495 (50.9) | 241 (24.8) | 237 (24.4) |
| Tingling/numbness in hands/feet | 981 | 507 (51.7) | 243 (24.8) | 231 (23.6) |
| Bowel or bladder changes | 964 | 528 (54.8) | 246 (25.5) | 190 (19.7) |
| Pain | 965 | 540 (56.0) | 237 (24.6) | 188 (19.5) |
| Bone thinning/pain | 966 | 563 (58.3) | 215 (22.3) | 188 (19.5) |
| Hot flashes | 968 | 595 (61.5) | 193 (20.0) | 180 (18.6) |
| Hair and skin care issues | 976 | 580 (59.4) | 218 (22.3) | 178 (18.2) |
| Swelling in arms or legs | 977 | 697 (71.3) | 135 (13.8) | 145 (14.8) |
| Dental or mouth problems | 974 | 667 (68.5) | 172 (17.7) | 135 (13.9) |
| Ability to take care of myself | 978 | 740 (75.7) | 141 (14.4) | 97 (9.9) |
| Poor appetite | 972 | 769 (79.1) | 121 (12.5) | 82 (8.4) |
| Trouble swallowing | 970 | 779 (80.3) | 117 (12.1) | 74 (7.63) |
| Nausea/vomiting | 971 | 802 (82.6) | 112 (11.5) | 57 (5.9) |
| *Social effects* | | | | |
| Financial concerns | 965 | 524 (54.3) | 176 (18.2) | 265 (27.5) |
| Debt from medical bills | 923 | 514 (55.7) | 177 (19.2) | 232 (25.1) |
| Health insurance | 961 | 586 (61.0) | 151 (15.7) | 224 (23.3) |
| Genetic counseling | 951 | 547 (57.5) | 191 (20.1) | 213 (22.4) |
| Managing household activities | 953 | 633 (66.4) | 180 (18.9) | 140 (14.7) |
| Caring for family members | 933 | 694 (74.4) | 132 (14.2) | 107 (11.5) |
| Talking about cancer | 970 | 668 (68.9) | 192 (19.8) | 110 (11.3) |
| Legal concerns | 956 | 758 (79.3) | 104 (10.9) | 94 (9.8) |
| Returning to work | 908 | 766 (84.4) | 73 (8.04) | 69 (7.6) |
| Fertility issues | 896 | 817 (91.2) | 43 (4.8) | 36 (4.0) |
| *Emotional effects* | | | | |
| Fear the cancer will return | 953 | 169 (17.7) | 298 (31.3) | 486 (51.0) |
| Fear of developing new cancer | 967 | 200 (20.7) | 308 (31.9) | 459 (47.5) |
| Managing stress | 956 | 345 (36.1) | 332 (34.7) | 279 (29.2) |
| Managing difficult emotions (anger, fear, sadness, depression, guilt, anxiety, uncertainty) | 973 | 412 (42.3) | 317 (32.6) | 244 (25.1) |
| Defining a new sense of normal | 927 | 383 (41.3) | 321 (34.6) | 223 (24.1) |
| Looking for the higher side (hope, gratitude, forgiveness, love, happiness, contentment) | 951 | 498 (52.4) | 243 (25.6) | 210 (22.1) |
| Coping with grief and loss | 962 | 531 (55.2) | 252 (26.2) | 179 (18.6) |
| Changing relationships with spouse, family, friends, coworkers | 962 | 652 (67.8) | 187 (19.4) | 123 (12.8) |
| Finding support resources | 952 | 672 (70.6) | 173 (18.2) | 107 (11.2) |
| Connecting to counseling services | 940 | 699 (74.4) | 154 (16.4) | 87 (9.3) |
| *Spiritual effects* | | | | |
| End-of-life concerns | 963 | 577 (59.9) | 197 (20.5) | 189 (19.6) |
| Isolation/feeling alone | 962 | 643 (66.8) | 189 (19.7) | 130 (13.5) |
| Religious or spiritual support | 967 | 718 (74.3) | 135 (14.0) | 114 (11.8) |
| Religious distress | 959 | 810 (84.5) | 104 (10.8) | 45 (4.7) |
| Loss of faith | 966 | 796 (82.4) | 130 (13.5) | 40 (4.1) |

**TABLE 3** Logistic regression models for most frequent moderate/high physical concerns[a]

| Independent variable | Concern, OR [95% CI] | | | | | |
|---|---|---|---|---|---|---|
| | Fatigue | Body change | Sleep | Sexual intimacy | Memory | Weight change |
| Age | 0.86 | 0.75 [0.63, 0.89][d] | 0.88 | 0.81 [0.68, 0.97][b] | 0.83 [0.70, 1.00][b] | 0.77 [0.64, 0.92][c] |
| Sex | 1.16 | 0.79 | 1.17 | 0.30 [0.18, 0.51][d] | 1.78 [1.06, 3.00][b] | 1.05 |
| Living alone | 1.31 | 1.16 | 1.27 | 1.13 | 0.9 | 1.24 |
| Race (Reference group: non-white) | | | | | | |
| White | 0.46 | 0.46 [0.31, 0.69][d] | 0.50 | 0.69 | 0.76 | 0.46 [0.30, 0.70][d] |
| Marital status (Reference group: single status) | | | | | | |
| Married | 0.67 | 1.55 | 1.12 | 1.35 | 0.82 | 0.92 |
| Divorced | 0.72 | 1.23 | 0.86 | 0.99 | 0.65 | 0.77 |
| Widowed | 0.82 | 0.91 | 1.04 | 0.57 | 1.10 | 1.21 |
| Partnered | 1.04 | 1.21 | 1.08 | 2.20 | 0.24 | 0.88 |
| Employment (Reference group: employed full-time) | | | | | | |
| Part-time | 1.09 | 0.70 | 1.1 | 1.06 | 0.60 | 0.69 |
| Unemployed | 2.08 [1.18, 3.65][b] | 1.72 [1.00, 2.96][b] | 1.45 | 2.18 | 2.45 [1.39, 4.32][c] | 2.17 [1.22, 3.87][c] |
| Retired | 1.52 | 1.06 | 1.09 | 1.13 | 1.53 | 1.60 |
| Treatment status (Reference group: on-treatment) | | | | | | |
| <2 years posttreatment | 0.56 [0.35, 0.92][b] | 0.73 | 0.67 | 0.54 [0.32, 0.93][b] | 0.64 | 0.55 [0.31, 0.96][b] |
| 2-5 years posttreatment | 0.72 | 1.00 | 0.75 | 0.78 | 0.85 | 1.23 |
| >5 years posttreatment | 0.45 [0.29, 0.69][d] | 0.82 | 0.69 | 0.72 | 0.77 | 0.87 |

OR, odds ratio; CI, confidence interval

[a]Only CI of significant odds ratios are displayed. Cancer type was not significantly associated with any physical concern. [b]$P \leq .05$. [c]$P \leq .01$. [d]$P \leq .001$.

debt (OR, 0.40), managing stress (OR, 0.55), and managing difficult emotions (OR, 0.49). The odds of having a moderate/high concern regarding debt was 2.25 times higher given widowed marital status compared with those survivors who were single. Unemployment status, when compared with full-time employment, was significantly associated with increased odds of having moderate/high concerns related to fatigue (OR, 2.08), bodily changes after cancer (OR, 1.72), memory and concentration (OR, 2.45), weight changes (OR, 2.17), finances (OR, 1.93), developing a new cancer (OR, 1.91), and managing difficult emotions (OR, 1.80).

As expected, respondents who had completed treatment were less likely to have many of the moderate/high concerns as those still undergoing treatment. Survivors who were up to 2 years posttreatment were significantly more likely than those survivors receiving treatment to have fewer moderate/high concerns regarding fatigue (OR, 0.56), sexual intimacy (OR, 0.54), weight change (OR, 0.55), fears of the cancer returning (OR, 0.48), developing a new cancer (OR, 0.35), managing stress (OR, 0.43), and managing difficult emotions (OR, 0.49).

However, those improved odds were not sustained over the cancer trajectory. Compared with survivors who were receiving treatment, survivors who were between 2-5 years posttreatment did not have significantly reduced odds for moderate/high concerns related to fatigue, sleep, sexual intimacy, body changes, weight changes, memory, fears of the cancer returning, developing a new cancer, managing stress, and managing difficult emotions. They did have significantly reduced odds for having concerns only related to

**TABLE 4** Logistic regression models for most frequent moderate/high social and emotional concerns

| Independent variable | Concern, OR [95% CI] | | | | | |
|---|---|---|---|---|---|---|
| | Financial | Debt | Cancer return | New cancer | Stress | Emotions |
| Age | 0.75 [0.63, 0.90][c] | 0.71 [0.58, 0.85][d] | 0.66 [0.56, 0.78][d] | 0.67 [0.57, 0.80][d] | 0.67 [0.56, 0.81][d] | 0.67 [0.56, 0.81][d] |
| Sex | 1.28 | 1.28 | 0.93 | 1.38 | 2.35 [0.19, 3.97][c] | 1.77 [1.04, 3.00][b] |
| Living alone | 1.07 | 0.47 [0.24, 0.89][b] | 0.93 | 1.15 | 1.07 | 0.96 |
| Race (Reference group: non-white) | | | | | | |
| White | 0.46 [0.30, 0.70][d] | 0.40 [0.26, 0.63][d] | 0.69 | 0.90 | 0.55 [0.36, 0.84][c] | 0.49 [0.32, 0.76][c] |
| Marital status (Reference group: single status) | | | | | | |
| Married | 0.74 | 0.62 | 1.01 | 0.86 | 0.73 | 0.69 |
| Divorced | 1.03 | 0.88 | 0.83 | 0.77 | 1.07 | 1.09 |
| Widowed | 1.14 | 2.25 [1.02, 4.94][b] | 1.03 | 0.54 | 0.82 | 0.91 |
| Partnered | 0.57 | 0.25 | 0.52 | 0.61 | 0.12 | 0.59 |
| Employment (Reference group: employed full-time) | | | | | | |
| Part-time | 1.43 | 1.28 | 1.03 | 0.83 | 0.73 | 0.68 |
| Unemployed | 1.93 [1.08, 3.43][b] | 1.23 | 1.67 | 1.91 [1.07, 3.41][b] | 1.65 | 1.80 [1.01, 3.21][b] |
| Retired | 1.26 | 1.30 | 1.27 | 1.27 | 1.36 | 1.50 |
| Treatment status (Reference group: on-treatment) | | | | | | |
| <2 y posttreatment | 0.71 | 0.77 | 0.48 [0.30, 0.78][c] | 0.35 [0.22, 0.58][d] | 0.43 [0.25, 0.75][c] | 0.49 [0.29, 0.85][b] |
| 2-5 y posttreatment | 0.61 [0.39, 0.95][b] | 0.52 [0.33, 0.84][c] | 0.98 | 0.84 | 0.81 | 0.69 |
| >5 y posttreatment | 0.52 [0.33, 0.82][c] | 0.47 [0.29, 0.75][c] | 0.74 | 0.69 | 0.65 | 0.54 [0.34, 0.85][c] |

OR, odds ratio; CI, confidence interval

[a]Only CI of significant odds ratios are displayed. Cancer type was not significantly associated with any social or emotional concern. [b]$P \leq .05$. [c]$P \leq .01$. [d]$P \leq .001$.

finances (OR, 0.61) and debt (OR, 0.52).

Long-term survivors, who were beyond 5 years post-treatment, had significantly reduced odds for having moderate/high concerns related to fatigue (OR, 0.45), finances (OR, 0.52), debt (OR, 0.47), and managing difficult emotions (OR, 0.54), compared with survivors receiving treatment. Moderate/high concerns related to sleep, sexual intimacy, body changes, weight changes, memory, fears of the cancer returning, developing a new cancer, managing stress did not have improved odds for these long-term survivors.

### Attention to needs

The health care teams were rated highly for their attention to the patients' physical needs. Most respondents (n = 845, 92.4%) viewed the health care team's attention their physical needs as important and 763 (77.6%) survivors rated the team's attention to these needs as excellent. The importance of addressing emotional needs was affirmed by 723 (78.5%) respondents, and although 454 (46.8%) viewed the team's attention to these needs as excellent, 119 (12.3%) reported that the health care team did not ask about emotional needs. In addition, 566 respondents (60%) viewed having the health care team address their social needs as important, and most (n = 715, 74.2%) rated the team's attention to social needs as good or excellent. Yet, 162 (16.8%) respondents reported that team did not ask about their social needs. The health care team's addressing of spiritual needs was viewed as important by 346 (37.5%) respondents and ratings for how well the team attended to spiritual needs were: 148 (15.6%) poor or fair, 204 (21.5%)

good, and 150 (15.8%) excellent. However, 448 (47.2%) respondents reported that the health care team did not ask about their spiritual needs.

## Discussion

The primary purpose of this project was to prioritize survivors' most salient physical, social, emotional, and spiritual concerns or needs and to assess the perceived importance of these needs and the extent to which the cancer center staff were attentive to those needs. The overall goal of this assessment was to inform the development of survivorship and supportive care programs by highlighting common concerns, demographic and medical factors associated with specific concerns, and timing of moderate/high level concerns along the cancer trajectory. There were 3 main findings.

First, the results support the need for enhancing supportive care services to meet emotional concerns of survivors beyond the treatment phase. Similar to other studies,[8,9] emotional concerns ranked higher than all other concerns in this study with about 50% of the sample rating "fear the cancer will return" and "fear of developing a new cancer" as moderate/high concern. Although the odds of not having these emotional concerns improved up to 2 years posttreatment, these concerns are likely to resurface, as odds for survivors beyond 2 years were not significantly different from those receiving treatment. A recent systematic review reported that fear of cancer recurrence is experienced by about 73% of cancer survivors, with 49% reporting a moderate to high degree.[10] It can have a chronic, stable trajectory for some survivors and is strongly associated with higher levels of anxiety, distress, and depression, and less global, emotional/mental, physical, role, social, and cognitive quality of life.[10] In this sample, managing stress and difficult emotions were also rated as moderate/high concerns by at least 25% of the sample.

Second, the findings identified patients at risk for cancer-related concerns throughout the cancer trajectory. As demonstrated in other studies, younger age was associated with greater odds of having multiple greater moderate/high concerns.[11-13] Unemployment was the second most common demographic factor associated with multiple moderate/high concerns related to physical symptoms, finances and emotions. Similarly, identifying as black, Asian, American Indian/Alaskan Native, or other was also associated with greater odds of having numerous physical, financial, and emotional concerns. Women had greater concerns related to memory, sexual intimacy, coping with difficult emotions, and stress.

Third, the results helped to identify gaps in supportive care at our cancer center. Although spiritual concerns were not prevalent as being moderate/high, they were still viewed by about a third of survivors as being an important area for the health care team to address. Yet, consistent with other need assessments, spiritual concerns in this study were least often addressed by staff.[1] Assessment of spiritual care needs, screening for spiritual distress, and providing spiritual care are essential components of a clinician-patient relationship that supports healing.[14] The importance of attending to spiritual care needs was underscored by a recent systematic review that found a positive association between overall spiritual well-being and quality of life in patients with cancer, with the meaning/peace factor consistently and positively associated with physical and mental health.[15] Another identified gap was the health care team's lack of attention to the patient's social needs, which included concerns related to finances and debt from medical bills. In all, 46% of the respondents reported having financial concerns, with the odds of having moderate/high financial concerns being greatest during treatment to 2 years posttreatment. Attention to the financial burden of cancer patients is critical because the magnitude of cancer-related financial concerns is a significant, strong predictor of quality of life and adverse psychological issues such as depression, anxiety, and distress.[16,17]

There were several program implications based on the results. A periodic audit of the concerns of survivors and their views on how well their needs were being met was a relatively low cost endeavor. Although the findings were consistent with the literature, the results, when shared with administrators and clinicians, were instrumental in effecting change because they represented the concerns of survivors at the cancer center. Another program directive, based on the results, was to extend the routine screening of patients' needs during treatment to posttreatment survivorship. Patients who are young, unemployed, do not identify as white, and female warrant more thorough assessment of needs and concerns along the cancer trajectory. Integral to these screenings is the need for patient-centered communication, with discussion of how cancer is affecting the different domains of quality of life within the context of the patient's life. Lastly, the results clearly indicated the need for additional training of health care providers on how to assess and address spiritual well-being in cancer survivors.

There were limitations to this study, including use of a nonvalidated survey and cross-sectional approach that limited our ability to explore how concerns might change over the trajectory. Also, it was not possible to clarify medical information of the respondents, such as cancer stage. Although the response rate of this study was not high, we are confident in the results because of the large sample size and the finding that the large proportion of respondents with breast cancer was not influential. Despite these limitations, this needs assessment of cancer survivors over the trajectory of care provided insight into the scope of their concerns, identified vulnerable groups of survivors, and highlighted gaps in addressing those concerns. A quality-of-life framework for assessing needs assured a comprehensive focus and generated practice changes to strengthen holistic, comprehensive oncology care.

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# Perceived financial hardship among patients with advanced cancer

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**Background** Patients with advanced cancer experience distress in many forms. Perceived financial hardship is increasingly recognized as a toxicity of cancer, and much has been written about it in general – what it is, what causes and aggravates it, the implications on patient outcomes and cost and quality of care/life, and possible interventions to ease the impact on patients. However, it has not been extensively considered in patients with advanced cancer.

**Objective** To describe the financial challenges of persons with advanced cancer, and the association of financial distress with quality of life, symptom severity, and overall cancer-related distress.

**Methods** This is a cross-sectional, comparative, descriptive study of 100 patients with advanced cancer in outpatient medical oncology clinics in Western Pennsylvania. Five instruments measured patient demographics, symptom severity, quality of life, perceived financial hardship, and overall cancer-related distress. Descriptive statistics and correlation coefficients were used. Quality of life, symptom severity and cancer-related distress were compared with high or low levels of perceived financial hardship using a 2-sample t test.

**Results** The mean age of participants was 63.43 years (n = 100). Perceived financial hardship was mildly correlated with overall cancer-related distress (r, 0.409; $P < .001$), symptom distress (r, 0.409; $P < .001$), and overall quality of life scores (r, 0.323; $P < .001$). In addition, patients experiencing higher levels of perceived financial hardship experienced worse quality of life overall ($P = .002$), higher levels of cancer-related distress ($P < .001$), and worse symptom distress ($P < .001$).

**Limitations** Cross-sectional design

**Conclusions** These results illuminate our understanding of disparities that may be present in end of life care. Perceived financial hardship appears to negatively influence symptom severity and quality of life. These results illuminate targeted areas for cancer-related distress mitigation.

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The American Cancer Society has identified a disparity in cancer death rates, noting that persons with lower socioeconomic status have higher rates of mortality.[1] This is attributed to many factors, but it is largely owing to the higher burden of disease among lower-income individuals.[1] A component of this disease burden is measured by assessing the patient-reported outcome of cancer-related distress. The National Comprehensive Cancer Network (NCCN) Distress Management Guidelines have defined distress as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope with cancer, its physical symptoms and its treatment."[2]

Financial hardship related to cancer diagnosis and treatment is increasingly being recognized as an important component of disease burden and distress. The advancements in costly cancer treatments have produced burdensome direct medical costs as well as numerous indirect costs that contribute to perceived financial hardship.[3,4] These indirect costs include nonmedical expenses such as increased transportation needs or childcare, loss of earnings, or loss of household income due to caregiving needs.[3] Moreover, indirect costs are often managed by patients and families through their use of savings, borrowing, reducing leisure activities, and selling possessions.[3] Even though efforts to increase health coverage, such as the Affordable Care Act, have reduced the rates of individuals who are uninsured, persons with cancer who have insurance also face challenges because they cannot afford copays, monthly premiums, deductibles, and other high out-of-pocket expenses related to cancer treatment that are not covered by their insurance such as out-of-network services or providers.[5-7]

Thus, financial hardship may have an impact

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on several areas of a patient's life and well-being, but the effects are commonly undetected.[8-10] Research has established that financial strain can influence treatment choices and adherence to therapy.[11] Furthermore, the effects of financial strain have been identified across the cancer care continuum, from diagnosis through survivorship, suggesting a bidirectional relationship between financial strain and well-being.[11] Financial strain may reduce patient quality of life and worsen symptom burden because of the patient's inability to access needed care, poor social supports, and/or increased stress.[11-12] These worsening outcomes may also increase the use of financial reserves and affect their ability to work.[7,11] Financial difficulties may also be associated with anxiety and depression, leading to worse quality of life and greater distress and symptom burden.[12] Identifying groups at high risk for financial strain is crucial to ensure that resources are available to assist these populations.[13] This burden can be even more pronounced in minority and underserved patients with cancer.[7] Patients with advanced cancer are especially vulnerable to the burden of increased costs because of the use of expensive targeted therapies; their improved survival, which extends the time of expenditure; and increased use of financial reserves.[9] Financial hardship in patients with advanced cancer is not well understood or characterized,[9] which is why this study aimed to better quantify distress in advanced stage cancers by describing :

- A cohort of patients with advanced cancer and their levels of quality of life, symptom distress, cancer-related distress and perceived financial hardship;
- The relationship between perceived financial hardship, quality of life, symptom distress and overall cancer-related distress; and
- Quality of life, symptom distress, and overall cancer-related distress according to level of perceived financial hardship.

## Methods

This study is a cross-sectional, descriptive, comparative study of distress, including perceived financial hardship, among patients with advanced cancer who were receiving palliative care treatment in two outpatient medical oncology clinics in Western Pennsylvania. The data were collected during May 2013-November 2014. The study protocol was approved by the Institutional Review Board at the University of Pittsburgh. Eligible participants had to be 18 years or older and have an advanced solid tumor of any kind, with a prognosis of 1 year or less confirmed by a physician or clinic nurse practitioner/physician assistant, and be able to read and understand English at the fourth-grade level. The sample was recruited from two clinics at the University of Pittsburgh Cancer Institute, a National Cancer Institute-designated Comprehensive Cancer Program.

### Measurements

**Sociodemographic factors.** These were measured using an investigator-derived Sociodemographic Questionnaire, a 12-item form that includes variables such as age, race, marital status, cancer type, religion and spirituality, employment status, years of education, health insurance status, and income level.

**Cancer-related distress.** The NCCN Distress Thermometer is a self-report visual analog scale (0, no distress; 10, great distress) formed in the shape of a thermometer combined with a problem list that is often used in outpatient cancer settings for reporting of cancer-related distress.[14-16] The sensitivity, specificity and convergent validity with the Brief Symptom Inventory and the Hospital Anxiety and Depression Scale have been established and appropriate cut-off score of the distress thermometer identified.[14-16] A score of 4 or above indicates a clinically significant level of distress.[14-16]

**Symptom distress.** The McCorkle Symptom Distress Scale was developed in 1977 based on interviews that focused on the symptom experiences of patients. Psychometric testing among patients with cancer using the modified Symptom Distress Scale revealed high reliability (Cronbach alpha, 0.97).[17] The instrument is a 13-item Likert scale (1-5) assessing the severity of distress experienced by a symptom. Total scores range from 13 to 65, where a higher score indicates greater distress. Moderate distress is indicated with a score of 25-33, and a score above 33 indicates severe distress, identifying the need for immediate intervention.[17]

**Quality of life and spiritual well-being.** The Functional Assessment of Cancer Therapy (FACT-G) is used to assess general cancer-related quality of life. It has four subscales: physical, emotional, social and family, and functional well-being, with a total score that ranges from 0-112, where higher scores show higher quality of life. The Spiritual Distress Well-Being questionnaire was used alongside the valid FACT-G assessment.[18,19] The Spiritual Well-Being Short Form was developed with an ethnically diverse population and adds 12 items to the FACT-G. The items do not necessarily assume a faith in God, allowing a wide flexibility in application and tapping into issues such as faith, meaning, and finding peace and comfort despite advanced illness. Higher scores on the Spiritual Well-Being subscore (range, 0-48) are correlated with higher scores of quality of life. The possible scores for the combined FACT-G and Spiritual Well-Being assessment range from 0-160, with higher scores showing higher quality of life.

**Economic hardship.** Perceived financial hardship was measured using Barrera and colleagues' Psychological Sense of Economic Hardship Scale.[20] The scale consists of 20-items

broken down into 4 subscales: financial strain, inability to make ends meet, not enough money for necessities, and economic adjustments.[20] Economic adjustments in the 3 months before administration of the questionnaire were assessed with 9 Yes or No items, such as *added another job*, *received government assistance*, or *sold possessions to increase income*. The subscale of not enough money for necessities was assessed with seven 5-point scale items in which respondents noted whether they felt they had enough money for housing, clothing, home furnishings, and a car over the previous 3 months. Inability to make ends meet included two 5-point scale items that assessed the difficulty in meeting financial demands in the previous 3 months. Financial strain consisted of two 5-point scale items concerned with expecting financial hardships in the coming 3 months. Scores can range from 20-73, with a higher score indicating worse economic hardship.

### Data collection and analysis

In-person data collection occurred in the clinical waiting area before the clinician visit or in the treatment room with the patient using a consecutive, convenience sample. The nursing staff checked the clinic lists daily for possible patient participants. Patients with metastatic cancer were identified and then approached for consent. After we had received the patient's consent, the administration of the instruments took about 20 minutes to complete. The data were then entered and verified in REDCap (Research Electronic Data Capture), which is hosted at the University of Pittsburgh.[21] The levels of symptom distress, quality of life, perceived financial hardship, and cancer-related distress were described through continuously measured variables. Descriptive statistics, measures of central tendency (mean and median), and dispersion (standard deviation and range), were obtained for the subscales and total scores. Correlation analysis was used to describe the relationship between perceived financial hardship and quality of life, symptom distress, and cancer-related distress. These primary outcome variables were further explored according to the level of dichotomized perceived financial hardship using mean score as the cut point. Independent sample *t* tests were used to compare patients experiencing high perceived financial hardship with those experiencing low perceived financial hardship.

## Results

In all, 100 patients participated in the study. Any missing data points were replaced with the mean score for that variable, although this was minimal in this study. Most of the participants were women (67%), and the average age of the participants was 63.43 years (SD, 13.05; Table 1). Of the total number of participants, 73% were white, 26% were black, and 1% were Asian. Most of the participants were either retired and not working (39%) or disabled or unable

**TABLE 1** Sociodemographic characteristics of the participants (N = 100)

| Characteristic | Value |
|---|---|
| | Mean no. years (SD) |
| Age at consent | 63.43 (13.05) |
| Formal education | 13.48 (2.78) |
| | Percentage |
| Gender | |
| Male | 33 |
| Female | 67 |
| Race | |
| White | 73 |
| African American/black | 26 |
| Asian | 1 |
| Type of cancer | |
| Breast | 25 |
| Gynecologic | 10 |
| Lung | 19 |
| Colon/rectal | 15 |
| Brain | 1 |
| Pancreatic | 5 |
| Kidney | 1 |
| Prostate | 5 |
| Other | 19 |
| Gross annual household income, US$ | |
| <10,000 | 13 |
| 10,000-<13,000 | 6 |
| 13,000-<20,000 | 16 |
| 20,000-<30,000 | 14 |
| 30,000-50,000 | 24 |
| >50,000 | 12 |
| Refused to reveal | 15 |
| Current employment status | |
| Full time | 15 |
| Part time (<35 h) | 3 |
| Retired, not working at all | 39 |
| Retired, employed full/part time | 3 |
| Disabled/unable to work | 34 |
| Other | 6 |
| Marital status | |
| Never married | 24 |
| Currently married | 42 |
| Living with partner/significant other | 4 |
| Widowed | 14 |
| Separated | 2 |
| Divorced | 13 |
| Other | 1 |
| Importance of religion/spirituality | |
| Not important at all | 10 |
| Somewhat important | 19 |
| Extremely important | 71 |
| Insurance status | |
| Public/private insurance | 99 |
| No insurance | 1 |

**TABLE 2** Summary statistics of measured outcome variables (N = 100)

| Outcome variable | Score range | Average score (SD) |
|---|---|---|
| NCCN Distress Thermometer[c] | 0-10 | 4.16 (3.26) |
| McCorkle Symptom Distress Scale[a] | 13-65 | 25.45 (9.34) |
| FACT-G[b] | 0-112 | 73.77 (19.40) |
| Physical Well-Being subscale | 0-28 | 17.35 (7.50) |
| Social/Family Well-Being subscale | 0-28 | 24.21 (5.25) |
| Emotional Well-Being subscale | 0-28 | 16.34 (5.42) |
| Functional Well-Being subscale | 0-28 | 15.87 (6.78) |
| Spiritual Well-Being Short Form | 0-48 | 35.20 (9.25) |
| Combined FACT-G, Spiritual Well-Being | 0-160 | 108.97 (26.07) |
| Psychological Sense of Economic Hardship Scale[d] | 20-73 | 35.70 (13.87) |
| Financial Strain subscale | 2-10 | 3.44 (2.36) |
| Inability to Make Ends Meet subscale | 2-10 | 5.73 (1.91) |
| Not Enough Money for Necessities subscale | 7-35 | 16.43 (8.92) |
| Economic Adjustments subscale | 9-18 | 10.63 (2.70) |

FACT-G, Functional Assessment of Cancer Therapy-General; NCCN, National Comprehensive Cancer Network

[a]Higher score indicates greater distress. [b]Higher score indicates better quality of life. [c]0 = no distress, 10 = great distress; ≥4 indicates a clinically significant level of distress. [d]Higher score indicates worse economic hardship.

to work (34%). Almost all of the participants had some form of insurance, with 99% having either private or public health insurance. A variety of cancer types were represented in this patient population, with higher percentages of breast (25%), gynecologic (10%), lung (19%), and colon/rectal cancer (15%). Of the total number of participants, 35% had annual household incomes below $20,000, and 50% had annual household incomes of more than $20,000. On average, participants had 13.48 years (SD, 2.78) of formal education.

Descriptive statistics for the primary outcome variables can be found in Table 2. The average score for cancer-related distress based on the NCCN Distress Thermometer tool was 4.16 (SD, 3.26). The average score for the McCorkle Symptom Distress measurement was 25.45 (SD, 9.34). For quality of life, the average FACT-G total score was 73.77 (SD, 19.40). Of the FACT-G subscale average scores, physical well-being was 17.35 (SD, 7.50), social/family well-being 24.21 (SD, 5.25), emotional well-being 16.34 (SD, 5.42), and functional well-being 15.87 (SD, 6.78). Participants' average score for the spiritual well-being measure was 35.20 (SD, 9.25) and the combined FACT-G and spiritual well-being average score was 108.97 (SD, 26.07). The total average score for perceived financial hardship was 35.70 (SD, 13.87), with subscale average scores of 3.44 (SD, 2.36) for financial strain, 5.73 (SD, 1.91) for inability to make ends meet, 16.43 (SD, 8.92) for not enough money for necessities, and 10.63 (SD, 2.70) for economic adjustments.

We conducted a bivariate correlation analysis to assess the relationship between perceived financial hardship and three other primary outcome variables (Table 3). These analyses showed significant low to moderate correlations with overall cancer-related distress (r, 0.439; $P < .001$), symptom distress (r, 0.409; $P < .001$) and overall quality of life scores (FACT-G and spiritual well-being combined score: r, -0.323; $P < .001$).

**TABLE 3** Correlation analysis of primary outcome variables and economic hardship (N = 100)

| | Psychological Sense of Economic Hardship Scale total score | McCorkle Symptom Distress Scale total score | Combined FACT-G and Spiritual Well-Being | NCCN Distress Thermometer |
|---|---|---|---|---|
| **Psychological Sense of Economic Hardship Scale total score** | 1.00 | — | — | — |
| **McCorkle Symptom Distress Scale total score** | 0.409* | 1.00 | — | — |
| **Combined FACT-G and Spiritual Well-Being** | -0.323* | -0.737* | 1.00 | — |
| **NCCN Distress Thermometer** | 0.439* | 0.602* | -0.483* | 1.00 |

FACT-G, Functional Assessment of Cancer Therapy-General; NCCN, National Comprehensive Cancer Network

*Significant at alpha <0.01

**TABLE 4** Difference between group means based on level of economic hardship (N = 100)

| | Level of economic hardship, mean score (SD) | | | |
|---|---|---|---|---|
| | High (n = 43) | Low (n = 57) | *P*-value | Confidence interval |
| NCCN Distress Thermometer total | 6.17 (2.91) | 2.65 (2.64) | <.001* | 2.41–4.63 |
| McCorkle Symptom Distress total | 29.70 (9.97) | 22.25 (7.44) | <.001* | 4.01–10.91 |
| FACT-G total | 65.62 (19.29) | 79.92 (17.23) | <.001* | -21.58–7.02 |
| Physical Well-Being subscale | 13.56 (7.63) | 20.21 (6.04) | <.001* | 9.36–3.94 |
| Social/Family Well-Being subscale | 22.79 (6.63) | 25.28 (3.61) | .029* | -4.73–0.26 |
| Emotional Well-Being subscale | 14.77 (6.06) | 17.53 (4.58 | .011* | -4.87–0.65 |
| Functional Well-Being subscale | 14.51 (6.52) | 16.89 (6.84) | .082 | -5.07–0.30 |
| Spiritual Well-Being Short form total | 34.40 (10.01) | 35.81 (8.67) | .453 | -5.13–2.30 |
| Combined FACT-G and Spiritual | 100.02 (27.50) | 115.72 (22.94) | .002* | -25.73–5.67 |

FACT-G, Functional Assessment of Cancer Therapy-General; NCCN, National Comprehensive Cancer Network

*Significant at alpha <0.05

Forty-three participants reporting high perceived financial hardship experienced worse quality of life overall (FACT-G and spiritual well-being; $P = .002$), worse FACT-G total scores ($P < .001$), worse physical well-being ($P < .001$), worse social/family well-being ($P = .029$), worse emotional well-being, and no significant difference for functional ($P = .082$) or spiritual well-being ($P = .453$), compared with those with lower economic hardship. In overall cancer-related distress, participants with higher perceived financial hardship reported higher levels of cancer-related distress ($P < .001$) than those with lower perceived financial hardship. For those participants reporting higher perceived financial hardship there was also worse symptom distress ($P < .001$), compared with those with lower economic hardship (Table 4).

## Discussion

Overall, this report provides data to illuminate our understanding of disparities in well-being that may be present in patients with advanced cancer. Our analysis found that patients with advanced cancer who have higher perceived financial hardship have significantly higher overall cancer-related distress, symptom distress, and poorer overall quality of life. In this study's population of patients with advanced cancer, the most notable areas of economic hardship identified by participants were: not having enough money for necessities in the 3 months before the survey and the inability to make ends meet during the same time span, with difficulty paying bills and not having enough money left at the end of the month being most noteworthy among this study's patient population. Financial strain and making economic adjustment were not as notable in the category of perceived financial hardship. In regard to not having enough money, participants most commonly cited not being able to afford everyday necessities such as food, clothing, medical care, or a home, as well as leisure and recreational activities. These findings are further supported with the positive, moderate associations between perceived financial hardship and symptom distress and overall cancer-related distress found in this cohort of patients with advanced cancer and the negative, moderately associated relationship between perceived financial hardship and overall quality of life in this study's sample. Although these findings have been confirmed in the literature on cancer-related distress, our findings add to our knowledge on both economic and cancer-related distress exclusively in patients with advanced cancer.[9,22] The broader cancer-related distress literature has also found an association between being younger and having a lower household income as risk factors for increased financial hardship; however, the perception of financial strain and magnitude was a more significant predictor of quality of life and perception of overall well-being.[6,8-9,12,22-23] Furthermore, patients with cancer who noted having higher financial distress typically reported decreased satisfaction with cancer care which also influenced their adherence to treatment and quality of life.[24]

Our work now adds the important element of perceived financial hardship to the advanced cancer-related distress puzzle. We should consider integrating a financial distress assessment into routine cancer care, particularly with patients and families with advanced cancer, to proactively and routinely assess and intervene with available distress mitigating resources. Therefore, understanding the patients most likely to experience financial distress will help personalize supportive therapy. This study's results as

well as the existing literature describing financial distress support the use of comprehensive screening instruments to capture elements of financial burden beyond out-of-pocket costs.[8,25] This screening is particularly relevant because we are increasingly recognizing that gross annual household income does not always reflect financial hardship or distress. The instrument we used for this analysis, the Psychological Sense of Economic Hardship, provides a broad view of financial toxicity including the specific components of financial strain, the inability to make ends meet, not having enough money for necessities, and economic adjustments experienced by patients with advanced cancer.[20] Another measure to evaluate financial toxicity among patients with cancer includes the Comprehensive Score for Financial Toxicity (COST), which is a widely used patient-reported outcome measure. It was developed with input from both patients and oncology experts.[25] Use of a financial toxicity assessment tool adds to our understanding of the economic financial burden experienced by patients with cancer, specifically those with advanced cancer.

Tucker-Seeley and Yabroff have identified several areas in which the research agenda for financial toxicity should focus, including: documentation of the socioeconomic context among patients across all areas of the cancer care continuum, further identification and characterization of at risk populations to address health disparities, and the inclusion of cost discussions in the health care context.[26] Furthermore, research is needed to identify key areas to target for interventions addressing financial toxicity, such as addressing lack of financial resources to cover the cost of cancer care, focusing on managing or preventing the distress that results from a lack of financial resources, or addressing coping behaviors used by families to manage the financial burden of cancer care.[26] Although cost discussions between health care providers and patients have been identified as important in reducing the financial burden of cancer care, the content, timing, and goals of those discussions still need to be better articulated for different patient populations, including patients with advanced cancer.[3,27-28] In addition, resources such as social workers, patient navigators, or financial counselors have been identified as effective in assisting patients with financial planning and accessing community resources to address financial burden and assistance.[4]

### Design considerations

This study has limitations that need to be noted. Its cross-sectional design does not allow for the analysis of causal inferences. In addition, certain groups were underrepresented in this study's sample, including uninsured patients, men, and some minority groups, which may have underestimated the amount of financial burden experienced by patients with advanced cancer. The lack of representativeness of uninsured individuals may be a result of the eligibility of persons with advanced cancer for Medicaid. However, a strength of this study is its ability to increase the representativeness of African American/black patients in the study of advanced cancer and financial hardship. In our study, just over a quarter of the participants (26 of 100; 26%) were black/African American, compared with the US Census Bureau's national census level of 13.3% and 13.4% in Allegheny County, Pennsylvania .[29]

The lack of employed participants in this study could be because many were not able to work because of the advanced stage of their disease. The low level of partnered status is a limitation, although one study site was a low-income hospital where one generally tends to see higher levels of unpartnered status. This study did not control for demographic information such as gender or age, thus, the relationships between the primary outcome variables and financial hardship may be overestimated. Moreover, this analysis of financial distress is limited to the context of the United States due to our lack of universal health care and unique payment system. Although we included only patients who were in the palliative phase of cancer treatment, no medical record review was conducted to determine previous cancer history and treatments, which might have provided more insight into other financial loss or cost of cancer treatment. Furthermore, we note that it can be difficult to prognosticate with accuracy and identify that some patients with advanced cancer may have been excluded from the study due to the inclusion criteria of less than 1 year of survival.

## Conclusion

Perceived financial hardship is an important assessment of the burden placed on patients due to the cost of disease; and is a good start in assessing indirect costs that patients take on when coping with advanced stages of cancer and can shed light on an aspect of distress experienced by this patient population that is not commonly addressed. Subjective measures of perceived financial hardship complement objective measures that are commonly indicative of economic resources and can further our understanding of the impact of financial distress experienced by patients with cancer. Further study of financial impacts of advanced cancer as well as predictors of financial distress are essential to the early identification of financial hardship and the development of interventions to support those at high risk or experiencing financial distress.

**Acknowledgments**

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# Metastatic Kaposi sarcoma with osseous involvement in a patient with AIDS

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Kaposi sarcoma is an AIDS-defining illness associated with human herpes virus-8 (HHV-8) co-infection. It was described in 1872 by the Hungarian dermatologist Mortiz Kaposi, and was an isolated and sporadic occurrence before the emergence of HIV infection and AIDS.[1] It was first affiliated as an AIDS-associated neoplasm in 1981.[1] Kaposi sarcoma is a systemic disease that can present with cutaneous lesions with or without internal involvement. There are four subtypes: Classic, African endemic, AIDS-related (CD4 count, <200), and Kaposi sarcoma in iatrogenically immunosuppressed patients. The disease has the propensity to manifest in the skin and gastro-intestinal and respiratory tracts, and osseous involvement is rarely encountered. We present here the case of an AIDS-positive man with generalized bone pain as a result of metastasis from Kaposi sarcoma. Our discussion includes the epidemiological, clinical, pathological, and radiological facets of AIDS-related Kaposi sarcoma, and the anomaly of osseous involvement.

## Case presentation and summary

A 26-year-old African American man with a history of AIDS (CD4 count, 13 cells/mm$^3$ [normal, 500-1,600 cells/mm$^3$]) who was noncompliant with HAART (highly active antiretroviral therapy), presented to the emergency department in January 2016 with chest, abdominal, and back pain. His HAART regimen included darunavir 8 mL oral suspension daily, emtricitabine 4 mL oral suspension daily, and ritonavir 100 mg tab daily. A computed-tomography (CT) scan of the man's abdomen revealed axillary, mediastinal, and abdominal lymphadenopathy, with splenomegaly and innumerable osseous lucent spinal lesions. A left axillary lymph node biopsy was positive for Kaposi sarcoma; pathology showed fascicles of spindle, oval- to round-shaped atypical cells positive for HHV-8 (granular nuclear staining), CD31, and CD34 (partial; Figure 1). Serum and urine protein electrophoresis showed no paraproteins.

He restarted his previous HAART regimen in March 2016, and was subsequently started on chemotherapy with liposomal doxorubicin (50 mg [20 mg/m$^2$] in 250 ml D5W IV every 2 weeks) because of his extensive disease.[2] He completed 6 cycles by June 2016. However, he returned in July 2016 with worsening back pain. A repeat CT scan revealed significant improvement in the disseminated lymphadenopathy, but worsening osseous metastatic disease was seen in the lumbar, thoracic, and pelvic regions. A pelvic lytic lesion biopsy revealed Kaposi sarcoma; pathology showed spindle cells positive for CD34, CD31, and HHV-8 (Figure 2). The patient received palliative radiation to the spine, aiding in pain management and ambulatory dysfunction. He continued with his noncompliance with all medications and outpatient follow-ups, and after XXX succumbed to his disease burden.

## Discussion

Kaposi sarcoma is a low-grade mesenchymal tumor that involves the blood and lymphatic vessels.[3] Its association with AIDS was revealed in the early 1980s at the start of the HIV epidemic in the United States. In 1994, Chang and colleagues discovered the association between Karposi sarcoma and HHV-8 by isolating DNA fragments of HHV in Kaposi sarcoma tumors from AIDS patients.[4] The mode of transmission of HHV-8 has not been fully decoded. It has been presumed that adult homosexual contact continues to be an important route of transmission, inferring a common route of infection. In 1990, the

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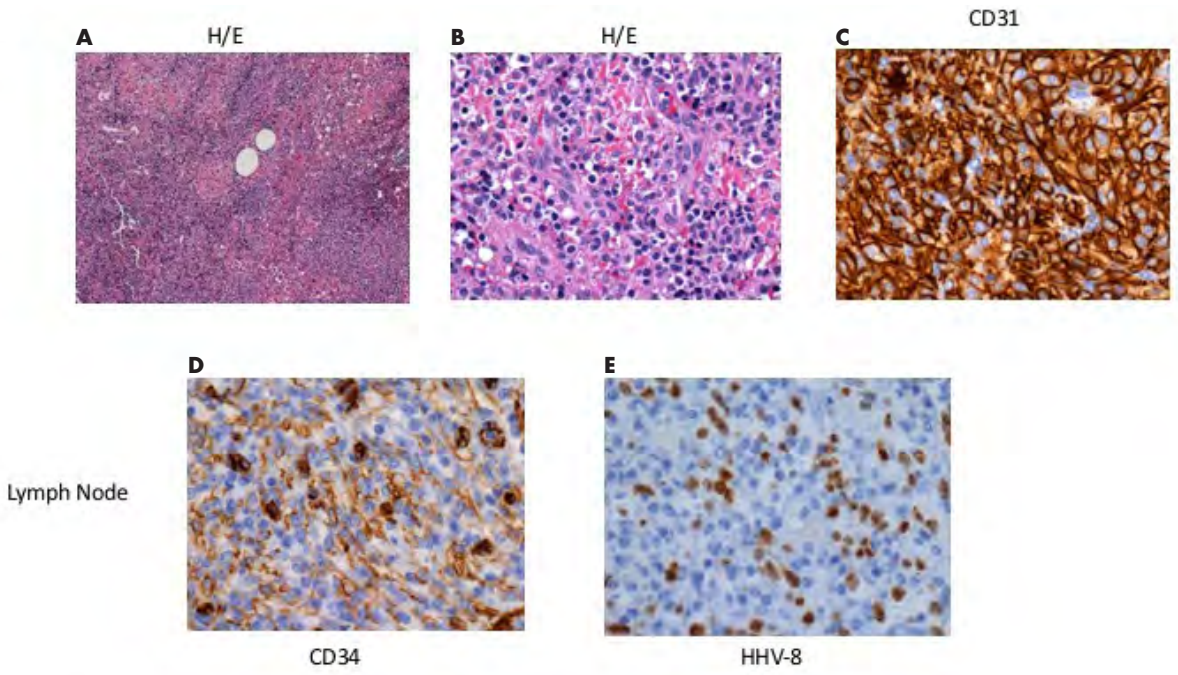


**FIGURE 1** Results of left axillary lymph node biopsy (scale bar, 40μm). **A,** The node architecture is partially effaced with interwoven fascicles of spindle, oval- to round- shaped atypical cells, vascular slits and erythrocytes, predominantly located in interfollicular areas, sinusoids, and with extension into perinodal adipose tissue. Some residual follicles are present. The preserved B-cell follicles are positive for CD20. **B,** Increased magnification of the picture A demonstrating atypical cells. CD10 and BCL-6 are positive in scattered cells. **C,** The atypical cells are positive for CD31. **D,** The atypical cells are positive for CD34. **E**, The atypical cells are positive for latency-associated nuclear antigen human herpes virus-8 (granular nuclear staining**)**.

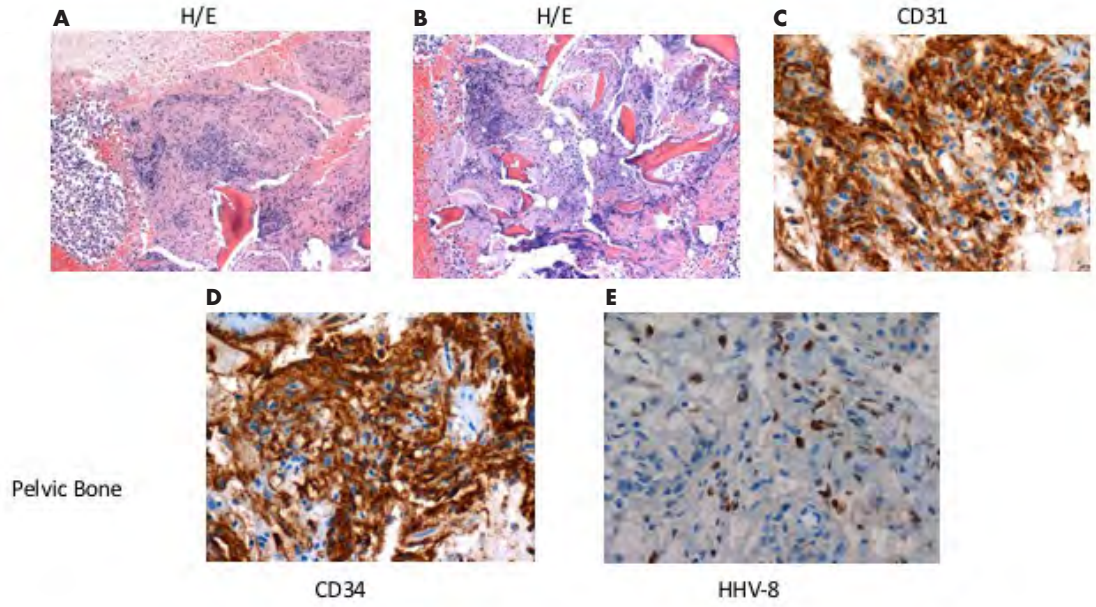


**FIGURE 2** Results of the pelvic bone biopsy (scale bar, 40μm). **A,** A focus of proliferation of ill-defined fascicles of oval spindle cells separated by slit-like spaces containing erythrocytes. The stroma shows infiltration of lymphoid proliferation with numerous plasma cells and immunoblasts. **B,** Increased magnification of the picture A demonstrating atypical cells. **C,** The atypical cells are positive for CD31. **D,** The atypical cells are positive for CD34. **E,** The atypical cells are positive for latency-associated nuclear antigen human herpes virus-8 (granular nuclear staining).

overall risk of developing Kaposi sarcoma in AIDS patients was 20,000 times greater than it was in the general population, and 300 times greater than in other immunosuppressed patients.[5] This suggests an increase in incidence, in direct relation, with a decrease in the CD4 count.

Kaposi sarcoma can present with a range of clinical features, from negligible cutaneous lesions to a hastily progressing neoplasm. Involvement in the musculoskeletal system is infrequent, but encountered increasingly in the AIDS-related subtype. Moreover, it is recurrently observed in the African population.[6] In one of the largest reviews to date exploring Kaposi sarcoma involving the musculoskeletal system, Caponetti and colleagues observed the greatest osseous involvement distinctly in patients with CD4 and T-cell counts below 100 cells/mm$^3$.[6]

Kaposi sarcoma musculoskeletal involvement, specifically bone, is atypical. If it does occur, it usually manifests as a result of contiguous invasion from an adjacent nonosseous lesion. Caponetti and colleagues that isolated osseous Kaposi sarcoma lesions (with no overlying skin lesion) were found to be more likely to be associated with AIDS in the review by Caponetti and colleagues.[6] As in our patient, it is also typically a manifestation of more widely disseminated disease.[7]

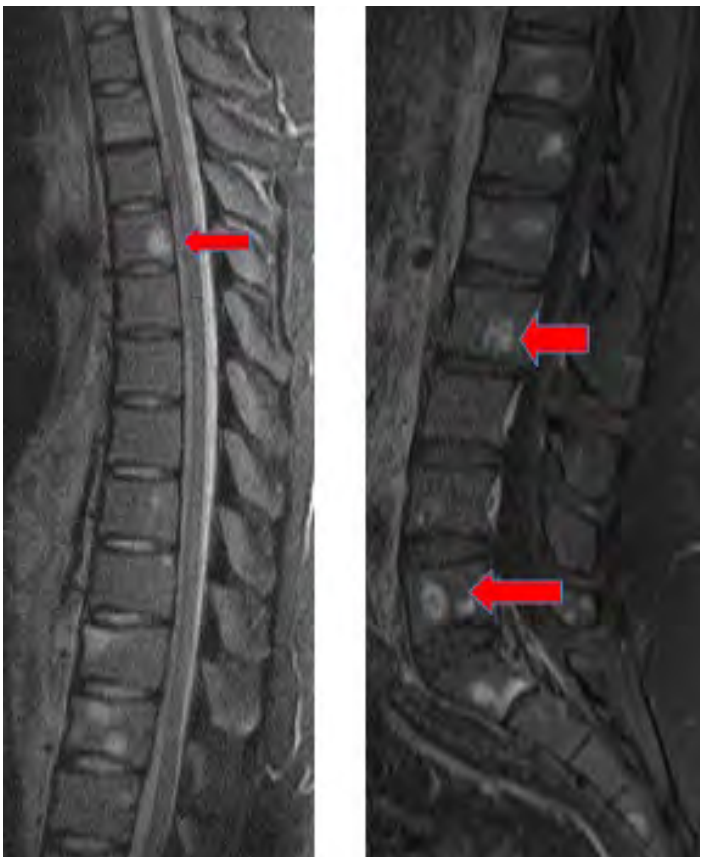

**FIGURE 3** Osteolytic vertebral lesions (sagittal view). Red arrows show the osteolytic lesions in the L2 (left) and in L2 and L5 (right) vertebrae.

Most of the osseous lytic lesions in AIDS patients are located in the axial skeleton. Radiological features of musculoskeletal Kaposi sarcoma are variable. As observed by Caponetti and colleagues, Kaposi sarcoma lesions can appear as a periosteal reaction, cortical erosions, osteolysis, or osseous destruction, with irregular-shaped cortical erosions being most typical.[6] Despite their osteolytic features, Kaposi sarcoma lesions are often not visualized by conventional radiography.[6] The preferred imaging for identification of lytic bone changes is CT (Figure 3). Magnetic resonance imaging can also help distinguish marrow abnormalities as well as adjacent soft tissues masses. Radiologically, Kaposi sarcoma osseous lesions have parallel features to bacillary angiomatosis, tuberculosis, or lymphoma.[8] Therefore, biopsy of the lesion is essential in establishing the diagnosis of Kaposi sarcoma.

The etiologic prompt for Kaposi sarcoma has not been fully elucidated. However, it has been hypothesized that HHV-8 infection may initiate the process. Guihot and colleagues showed that patients with Kaposi sarcoma have notably fewer HHV-8–specific T cells than patients who are asymptomatic HHV-8 carriers, regardless of CD4 T-cell count or HHV-8 load.[8] As per Guihot's conclusions, this impairment may be culpable for the deranged proliferation of HHV-8-transformed cells and the ultimate manifestation of Kaposi sarcoma.[9] An insufficient T-cell response to HHV-8 lytic antigens is associated with Kaposi sarcoma and continues to support the notion that such genes are important in Kaposi sarcoma oncogenesis.

In theory, there should be clinical improvement in Kaposi sarcoma when immunity is restored. Cancers caused by the Epstein-Barr virus and Kaposi sarcoma-associated herpes virus may eventually also be preventable with vaccines.[10]

There is rarely bone involvement without the foreshadowing of a poor prognosis. Erroneous patient care may inevitably arise from Kaposi sarcoma in uncharacteristic sites. A differential of Kaposi sarcoma should be included if a patient with AIDS presents with osteolytic lesions on imaging. Biopsying the lesion cements the diagnosis and eliminates the possibility of mimicry conditions such as bacillary angiomatosis, benign vascular lesions, and angiosarcoma. As of today, a HAART regimen remains the standard initial care for patients with Kaposi sarcoma.

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# Bilateral chylothorax in an AIDS patient with newly diagnosed Kaposi sarcoma

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Kaposi sarcoma is an angioproliferative tumor that is associated with human herpes virus-8 (HHV-8). Mucocutaneous disease is the most common site for manifestation of AIDS-related Kaposi sarcoma, commonly affecting the lower extremities, oral mucosa, face, and genitalia. Pleural effusions can occur in 36%-60% of patients with Kaposi sarcoma, and it has been documented that chylothorax is a rare, but plausible presentation in patients with Kaposi sarcoma.[1] We present here a case of bilateral chylothorax in a patient with AIDS-related Kaposi sarcoma.

## Case presentation and summary

A 52-year-old MSM male with AIDS (CD4, <20 $mm^3$; viral load, 58 copies/ml) presented to the emergency department with complaints of shortness of breath, productive cough, and diarrhea for 2 days prior to presentation. His medical history also included chronic obstructive pulmonary disease, coronary artery disease, and hyperlipidemia. The patient was not on HAART because of his history of noncompliance. The results of a chest X-ray and computed-tomography (CT) scan showed that the patient had bilateral pleural effusion and a spiculated 14-mm nodule in the left upper lobe. The patient underwent ultrasound-guided placement of a 12-French left-sided chest catheter, and a milky white fluid was aspirated from the left pleural space. Laboratory analysis of the pleural fluid confirmed an exudate with an elevated triglyceride level of 120 mg/dL (chylous, >110 mg/dL) indicating chylothorax.

On close physical examination, the patient was found to have multiple irregular plaques on the back and lower extremities. As described by dermatology, there was a violaceous indurated plaque on the left axillae, violaceous indurated plaques with superficial scale grouped on the left midlateral back, and hyperpigmented lichenified plaques and papules on bilateral shins, with some with plate-like scale. Two punch biopsies were taken of the skin lesions, which confirmed Kaposi sarcoma, plaque stage from the lesion biopsied on the back, and patch stage from the lesion biopsied in the left axilla. Cytology of the pleural fluid was negative for malignant cells. On review by the radiologist of the CT scan of the chest, there was no indication of gross distention of the thoracic duct. Treatment options were offered to the patient, and the patient was considering options for chemotherapy and home hospice given his advanced disease state at the time of discharge.

## Discussion

Chylothorax occurs with a thoracic duct obstruction, which results in leakage of lymphatic fluid into the pleural cavity. The two leading causes of chylothorax are trauma and malignancy, with lymphoma being the most common cause of chylothorax among those with malignancy.[2] Chylothorax, however, is a rare but documented complication of Kaposi sarcoma. Marais and colleagues reported the case of a 3-year-old HIV-positive patient with newly diagnosed Kaposi sarcoma who was found to have tumor infiltration in the thoracic duct leading to bilateral chylothorax.[3] Maradona and colleagues described a 40-year-old man with AIDS-related Kaposi sarcoma who was found to have pleural and pericardial Kaposi sarcoma with chylothorax.[4] Priest and colleagues wrote about a 32-year-old patient with AIDS with biopsy-proven Kaposi sarcoma who required multiple therapeutic thoracenteses for rapidly recurrent left chylothorax effusions.[5]

There are two leading discussions as to the pathophysiology of chylothorax that is related to Kaposi sarcoma: chylothorax developing secondary to metastatic disease or the development of chylotho-

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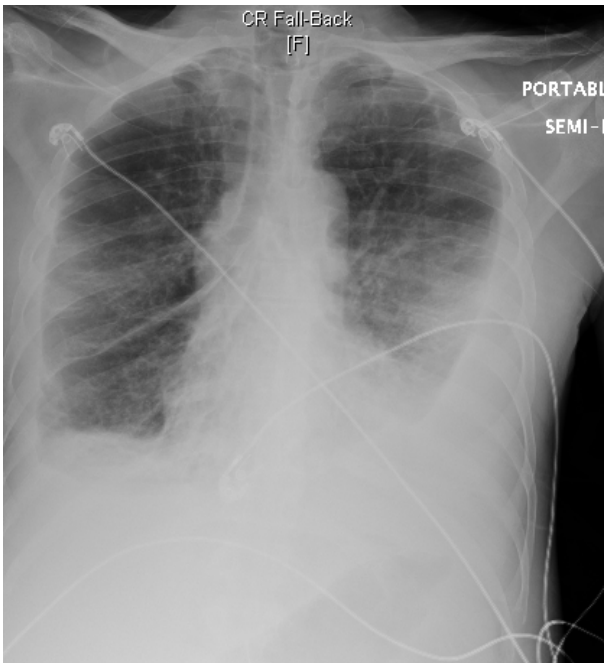


**FIGURE 1** Chest X-ray showing bilateral pleural effusion blunting the costophrenic angles.

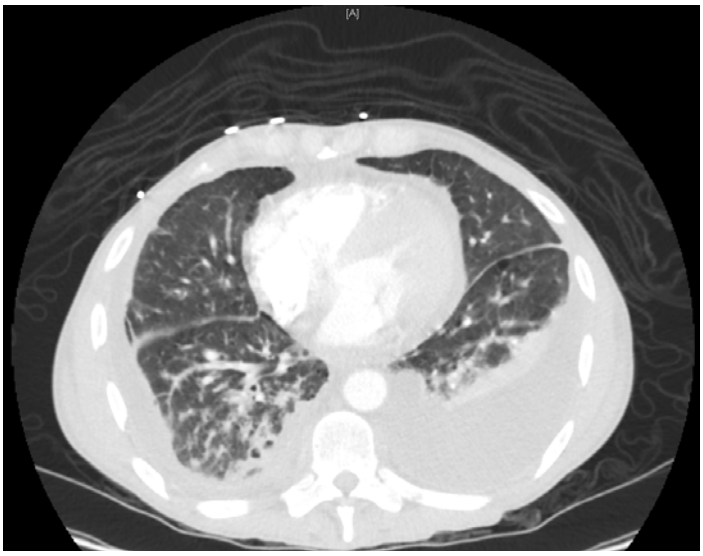


**FIGURE 2** A helical computed-tomography scan of the chest showed bilateral pleural effusion.

rax secondary to primary Kaposi sarcoma arising from the pleural region.[6] One case report examined pleural and lung biopsies in a 34-year-old patient with AIDS-related Kaposi sarcoma that showed immunohistochemical staining that was suggestive of early-stage Kaposi sarcoma of lymphatic endothelial origin. The authors were attempting to illustrate that Kaposi sarcoma may have a stem-cell origin which can differentiate into lymph cells. Kontantinopoulos and colleagues postulated that in situ Kaposi sarcoma can arise from the lymphatic system with a resultant clinical presentation of chylothorax.[7] The more mainstream thought however, is that chylothorax has been found to develop secondary to metastatic disease. The present case, therefore, illustrates an unusual presentation of cytology negative chylothorax in a patient with AIDS-related Kaposi sarcoma.

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# A rare case of hypoglycemia induced by a classic gastrointestinal stromal tumor

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Hypoglycemia, a frequently encountered medical emergency, is usually seen in patients with diabetes, most commonly as a result of iatrogenesis. However, it can also be encountered in nondiabetic patients. Various causes, such as pancreatic islet cell tumors producing insulin, primary or secondary adrenal insufficiency, advanced liver disease, pheochromocytoma and hypothyroidism, have been found to contribute to the condition in the nondiabetic population.[1] In rare cases, an excessive production of insulin-like growth factor (IGF-2) – a condition known as nonislet cell tumor-induced hypoglycemia (NICTH) – has also been found to cause hypoglycemia. Hypoinsulinemic hypoglycemia, with low IGF-1 levels and an IGF-2-IgF1 ratio of greater than 10, is found to be suggestive of NICTH.

## Case presentation and summary

An 81-year-old man with a history of diabetes mellitus, systolic heart failure, chronic kidney disease, and metastatic classical gastrointestinal spindle cell sarcoma presented to the emergency department with an acute change in mental status resulting from a new onset hypoglycemia. He was admitted, and during his hospital stay, he experienced severe hypoglycemic episodes with symptomatic presentations of diaphoresis on multiple occasions. A detailed history revealed that for diabetes, the patient had been on insulin for the first 12 years after his diagnosis, after which he was switched to metformin 500 mg twice daily for about 2 years, and as a satisfactory glycemic control was attained, eventually metformin had also been stopped 3 years prior to the current presentation.

The patient's past medical records were obtained from the hospital at which he had been diagnosed gastrointestinal spindle cell sarcoma. Patient had not received treatment for the cancer as the disease was too widespread to be treated. The gastrointestinal spindle cell sarcoma, which had initially been surgically resected 7 years before the current presentation, had a recurrence 3 years later with abdominal and pulmonary metastasis, but no liver metastasis. No further intervention was carried out because the widely metastasized disease would not have benefited from any more surgical intervention and chemotherapy was not initiated because of the patient's comorbid illnesses.

A blood sample drawn from the patient at the time of one hypoglycemic event, revealed low serum insulin <0.1 U/ml (normal, 2-19.6 U/ml); low C-peptide level, 0.59 ng/ml (0.8-3.85 ng/ml); low IGF-1, 16 ng/ml (5-4 ng/ml); and IGF-3, 0.9 ng/ml (2.2-4.5 ng/ml). IGF-2 levels were found to be markedly elevated at 945 ng/ml (47-350 ng/ml). The calculated IGF-2-IGF-1 ratio was 59.06 (normal, <10), suggesting NICTH as the etiology for the patient's hypoglycemia.

The hypoglycemic episodes were initially treated with a continuous dextrose infusion followed by diazoxide treatment. However, diazoxide did not prevent his hypoglycemic episodes, so dexamethasone was considered as an alternative for his condition. The dexamethasone treatment resulted in the normalization of the patient's serum glucose levels and resolution of his symptoms. The patient was discharged in a satisfactory state few days later and followed up thereafter. No recurrence of hypoglycemic episodes was found, and he was continued on dexamethasone therapy.

## Discussion

Hypoglycemia due to NICTH is rare, with a preva-

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lence of four times less than that of insulinoma.[3] In most cases, NICTH occurs in patients with solid tumors of mesenchymal and epithelial origins such as hepatocellular carcinoma, gastric carcinoma or mesothelioma.[4] In NICTH, the serum levels of insulin, C-peptide, and IGF-1 are usually decreased or undetectable. However, the circulating levels of total IGF2 may be increased, decreased, or normal. Concurrent normal to high morning cortisol and normal response to cosyntropin stimulation can rule out adrenal insufficiency and suggest NICTH. An IGF-2: IGF-1 ratio of >10 is considered to be clinically significant and highly suggestive of NICTH.[5] Hypoglycemia in NICTH can be managed by administration of oral glucose, intravenous dextrose or glucagon. In some cases, diazoxide, a potent inhibitor of insulin secretion, has been found to be useful.[6] Diazoxide directly inhibits the release of insulin through stimulation of adrenergic receptors and also has an extra pancreatic hyperglycemic effect, probably by inhibiting cyclic adenosine monophosphate phosphodiesterase, resulting in higher plasma levels of cyclic AMP and enhanced glycogenolysis.

Glucocorticoid therapy has been shown to suppress IGF-2 in a dose dependent manner and also by increasing gluconeogenesis.[7] Surgical resection of the tumor whenever possible is the treatment of choice followed by radiotherapy and chemotherapy for inoperable disease and if successful, usually results in resolution of hypoglycemia. Imatinib, is the chemotherapeutic drug of choice for metastatic GIST, but many case reports have suggested worsening of hypoglycemia in advanced GIST with the use of the drug.[8] The patient described in our report was not on any chemotherapy, hence hypoglycemia could not be attributed to it. On the basis of findings among 24 patients with GIST, Rikhof and colleagues have recommended monitoring plasma levels of pro-IGF-IIE to identify patients at high risk for developing hypoglycemia, especially those with progressive disease.[9] Furthermore, over expression of IGF-2 as a predictor of potential relapse may be an area for potential research and further study.[10]

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# Oncology and the heart

**Interviewer** David H Henry, MD[a] **Interviewee** Joseph R Carver, MD[b]

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Given our chemotherapy, radiation therapy, and the advent of immune checkpoint inhibitors, oncology and cardiology may be more closely linked than ever before. This interview reviews the potential toxicities of today's radiation, chemotherapy, immunotherapy, and the structural involvement that tumors may cause in and around the heart. Although the immune checkpoint inhibitors are not commonly associated with cardiac toxicity, their increasing use may tell us otherwise. This interview summarizes the close association between oncology and cardiology, which we should bear in mind as we treat our patients.

**DR HENRY [DH] I am Dr David Henry with The Journal of Community and Supportive Oncology. I am speaking today with Dr Joe Carver at the University of Pennsylvania where he is chief of staff of the Abramson Cancer Center and holds the Bernard Fishman Clinical Professor of Medicine. The reason we're talking today is that Dr Carver specializes in two areas that rarely overlap, cardiology and oncology. We thought we'd talk about how oncologists think about the heart. Patients may have comorbid illness of the heart and then we treat them, or our treatments may cause cardiac issues. So, let us begin with radiation therapy and cardiac toxicity. We have increasingly modern techniques. We hear our colleagues in radiation talk about intensity-modulated radiation therapy, Gamma Knife, CyberKnife, proton therapy, and what those might do to the heart. I'm thinking of the coronary arteries, mechanical function, and ejection fraction. So, Joe how would you describe that to a colleague who is worried about radiation and these more modern techniques? What do we need to watch for and how do we watch for it with regard to these functions?**

**DR CARVER [JC]** It's a great question. The answer about radiation and the heart really has to be divided into two different areas. If you're talking to somebody who has had radiation in the past, especially in what we would call the premodern era, that population is at an increased risk for multiple different cardiac problems starting with myocardial dysfunction. In regard to the term premodern, depending on the facility, the transition to modern would have occurred sometime in the 1980s; prior to that shift, therapeutic radiation was delivered with little concern for cardiac exposure, and in many cases, the heart was blasted and nobody really monitored how much radiation the heart received. When due to radiation, myocardial dysfunction is more restrictive than congestive disease, valvular disease, coronary artery disease, and pericardial disease, as well as arrhythmias and conduction problems.

A typical example is a patient who had Hodgkin disease in his teens and received mediastinal mantle radiation. Fifteen to 25 years later, the patient has a pacemaker for heart block, coronary artery disease that requires a stent, and most recently has two valves replaced—so aortic and mitral valve replacement because of late radiation effects. This scenario is typical for the "old" days. The 20-year cumulative incidence of radiation-induced cardiac toxicity is 15%-20% (Table, Figure).[1] Sitting with a patient about to begin chest radiation, the absolute risks are unknown but presumed to be less as treatment is delivered according to the modern techniques that you described in the question.

**DH They're so much better now, so this is less common.**

**JC** With the shielding and breath-holding techniques and position changes, doing upright radiation rather than supine, and because the technology has improved both in the delivery of radiation and the technology in understanding where all the radiation is going, in today's world, we can calculate pretty precisely how much radiation the heart actually receives. Ultimately, with the protective mechanisms that are in place going forward, the risks that I described for that survivor are probably exponentially less than what's reported in the literature and what we see clinically. Radiation has become much, much safer. There is still

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probably some small risk of development of late changes, but I don't think we know what that risk is today because the shielding and things we do to protect the heart have not yet been studied in the long term.

**DH Of course, the patient is breathing and there'll be some movement of the target. Some of the radiation techniques can follow the target despite the breathing?**

**JC** Yes, definitely true. Radiation delivery is much more precise today. Not only has the delivery changed, but so has what we know about the location of potential arterial disease. For example, if you read any textbook, it says that for the coronaries, that it's ostial and proximal disease of the left main, or the left anterior descending, or the right coronary artery. Today, somebody who gets chest/mediastinal radiation, for either breast cancer, lymphoma, or for a mediastinal tumor, the location of potential disease is more likely to mimic the location of classic coronary disease in the mid-portion of the left anterior descending artery rather than at the ostium. It's going to be a different disease going forward.[2,3]

**DH Let's switch from radiation to chemotherapy. Of course, all of us worry about and are very familiar with the toxicity potential of doxorubicin and trastuzumab. I remember an American Society of Clinical Oncology meeting a few years ago, one of the speakers was a cardiologist and was advising us that perhaps the ejection fraction, albeit readily available and reproducible, was probably too simple and we should watch more closely with other techniques. My final question and then I'll let you comment – I thought I recalled 5-fluorouracil (5-FU) infusions, which we do in some of our colorectal cancers, for example, can cause a vasospasm, Prinzmetal-type angina from time to time, and is that true in capecitabine? What are your thoughts on how to follow the doxorubicin, trastuzumab analogs, and anything about 5-FU and its analogs?**

**JC** Okay, this is a giant question. I'll take them in order. First, doxorubicin. Cumulative dose-related cardiotoxicity was first described by Von Hoff in 1979.[4] That is, the more you get, the higher likelihood of developing cardiotoxicity. Up to a total of 400 mg/m$^2$, the risk is <1%, with a sharp rise as the dose increases beyond this level.[4] That being said, there is a clear large and individual variation: I've seen sarcoma patients who've gotten close to 1,000 mg/m$^2$ without cardiac dysfunction, and some people with minimal exposure have full-blown cardiomyopathy. One of the protective strategies that we developed over the years is to give less of the drug, and with that get the same cancer treatment efficacy. There is definitely a risk for anthracyclines. Full-blown heart failure is probably in the 4%-8% range – and that's cumulative lifetime – it's not as high as we once thought it was. That doesn't mean that it isn't there, but, relatively speaking, from the standpoint of benefit of anthracyclines, the benefit certainly clearly outweighs the cardiac risk.

With administration of the anthracyclines, we try to do whatever protective things we can do. There are some people who believe that continuous infusion is safer for the heart than bolus injection. It's pretty controversial. Dexrazoxane, which is a chelating agent, has been shown to reduce cardiotoxicity, and using a lipophilic anthracycline preparation may also have less cardiac toxicity.

**TABLE** Cox multivariable regression analysis for all cardiac diagnoses and procedures

| | Cardiac diagnoses | | Cardiac procedures | |
|---|---|---|---|---|
| Age, y | **HR [95% CI]** | ***P*** | **HR [95% CI]** | ***P*** |
| 20–29 vs <20 | 1.48 [0.98–2.24] | .065 | 1.29 [0.71–2.35] | .398 |
| 30–39 vs < 20 | 2.63 [1.64–4.21] | < .001 | 3.12 [1.64–5.94] | .001 |
| 40–49 vs <20 | 7.70 [4.57–12.97] | < .001 | 6.37 [2.89–14.08] | < .001 |
| >50 vs <20 | 13.12 [7.87–21.89] | < .001 | 12.51 [5.99–26.11] | < .001 |
| Sex (male vs female) | 1.56 [1.16–2.11] | .003 | 1.84 [1.18–2.86] | .007 |
| Mediastinal dose (≥ 36 Gy vs < 36 Gy) | 0.93 [0.50–1.73] | .812 | 1.40 [0.44–4.49] | .568 |
| Any chemotherapy (Yes vs No) | 1.07 [0.77–1.48] | .7 | 1.00 [0.61–1.66] | .988 |

HR, hazard ratio; CI, confidence interval, Gy, gray. Reproduced with permission from the American Society of Hematology (ASH).

**DH I have a population in which a lot of liposomal doxorubicin is used and I've given a lot and rarely if ever get cardiac toxicity. You see that as well?**

**JC** Yes. There's a significant financial difference between doxorubicin and liposomal doxorubicin; the latter is more expensive. From the standpoint of safety, and from the standpoint of if I ever needed doxorubicin, I would probably jump on that and ask for the liposomal preparation and/or dexrazoxane.

**DH For trastuzumab, we are getting echocardiograms every 9 weeks. That seems awfully simple, but there's a whole algorithm we follow for particular change in ejection fraction and watch the drug or stop the drug. Are we doing that correctly?**

**JC** The first statement I would make about that is that there are too many women who need trastuzumab whose therapy has been prematurely stopped because of just looking at the ejection fractions. So, there has to be more to decision-making other than just the number of the ejection fraction. We're pretty aggressive and tend to try to get women to get the full dose and whatever dose-effective dose they need, especially with curative intent in the adjuvant setting that we make decisions based not only on the ejection fraction.

We also have, I would say, a handful of our medical breast oncologists who do not follow the package insert. We don't get ejection fractions every 3 cycles. We have substituted a little bit by following biomarkers so that we use N-terminal pro b-type natriuretic peptide (NT-proBNP) to monitor people, either with each cycle or every third cycle. The benefit of BNP is its negative predictive value. If it's normal, it's hard to have any clinically significant myocardial dysfunction.

What we're going to see over – I would hope – the next year or two is that the recommendations about getting echocardiograms frequently will go away.

**DH That would be welcome because in our electronic medical records, it's 9 weeks, stop, do this, etc. How about a comment on infusional 5-FU and possibly its cousins, such as capecitabine, and any coronary issues?**

**JC** Let me come back, just one more thing about trastuzumab. For metastatic disease, we do whatever is necessary

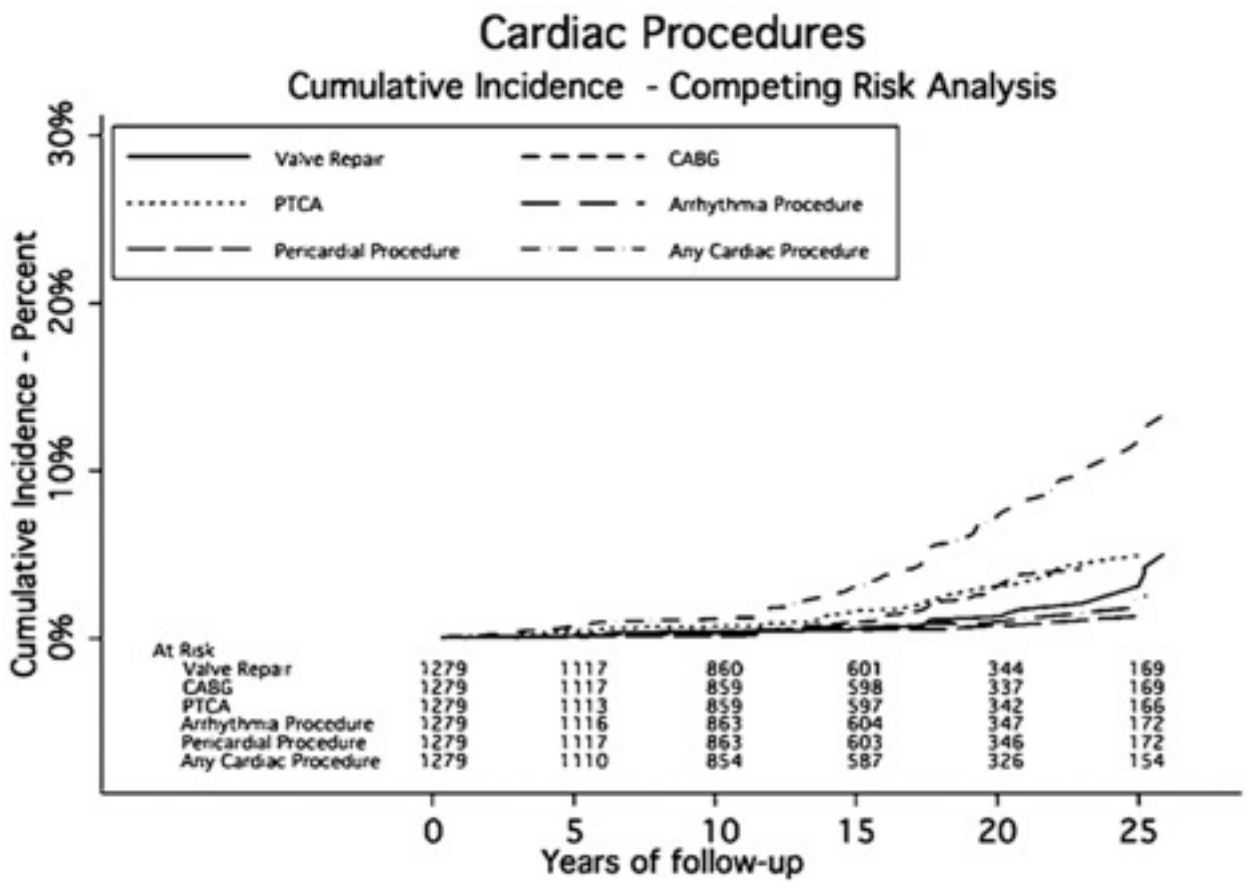


**FIGURE** Cumulative incidence rates of cardiac diagnoses1

CABG, coronary bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty. Reproduced with permission from the American Society of Hematology (ASH).

to continue effective cancer therapy and in the absence of any cardiac symptoms or abnormal physical findings, we continue cancer treatment without any serial echocardiographic monitoring.

**DH You think the NT-proBNP might be useful? I know that's excreted by the kidneys, so that might rise in renal failure, but we can adjust for that.**

**JC** The negative predictive value of having a normal BNP is helpful. I think what I wanted to say was that screening echocardiograms and looking at ejection fraction in low-risk populations probably is clearly not cost-effective. It probably never alters decision making. If you have a 30-year-old person with no cardiac risk factors and no past cardiac history who develops B-cell lymphoma and is going to get anthracycline-based chemotherapy, the likelihood of finding a reason not to give that therapy based on an echocardiogram is quite small. I would even go further and say close to zero. We've begun to look at this. There is literature that supports the concept. Also, that in low-risk people – if you can define the low-risk population in an accurate way – for lymphoma patients or women with breast cancer getting either anthracyclines, trastuzumab, or the other human epidermal growth factor receptor-2 (HER2)-directed therapies, there's probably little yield to even getting a baseline study.

**DH Very interesting. I would agree with you.**

**JC** We're going to talk about 5-FU, of course. The 5-FU thing has become a passion of mine. Over the last two to two-and-a- half years we have gotten very aggressive with treating coronary spasm that's induced by the fluoropyrimidines. That's 5-FU and capecitabine, the oral version.

There is an incidence that the literature says is less than 1%. It probably is somewhere between 3% and 5%. It's a little bit more common than has been reported. The reason is the way that it presents has classically been described in the literature as different than what occurs in real life. It is a phenomenon. It's the most common cardiac side effect. Sometimes it is large epicardial coronary artery spasm. Sometimes it's small vessel spasm. You can have chest pain with no electrocardiographic changes or ECG changes without chest pain (so-called silent ischemia). The description doesn't always sound like classic angina but symptoms are temporally related to getting the drug.

So, we've developed a protocol to treat documented spasm as an outpatient to be able to continue those drugs to their logical conclusion from an oncologic standpoint. In fact, we just submitted a manuscript to the American Journal of Cardiology describing our experience and the algorithm of how we treat people. We're uniquely aggressive in re-challenging patients who've had spasm.

**DH Finally, it occurred to me that we cause problems with radiation. We cause problems with chemotherapy and other infusions. Are there particular cancers that you think of or you're called in to see that you worry about cardiac involvement by their location? What comes to mind are cases I've had in which there is pericardial involvement and tamponade or restrictive pericarditis.**

**JC** We see metastatic disease to the pericardium with breast cancer, lung cancer, and lymphoma. Renal cell has an interesting predilection to go to the pericardium. We've seen in the last probably 6 months 2 cases of bladder cancer with pericardial metastases. When we reviewed the literature, we were only able to find 9 or 10 case reports. It's rare, but it occurs.

Fluid in the pericardium with and without tamponade is increasingly common, and because we do a better job in treating complicated cancer, people successively can receive cycles of sequential chemotherapeutic regimens – they are living longer, their cancer can get more complicated and/or resistant and with it, there's more time for metastatic disease to occur. Tamponade is a common phenomenon. We always say that at 4 o'clock on Friday we always see somebody who has tamponade. We see a lot of pericardial disease.

Then, another area of a concern is the tyrosine kinase inhibitors that can cause hypertension, which is very common. We've become pretty aggressive. The oncologists recognize the importance of being able to follow and treat blood pressures to allow patients to get these treatments. I guess we couldn't end without talking about checkpoint inhibitors and the recent lay press flurry about reporting myocarditis.

**DH I haven't personally experienced that. How common is that, and how do we watch for it?**

**JC** Personally, I've seen probably four or five people who were referred because of heart failure on checkpoint inhibitors. For each of them, there was historically something as a preexisting problem before the checkpoint inhibitor. It was coincident that with either fluid changes or blood pressure changes associated with the treatment that they had a flare-up of heart failure.

We have not seen, fortunately, the dynamics that were reported in the New England Journal of Medicine of three people with just rampant failure, incessant ventricular arrhythmias, and death.[5] There's probably some signal that may act as a cofactor. We've actually joined in a registry with Vanderbilt University in Nashville to try to understand this a little bit better.

**DH Well, certainly with the proliferation of the checkpoint inhibitors, and so many different tumors, and so much widespread use, it looks like there is a small safety signal there but still yet to be defined. How common is that, and what should we watch for?**

**JC** Actually, it's serendipitous that yesterday I was walk-

ing to the parking lot with one of the nurse practitioners who takes care of the melanoma population. She said to me, "Now, do you think that we should be getting BNP levels on everybody who is getting a checkpoint inhibitor?"

I don't think that we're there. Just the awareness to ask the right questions when you see a patient and before starting ask, is this somebody who, in the absence of a checkpoint inhibitor, could be at risk for myocardial disease? Recognize that and use the cardiology and oncology community to work together and try to make sure that you do whatever cardioprotective things you can do and to monitor them a little bit more closely. I'm not sure that everybody who is going to start a checkpoint inhibitor needs a cardiac evaluation, doesn't need an echocardiogram, and doesn't need baseline biomarkers to decide if there's a potential cardiotoxicity problem.

**DH Well certainly, you've raised my awareness. It was not something that I had been thinking of with checkpoint inhibitors. Now, I certainly would if the patient has some comorbid illness that involves the heart, maybe think about it, wait to see how these reports develop, and what you and the registry do.**

**JC** You've seen people who get this sort of immunologic reaction that they require steroids for fluid accumulation, rash, or other things that are in this constellation. I wouldn't be surprised if that group might have some subclinical myocarditis that just gets better when they get treated for the other things.

We have actually been trying to get a quick look at the left ventricle when patients on checkpoint inhibitors present with systemic, noncardiac symptoms to see if there is a cardiac signal we are missing. We have a handheld portable echocardiogram device called a Vscan (General Electric Company, Fairfield, CT). It's not much bigger than the larger cellphones that are available. We've been going to the bedside when people have the reaction and sticking the transducer on to get a feeling of what the ventricle looks like. There's a lot that we don't know. It's a fertile ground for investigation.

**DH Well, I couldn't ask you to end on a higher note than covering the checkpoint inhibitors, which are so popular and so interesting and used everywhere. We're still managing that whole concept. I want to thank you very much.**
**JC** It was a great pleasure. Thank you.

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