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The Journal of COMMUNITY and Supportive ONCOLOGY®

— RESEARCH AND REVIEWS FOR THE PRACTICE-BASED ONCOLOGY CARE TEAM —

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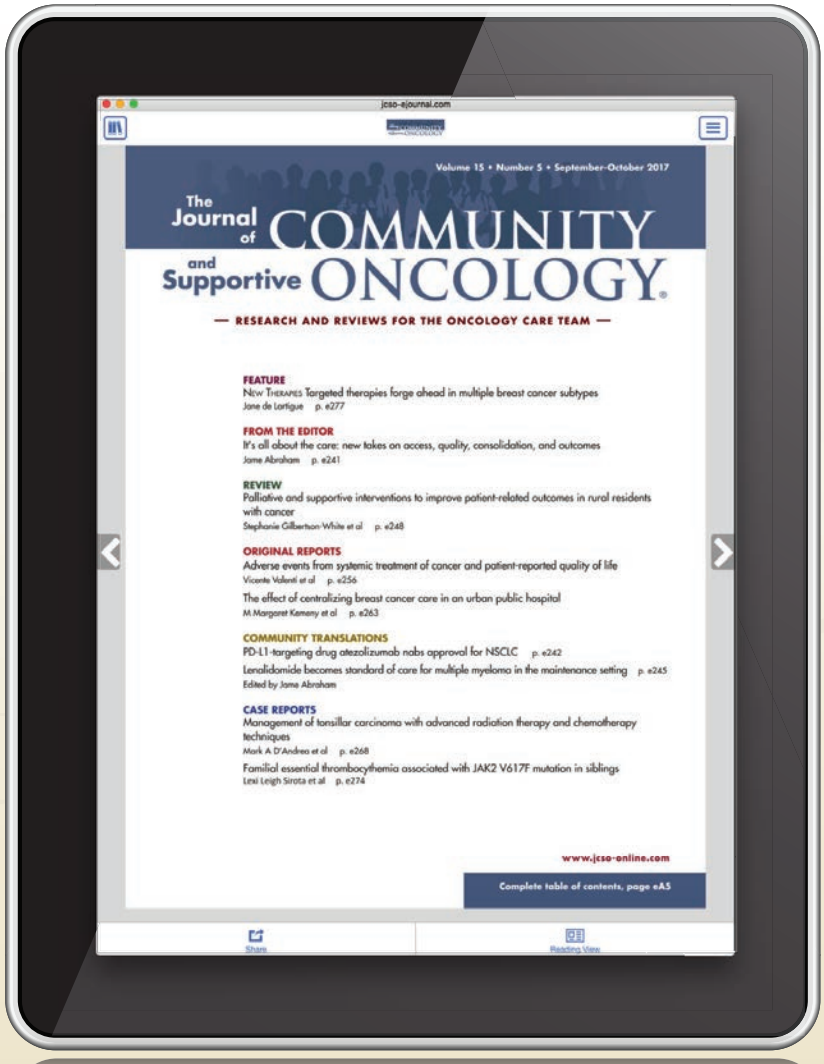

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Balancing quality and cost of care with patient well-being

Jame Abraham, MD, FACP

Welcome to the first issue of The Journal of Community and Supportive Oncology for this year. 2017 was a rollercoaster year for the oncology community, literally from day 1. January 1 saw the kick-off for participation in the MACRA [Medicare Access and CHIP Reauthorization Act] Quality Payment Program, and soon after came the growing concern and uncertainty around the future of President Barack Obama's Affordable Health Care Act. Attempts during the year to repeal the ACA failed, but with the December passage of the tax bill came Medicare cuts and the repeal of the individual mandate, which will effectively sever crucial revenue sources for the ACA. Nevertheless, against that backdrop, there was a slew of exciting therapeutic approvals – some of them landmark, as my fellow Editor, Linda Bosserman, noted in her year-end editorial (JCSO 2017;15[6]:e283-e290). As often happens, and as noted in the editorial, such advances come with concerns about the high cost of the therapies and their related toxicities, and the combined negative impact of those on quality and cost of care and patient quality of life. (QoL).

In this issue, 2 research articles examine bone metastasis in late-stage disease and their findings underscore the aforementioned importance of care cost and quality and patient QoL. Bone metastases are a common cause of pain in patients with advanced cancer. That pain is often associated with higher rates of depression, anxiety, and fatigue, and patient QoL will diminish if the pain is not adequately treated. Although radiotherapy is effective in palliating painful bone metastases, relief may be delayed and interim analgesic management needed. Garcia and colleagues (p. e8) examined the frequency of analgesic regimen assessment and intervention during radiation oncology consultations for bone metastases and evaluated the impact on analgesic management before and after implementation of a dedicated palliative radiation oncology service. They found that pain assessment and intervention were not common in the radiation oncology setting before establishment of the service and suggest that integrating palliative care within radiation oncology could improve the quality of pain management and by extension, patient well-being.

Patients with bone metastases are also at greater risk of bone fracture, for which they often are hospitalized at great cost. Nikkel and colleagues sought to determine the primary tumors in patients hospitalized with metastatic disease and who sustained pathologic and nonpathologic fractures, and to estimate the costs and lengths of stay for those hospitalizations (p. e14). The most common primary cancers in these patients were lung, breast, prostate, kidney, and colorectal – a novel finding in this study was that there were almost 4 times as many pathologic fractures from colorectal than from thyroid carcinoma. Patients hospitalized for pathologic fracture had higher billed costs and longer length of stay. The authors emphasize the importance of identifying patients at risk for pathological fracture based on primary tumor type, age, and socio-economic group; improving surveillance; and doing timely osteoporosis screening.

Therapeutic advances and the ensuing new options and combination possibilities are the substrate for our daily engagement with our patients. On page e53, Dr David Henry, the JCSO Editor-in-Chief, talks with Dr Kenneth Anderson of Harvard Medical School about advances in multiple myeloma therapies and how numerous therapy approvals have pushed the disease closer to becoming a manageable, chronic disease. On page e47, Jane de Lartigue describes the latest developments in the therapeutic targeting of altered metabolic pathways in cancer cells.

Also in this issue are new approval updates for abemaciclib as the first CDK inhibitor for breast cancer (p. e2) and the checkpoint inhibitors avelumab and durvalumab for metastatic bladder cancer (p. e5), a brief report on whether patient navigators' personal experience with cancer has any effect on patient experience (p. e43), a research article on physical activity and sedentary behavior in survivors of breast cancer, and Case Reports (pp. e30-e42).

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Abemaciclib becomes first CDK inhibitor to clinch single-agent approval for breast cancer

The fall 2017 approval by the US Food and Drug Administration (FDA) of abemaciclib made it the third cyclin-dependent kinase (CDK) inhibitor approved for the treatment of hormone receptor (HR)-positive breast cancer, and the first to receive an approved indication as monotherapy in that setting. Abemaciclib is a small-molecule inhibitor of the CDK4 and CDK6 proteins, which are key gatekeepers of the cell cycle and frequently dysregulated in HR-positive breast cancer. On the basis of the randomized, placebo-controlled, multicenter phase 3 MONARCH-2 trial, it was approved in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer who had progressed during endocrine therapy.[1]

A total of 669 women aged 18 years and older, with any menopausal status, an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) or nonmeasurable bone-only disease, were enrolled. Patients had progressed during neoadjuvant or adjuvant endocrine therapy, within 12 months of adjuvant endocrine therapy, or during frontline endocrine treatment for metastatic disease.

Those who had received more than 1 endocrine therapy or any prior chemotherapy for metastatic breast cancer or prior treatment with everolimus or CDK4/6 inhibitors, as well as those with the presence of visceral crisis or evidence or history of central nervous system (CNS) metastases, were excluded from the study.

Patients were randomized 2:1 to receive 150 mg abemaciclib or placebo, both in combination with 500 mg fulvestrant. The initial dose of abemaciclib was 200 mg, but this was amended to 150mg after enrollment of the first 178 patients to alleviate diarrhea-related toxicity concerns. Randomization was stratified according to metastatic site (visceral, bone only, or other) and endocrine therapy resistance (primary or secondary).

Tumors were measured by computed tomography (CT) and magnetic-resonance imaging (MRI) according to RECIST-1.1 within 28 days before random assignment, every 8 weeks for the first year, every 12 weeks thereafter, and then within 2 weeks of clinical progression. Bone scintigraphy was also performed at baseline and then every 6th cycle starting with cycle 7. Hematologic and blood chemistry laboratory tests were performed centrally on days 1 and 15 of the first cycle and day 1 of all remaining cycles.

The primary endpoint was progression-free survival (PFS); median PFS was 16.4 months in the abemaciclib arm, compared with 9.3 months in the placebo arm in the intent-to-treat population (hazard ratio [HR], 0.553; $P < .0000001$), translating to a 45% reduction in the risk of disease progression or death with the combination.

What's new, what's important

Based on findings from the 3 MONARCH-2 trial, the CDK inhibitor abemaciclib was approved in combination with fulvestrant for HR-positive, HER2-negative advanced or metastatic breast cancer in women who had progressed during endocrine therapy. Patients were randomized to receive 150 mg abemaciclib or placebo, both in combination with 500 mg fulvestrant. The initial dose of abemaciclib was 200 mg, but this was amended to 150 mg because of diarrhea-related toxicity concerns.

The primary endpoint was PFS. Median a PFS for abemaciclib was 16.4 months and for placebo, 9.3 months (HR, 0.553; $P < .0000001$), an effective 45% reduction in risk for progression or death with the combination. ORR among patients with measurable disease was 48.1% and 21.3%, respectively, including a CRR of 3.5% with abemaciclib. The median DoR was not yet reached in the study group (25.6 months for placebo). Overall survival data were not yet mature.

The most common adverse events experienced with abemaciclib–fulvestrant were neutropenia (23.6%) and diarrhea (13.4%). Grade 4 neutropenia was higher in the study arm compared with placebo (2.9% vs 0.4%), with 3 deaths with the combination linked to treatment-related AEs. Abemaciclib carries warnings and precautions relating to diarrhea, neutropenia, hepatotoxicity, VTE, and embryofetal toxicity. Pregnant women should be advised of the potential risk to a fetus, and those of reproductive potential should be counselled on the importance of using effective contraception during treatment and for at least 3 weeks after the last dose.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

Report prepared by Jane de Lartigue, PhD. JCSO 2018;16(1):e2–e4. ©2018 Frontline Medical Communications. doi: https://doi.org/10.12788/jcso.0378

Mechanism of action: abemaciclib

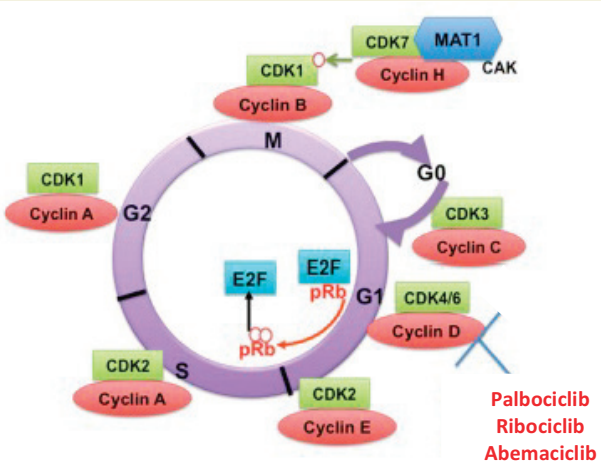
Targeting a classic hallmark of cancer. In the past several decades, characteristic alterations in cellular physiology that are essential to the transformation of a normal cell into a cancerous one, have been delineated and dubbed cancer "hallmarks." Among them is the unrestricted growth of cancer cells that is driven in part by the dysregulation of the cell cycle.

The cell cycle, the process by which cells go from a noncycling quiescent state, through stages of growth and DNA replication, to mitotic division into 2 genetically identical daughter cells, is tightly controlled by a wealth of gatekeeper proteins that ensure that it only proceeds at the appropriate time.

One key group of gatekeepers is the cyclin-dependent kinases (CDKs) and their cyclin regulators. CDK4 and CDK6, in particular, which are dependent on cyclin D for their activity, have an important role in the cell cycle. They function at the restriction point, the transition from the first growth phase (G1) to the DNA synthesis (S) phase, beyond which the cell commits to entering the cell cycle.

One of the best characterized signaling pathways downstream of CDK4/6 activation involves the retinoblastoma protein (pRb). The pRb protein forms multiprotein complexes with a number of other signaling proteins, including the E2F transcription factors, which it maintains in an inactive state. CDK4/6 phosphorylate pRb, deactivating it, removing its repression of the E2F transcription factors and therefore activating their target genes, many of which are involved in the G1-S transition.

A significant proportion of breast cancers exhibit dysregulation of the cell cycle, through the CDK4/6-cyclin D-pRb pathway, driving sustained activation of the cell cycle and, as a result, unchecked cell proliferation. This is especially true of hormone receptor (HR)-positive breast cancers, which seem to have a particular dependence on this pathway, in large part because CDK4/6 are downstream targets of estrogen receptor activation. Therefore, using small molecule inhibitors of CDK4/6 to interrupt this signaling pathway has emerged as a promising potential means of regaining control of the cell cycle and defeating breast cancer.



Cyclin-dependent kinases (CDKs) and their cyclin regulators play key roles as 'gatekeepers' of the cell cycle and their dysregulation contributes to the characteristic unrestricted growth of cancer cells. Using small-molecule inhibitors of CDKs to reestablish cell cycle control is an attractive approach to anti-cancer therapy. Reproduced under a creative commons license: Aleem E, Arceci RJ. Targeting cell cycle regulators in hematologic malignancies. Front Cell Dev Biol. 2015;3:16.

Furthermore, dysregulation of the CDK4/6 pathway has been shown to be associated with resistance to endocrine therapy, the standard of care for patients with HR-positive breast cancer. Preclinical studies demonstrated significant synergy between endocrine therapies and CDK inhibitors and this also seems to have been borne out in clinical trials. Indeed, abemaciclib is the third CDK inhibitor now on the market, which is approved in combination with fulvestrant.

Objective response rate in the 2 groups among patients with measurable disease was 48.1% and 21.3%, respectively, which included a complete response rate of 3.5% in the abemaciclib arm. The median duration of response was not yet reached in the study group, compared with 25.6 months for placebo. Overall survival data were not yet mature.

The agency also approved abemaciclib as monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. That approval was based on data from the single-arm MONARCH-1 trial of 132 patients who received 200 mg abemaciclib twice daily on a continuous schedule.[2]

Patients had adequate organ function, measurable disease per RECIST-1.1, and an ECOG performance status of 0 or 1. Patients must have progressed on or after previous endocrine therapy and have received prior treatment with at least 2 chemotherapy regimens, at least 1 of them, but no more than 2, having been administered in the metastatic setting. Exclusion criteria included prior receipt of a CDK inhibitor, major surgery within 14 days of the start of the study, and CNS metastases.

Tumor assessments were performed by CT or MRI according to RECIST-1.1 within the 4 weeks prior to the first dose of study drug and then subsequently at every other cycle. Responses were confirmed at least 4 weeks after the initial observation. The overall response rate was 19.7%, made up completely of partial responses. Median duration of response was 8.6 months, median PFS was 6 months and median OS was 17.7 months.

Adverse events

The most common adverse events experienced with the

combination of abemaciclib and fulvestrant were neutropenia (23.6%) and diarrhea (13.4%). The rate of grade 4 neutropenia was higher in the combination arm (2.9% vs 0.4%) and there were 3 deaths with the combination that were linked to treatment-related AEs. In the monotherapy trial, abemaciclib treatment most commonly caused diarrhea (90.2%), fatigue (65.2%), nausea (64.4%), decreased appetite (45.5%), and abdominal pain (38.6%). Grade 3 diarrhea and fatigue occurred in 19.7% and 12.9% of patients, respectively. Serious AEs occurred in 24.2% of patients and AEs led to treatment discontinuation in 7.6% of patients.

Warnings and precautions

Abemaciclib is marketed as Verzenio by Eli Lilly and Company. Warnings and precautions relating to diarrhea, neutropenia, hepatotoxicity, venous thromboembolism (VTE), and embryofetal toxicity are detailed in the prescribing information. In the event of diarrhea, patients should be treated with antidiarrheal therapy and should increase oral fluids and notify their health care provider. Treatment should be interrupted for grade 3 or 4 diarrhea and then resumed at a lower dose upon return to grade 1.

To guard against neutropenia, complete blood counts should be performed prior to starting therapy, every 2 weeks for the first 2 months, monthly for the subsequent 2 months, and then as clinically indicated. Treatment should be interrupted or delayed or the dose reduced for grade 3 or 4 neutropenia and patients should report episodes of fever.

Liver function tests should be performed before starting abemaciclib, every 2 weeks for the first 2 months, monthly for the next 2 months, and then as clinically indicated. For patients who develop persistent or recurrent grade 2, 3 or 4 hepatic transaminase elevation, dose interruption, reduction, discontinuation, or delay should be considered.

Patients should be monitored for signs and symptoms of VTE and pulmonary embolism, and treated appropriately. Pregnant women should be advised of the potential risk to a fetus, and those of reproductive potential should be counselled on the importance of using effective contraception during treatment and for at least 3 weeks after the last dose.[3]

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Checkpoint inhibitors forge new treatment paradigm for metastatic bladder cancer

Last spring, the US Food and Drug Administration (FDA) granted accelerated approval to 3 different immune checkpoint inhibitors for the treatment of patients with metastatic urothelial carcinoma in the second-line setting, bringing the total number of approved members of this drug class for this indication to 5.

Avelumab and durvalumab, like atezolizumab, are monoclonal antibodies that target the programmed cell death protein ligand-1 (PD-L1) and prevent it from binding to and activating the programmed cell death protein-1 (PD-1) and CD80 receptors, which transmit inhibitory signals into T cells. In this way, it is hypothesized that their use reactivates the anti-tumor immune response conducted by tumor-infiltrating T cells.

Both drugs were approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are refractory to platinum-based chemotherapy, and the approvals provide additional treatment options for this group of patients who typically have poor prognosis.[1,2]

Avelumab trial findings

The approval of avelumab was based on the urothelial cancer cohorts of the JAVELIN Solid Tumor trial, a phase 1, open-label, dose-escalation study.[3] Patients aged 18 years and older, with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (range, 0-5; 0, fully active, and 5, dead), life expectancy of at least 3 months, and cytologically or histologically confirmed metastatic or locally advanced solid tumors were eligible.

Patients were excluded from the study if they had a history of or active central nervous system metastases, had other malignancies within the previous 5 years, had undergone organ transplant, had conditions requiring immune suppression, had active HIV or hepatitis B or C infection, or had autoimmune diseases other than type 1 diabetes, vitiligo, psoriasis, or thyroid disease that does not require immunosuppressive treatment.

Patients were also required to have adequate end organ function (white blood cell count, ≥3 x 10^9 cells/L; absolute neutrophil count, ≥1.5 x 10^9 cells/L; lymphocyte count, ≥0.5 x 10^9 cells/L; platelet count, ≥100 x 10^9 platelets/L; hemoglobin, ≥9 g/dL; total bilirubin concentration, ≤1.5 x upper limit of normal [ULN] range; aspartate- and alanine- aminotransferase (ALT/AST) concentrations, ≤2.5 x ULN); and estimated creatinine clearance, >50 mL/min.

A total of 242 patients were treated with a 10 mg/kg intravenous dose of avelumab every 2 weeks until disease progression or unacceptable toxicity. Before avelumab infusion, all patients received premedication with an antihistamine and acetaminophen.

The primary endpoint was objective response rate (ORR), which was 13.3% among 226 patients followed for at least 13 weeks, including 4% complete response (CR) rate, and 16.1% among 161 patients followed for at least 6 months, including 5.6% CR rate. The median time to response was 2 months and the median response duration had not been reached at the time of data cut-off. PD-L1 expression was evaluable in 84% of patients and there was no discernable variation in the response rates according to the levels of PD-L1 expression on the tumor.

The most common adverse events (AEs) that occurred in at least 20% of patients included fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite,

What's new, what's important

The monoclonal antibodies avelumab and durvalumab were approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are refractory to platinum-based chemotherapy. Avelumab was approved on the basis of findings from the urothelial cancer cohorts of the JAVELIN Solid Tumor trial in which 242 patients were treated with a 10 mg/kg IV dose of avelumab every 2 weeks until disease progression or unacceptable toxicity. ORR was 13.3% in 226 patients followed for at least 13 weeks, including 4% CR rate, and 16.1% in 161 patients followed for at least 6 months, including 5.6% CR rate.

Durvalumab's approval was based on results from the phase 1/2 Study 1108. It was administered as an IV infusion at a dose of 10 mg/kg every 2 weeks, for up to 12 months or until disease progression or unacceptable toxicity. PD-L1 expression was evaluated before treatment using the Ventana PD-L1 (SP263) assay, which was also approved. The ORR was 17.8%, including 7 CRs (3.7%). In patients with high PD-L1 expression, the ORR was 27.6%, compared with 5.1% in those with low or no PD-L1 expression. Responses were observed across all subgroups, including patients with a poor prognosis.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

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Mechanism of action: avelumab and durvalumab

Re-establishing the anti-tumor immune response

Bladder cancer, which most often presents as urothelial carcinoma, is the most common cancer of the genitourinary system and the 5th most common type of cancer in the United States. For patients who present with metastatic disease, the standard of care is platinum-based chemotherapy, conferring a median overall survival of 9-15 months.

Unfortunately, for the large number of patients who subsequently relapse, or who are ineligible for chemotherapy because of their poor performance status, survival time is significantly shorter and few treatment options are available. Recently, immunotherapy has begun to fill that niche in bladder cancer; likely the high number of mutations in this cancer type makes it especially sensitive to this form of treatment.

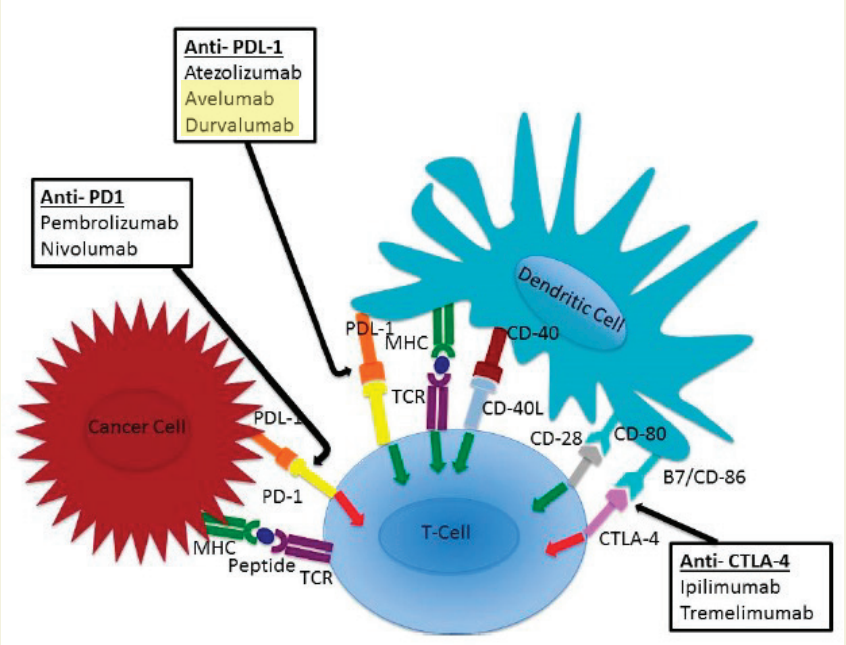
Tumors display foreign antigens on their surface as a result of these mutations and other molecular alterations, which provoke an anti-tumor immune response when they engage the major effectors of the immune system, the T cells, which patrol the body looking for abnormal or foreign cells. Tumors are able to suppress the immune system through numerous different mechanisms, and the goal of immunotherapy is to re-establish the anti-tumor immune response.

One of the best characterized mechanisms of tumor-mediated immunosuppression is the exploitation of signaling pathways that dampen T-cell activity, including the programmed cell death protein-1 (PD-1) pathway. Urothelial carcinomas often demonstrate high levels of expression of the PD-1 ligand, PD-L1, and this has been shown to correlate with more aggressive disease and poorer patient outcomes.

By expressing PD-L1, the tumor cells are in essence mimicking the signals released by healthy cells, engaging the PD-1 receptor on the surface of tumor-infiltrating T cells and sending an inhibitory signal into the cells and effectively switching them off.

The use of monoclonal antibodies that target either PD-1, such as nivolumab and pembrolizumab, or the ligand PD-L1, which include avelumab, durvalumab, and atezolizumab, has shown significant promise in the treatment of metastatic urothelial carcinoma. These antibodies block the interaction between the receptor and its ligand and help to re-establish the anti-tumor immune response by re-activating tumor-infiltrating T cells.

All 5 of these drugs are now approved by the FDA in this disease setting. Each has distinct binding properties and kinetics, which could ultimately mean they have different anti-tumor efficacy, though comparative studies have not yet been performed. As a class, they provide a much needed new treatment option for patients with this type of cancer.



Durvalumab and avelumab join atezolizumab, another PD-L1-targeting antibody and 2 PD-1-targeting drugs, nivolumab and pembrolizumab in the expanding immune checkpoint market for patients with metastatic urothelial carcinoma. These drugs block the T-cell inhibitory PD-1 pathway, reactivate tumor-infiltrating T cells, and re-establish the anti-tumor immune response.

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and urinary tract infection (UTI). Serious AEs occurred in 41% of patients and most commonly involved UTI, abdominal pain, musculoskeletal pain, creatinine increase/renal failure, dehydration, hematuria, intestinal obstruction, and pyrexia. Deaths owing to AEs occurred in 6% of patients and were related to pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal AEs.

Durvalumab approval

The agency's approval of durvalumab rested on the results of an ongoing single-arm phase 1/2 trial (Study 1108).[4] Eligibility criteria were the same as for the avelumab study. Patients were ineligible for the trial if they had received any immunotherapy within the previous 4 weeks, any monoclonal antibody within the previous 6 weeks, or had received concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy.

Durvalumab was administered as an intravenous infusion at a dose of 10 mg/kg every 2 weeks, for up to 12 months or until disease progression or unacceptable toxicity. PD-L1 expression was evaluated by immunohistochemistry in tumor tissue obtained before treatment using the Ventana PD-L1 (SP263) assay (Ventana Medical Systems), which was approved by the FDA alongside durvalumab as a companion diagnostic. The first 20 patients were enrolled regardless of their PD-L1 expression, and the subsequent 43 patients were required to have PD-L1 expression of at least 5% of their tumor cells, but that requirement was removed at an interim analysis when objective responses occurred in patients with a PD-L1 expression of less than 5%.

In the most up-to-date analysis, published after FDA approval, a total of 191 patients had been treated. The ORR as assessed by blinded independent central review per RECIST-1.1, was 17.8%, including 7 CRs (3.7%). In patients with high PD-L1 expression, the ORR was 27.6%, compared with 5.1% in those with low or no PD-L1 expression. Responses were observed across all subgroups, including patients with a poor prognosis. The ORRs in patients with visceral and liver metastases were 15.3% and 7.3%, respectively. The median time to response was 1.41 months, and the median duration of response had not yet been reached.

The most common AEs experienced by patients treated with durvalumab included fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and UTI. Serious treatment-related AEs occurred in 4.7% of patients, and treatment-related AEs leading to death occurred in 2 patients owing to autoimmune hepatitis and pneumonitis.

Toxicities and warnings for both therapies

Avelumab is marketed as Bavencio by EMD Serono, and durvalumab as Imfinzi by AstraZeneca. According to the prescribing information for both drugs, the recommended dose is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks.[5,6]

Both drugs are associated with serious or potentially life-threatening toxicities for which warnings and precautions are detailed in the prescribing information, predominantly for immune-mediated toxicities such as pneumonitis, hepatitis, colitis, nephritis, and endocrinopathy. Patients should be monitored for signs and symptoms of these toxicities and managed appropriately. Avelumab and durvalumab should both be withheld for grade 2 or higher pneumonitis, hepatitis, colitis, severe or life-threatening adrenal insufficiency, thyroid disorders or hyperglycemia, and moderate or severe nephritis or renal dysfunction.

These drugs should be permanently discontinued in the event of life-threatening or recurrent AEs. Immune-mediated pneumonitis, colitis, and hepatitis and adrenal insufficiency can be managed with corticosteroids; hypothyroidism, with hormone-replacement therapy; and hyperglycemia, with hyperglycemics or insulin.

To manage infusion-related reactions, patients should be premedicated with antihistamines and acetaminophen before the first 4 infusions and closely monitored for symptoms such as pyrexia, chills, flushing, hypotension, and dyspnea. Infusion can be interrupted or slowed for mild to moderate infusion-related reactions, but should be stopped and the drug discontinued for severe or life-threatening reactions.

Durvalumab is also associated with a risk of infection and patients should be monitored for signs and symptoms of infection and treated with anti-infectives. Durvalumab should be withheld for grade 3 infections. Patients being treated with durvalumab or avelumab should also be warned of the potential for embryofetal toxicity and advised to take appropriate precautions.

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Analgesic management in radiation oncology for painful bone metastases

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Background Radiotherapy (RT) effectively palliates bone metastases, but pain relief may be delayed and need analgesic management. National Comprehensive Cancer Network (NCCN) Guidelines for Adult Cancer Pain recommend alteration of analgesic regimen for a pain intensity rating (PIR) of ≥4/10 (range, 0-10; 0 denotes no pain and 10, worst pain imaginable).
Purpose To evaluate frequencies of analgesic regimen assessment and intervention in radiation oncology (RO) consultations for bone metastases and evaluate the impact of a dedicated palliative RO service.
Methods Investigators reviewed consultation notes for 271 patients with bone metastases who were treated at 2 cancer centers at time points before and after implementation of a palliative RO service at Center 1. The service had not been implemented at Center 2 during the study time periods. The analgesic regimen assessment rate was recorded for symptomatic patients, and the analgesic intervention rate was recorded for those with a PIR of ≥4.
Results The median PIR for painful metastases was 5 (interquartile range [IQR], 2-7), and 51% of those assessed had a PIR of ≥4. Analgesic regimen was reported for 38% of symptomatic patients. Analgesic intervention occurred for 17% of patients with a PIR of ≥4. Palliative RO service patients had higher rates of analgesic assessment (59.5% vs 33.5%, respectively; $P = .002$) and intervention (31.6% vs 9.2%, $P = .01$) compared with those not seen in the service. There was no significant difference in analgesic assessment or intervention between nondedicated palliative RO care at the 2 centers.
Limitations Retrospective design, reliance on documentation for evaluating analgesic management
Conclusions At 2 cancer centers, half of the patients with bone metastases who received RT had a PIR of ≥4, yet only a minority had analgesic assessment and intervention, indicating a need for quality improvement in RO. Integrated palliative RO care is associated with improved analgesic management in accordance with NCCN guidelines.

Bone metastases are a common cause of pain in patients with advanced cancer, with about three-quarters of patients with bone metastases experiencing pain as the dominant symptom.[1] Inadequately treated cancer pain impairs patient quality of life, and is associated with higher rates of depression, anxiety, and fatigue. Palliative radiotherapy (RT) is effective in alleviating pain from bone metastases.[4] Local field external beam radiotherapy can provide some pain relief at the site of treated metastasis in 80%-90% of cases, with complete pain relief in 50%-60% of cases.[5,6] However, maximal pain relief from RT is delayed, in some cases taking days to up to multiple weeks to attain.[7,8] Therefore, optimal management of bone metastases pain may require the use of analgesics until RT takes adequate effect.

National Comprehensive Cancer Network (NCCN) Guidelines for Adult Cancer Pain (v. 2.2015) recommend that pain intensity rating (PIR; range, 0-10, where 0 denotes no pain and 10, worst pain imaginable) be used to quantify pain for all symptomatic patients. These guidelines also recommend the pain medication regimen be assessed for all symptomatic patients. For patients with moderate or severe pain (PIR of ≥4), NCCN guidelines recommend that analgesic regimen be intervened upon by alteration of the analgesic regimen (initiating, rotating, or titrating analgesic) or consideration of referral to pain/symptom management specialty.

Previous findings have demonstrated inadequate analgesic management for cancer pain,[2,9] including within the radiation oncology (RO) clinic, suggest-

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ing that patients seen in consultation for palliative RT may experience uncontrolled pain for days to weeks before the onset of relief from RT. Possible reasons for inadequate acute pain intervention in the RO clinic may be provider discomfort with analgesic management and infrequent formal integration of palliative care within RO.[10]

Limited single-institution data from the few institutions with dedicated palliative RO services have suggested that these services improve the quality of palliative care delivery, as demonstrated by providers perceptions' of the clinical impact of a dedicated service[11] and the implementation of expedited palliative RT delivery for acute cancer pain.[12,13] To our knowledge, the impact of a dedicated palliative RO service on analgesic management for cancer pain has not been assessed.

Here, we report how often patients with symptomatic bone metastases had assessments of existing analgesic regimens and interventions at RO consultation at 2 cancer centers. Center 1 had implemented a dedicated palliative RO service in 2011, consisting of rotating attending physicians and residents as well as dedicated palliative care trained nurse practitioners and a fellow, with the service structured around daily rounds,[11] whereas Center 2 had not yet implemented a dedicated service. Using data from both centers, we assessed the impact of a palliative RO service on analgesic assessment and management in patients with bone metastases.

Methods

We searched our institutional databases for patients seen in RO consultation for bone metastases using ICD-9 code 198.5, and retrospectively reviewed consultation notes for those patients during June-July 2008, January-February 2010, January-February 2013, and June-July 2014. Those time periods were chosen as evenly spaced representative samples before and after implementation of a dedicated palliative RO service in 2011 at Center 1. Center 2 did not implement a dedicated palliative RO service in these time periods.

Within consultation notes, we recorded the following data from the History of the Present Illness section: symptoms from bone metastases (symptomatic was defined as any pain present); PIR (range, 0-10); and whether or not the preconsultation analgesic regimen was reported for symptomatic patients (including analgesic type, dosing, effectiveness, and adherence).

Documentation of the analgesic regimen in the history section of the notes was considered the proxy for analgesic regimen *assessment* at time of RO consultation. Analgesics within the Medications list, which were autopopulated in the consultation note by the electronic medical record, were recorded.

Whether or not pain was addressed with initiation or titration of analgesics for patients with a PIR of ≥4 was recorded from the Assessment and Plan portion of the notes, and that metric was considered the proxy for pain *intervention*. In addition, the case was coded as having had pain intervention if there was documentation of the patient declining recommended analgesic intervention, or the patient had been referred to a symptom management service for intervention (eg, referral to a specialty palliative care clinic), or there was recommendation for the patient to discuss uncontrolled pain with the original prescriber. A PIR of 4 was chosen as the threshold for analgesic intervention because at that level, NCCN guidelines for cancer pain state that the analgesic regimen should be titrated, whereas for a PIR of 3 or less, the guidelines recommend only consideration of titrating the analgesic. Only patients with a documented PIR were included in the pain *intervention* analysis.

Frequencies of analgesic assessment and analgesic intervention were compared using *t* tests (Wizard Pro, v1.8.5; Evan Miller, Chicago IL).

TABLE 1 Patients identified at Centers 1 and 2[a] (N = 271)

Period	Center 1, n (%)	Center 2, n (%)
Jun-Jul 2008	8 (3.0)	16 (5.9)
Jan-Feb 2010	37 (13.7)	16 (5.9)
Jan-Feb 2013	70 (25.8)	15 (5.5)
Jun-Jul 2014	85 (31.4)	24 (8.9)
Total patients	200 (73.8)	71 (26.2)

[a]The time periods were chosen as evenly spaced representative samples before and after implementation in 2011 of a dedicated palliative radiation oncology service at Center 1. The service was not implemented at Center 2.

Results

A total of 271 patients with RO consultation notes were identified at the 2 centers within the 4 time periods (Table 1). Patient characteristics included a median age of 63 years, and a median score on the Karnofsky Performance Status Scale (KPS) of 70 (range, 0-100; 100 = able to carry on normal activity and work, 0 = dead) and 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status measure (range, 1-5; 1 = fully active, able to carry on all predisease performance without restriction, 5 = dead). There were no significant differences between Center 1 and Center 2 patients for age, KPS/ECOG, cancer type, or bone metastasis site (Table 2). Ninety-two percent of all patients were reported as symptomatic from the bone metastases, and of those symptomatic patients, 62% had their PIRs recorded. Of patients who had a PIR recorded, 51% had a PIR of ≥4 at time of RO consultation. The median PIR for painful bone metastases was 5 (IQR 2-7). In all, 23% of patients at Center 1 were seen within the dedicated palliative RO service.

TABLE 2 Characteristics for patients with bone metastases treated at 2 cancer centers before and after implementation of a palliative RO service at Center 1

Characteristic	Group		Total (N = 271)
	Center 1 (n = 200)	Center 2 (n = 71)	
Median age, y (range)	64 (31-93)	62 (36-88)	63 (31-93)
Median KPS[a]/ECOG[b]	70/1	70/1	70/1
	% of 200 patients	**% of 71 patients**	**% of 271 patients**
Gender, %			
Male	51.0	59.2	53.1
Female	49.0	40.8	46.9
Primary cancer, %			
NSCLC	30.0	23.9	28.4
Breast	18.0	18.3	18.1
Prostate	13.5	18.3	14.8
RCC	7.0	8.4	7.4
Other	31.5	31.1	31.3
Bone metastasis site/s, %			
T spine	17.0	21.1	16.6
L spine	11.5	15.5	12.5
Femur	13.5	7.0	11.8
Pelvis	11.0	25.3	8.5
Multiple	28.0	15.5	25.8
Other	19.0	15.6	24.8
Bone metastasis symptomatic, %			
Yes	92.0	90.1	91.5
No	7.5	9.9	8.1
Not reported	0.5	0	0.4

ECOG, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky Performance Status Scale; NSCLC, non–small-cell lung cancer; RCC, renal cell carcinoma

[a]KPS range is 0-100, where 100 = able to carry on normal activity and work, and 0 = dead. [b]ECOG range is 1-5, where 1 = fully active, able to carry on all pre-disease performance without restriction, and 5 = dead.

Among symptomatic patients, any component of the preconsultation analgesic regimen (including analgesic type, dosing, pain response, and adherence) was documented for 37.9% of the entire cohort at RO consultation (Table 3). At Centers 1 and 2, the frequencies of analgesic regimen assessment were documented for 41.3% and 28.1%, respectively (P = .06). Among symptomatic patients, 81.5% had an opioid or nonopioid analgesic listed in the Medications section in the electronic medical record at time of consultation.

Patients seen on the dedicated palliative RO service at Center 1 had an analgesic assessment documentation rate of 59.5%, whereas the patients not seen on a palliative RO service (ie, patients seen on a nonpalliative RO service at Center 1 plus all patients at Center 2) had an assessment documentation rate of 33.5% (P = .002; Figure 1). There was no significant difference between rates of analgesic regimen assessment between patients seen at Center 2 and patients seen within nondedicated palliative RO services at Center 1 (28.1% vs 35.9%, respectively; P = .27).

In patients seen at Center 1 only, those seen on the palliative RO service had a higher documentation rate of analgesic assessment compared with those seen by other services after implementation of the dedicated service (59.5% vs 38%, respectively; P = .018). Time period (after versus before 2011) was not significantly associated with the rate of documentation of analgesic assessment at either Center 1 (after vs before 2011: 44.4% vs 31%, P = .23) or Center 2 (31.4% vs 24.1%, P = .60).

TABLE 3 Analgesic assessment

EMR section heading	All patients (N = 271)	Frequency reported: Palliative RO: Center 1 (n = 45)	Frequency reported: Nonpalliative RO: Centers 1, 2 (n = 226)
History of the present illness			
Any regimen component	37.9	59.5	33.5
Opioid type	33.5	52.4	29.6
Opioid dosing	21.4	33.3	18.9
Number of opioids	19.8	38.1	16
Nonopioid analgesics	16.5	23.8	15
Response to regimen	28.2	38.1	26.2
Adherence to regimen	8.5	16.7	6.8
Medication list			
Opioid analgesics	71.8	78.6	70.4
Nonopioid analgesics	56	73.8	52.4

Among patients with a PIR of ≥4, analgesic intervention was reported for 17.2% of patients within the entire cohort (20.8% at Center 1 and 0% at Center 2, $P = .05$). Among those with a PIR of ≥4, documentation of analgesic assessment noted in the History of the Present Illness section was associated with increased documentation of an analgesic intervention in the Assessment and Plan section (25% vs 7.3%; odds ratio [OR], 4.22; 95% confidence interval [CI], 1.1-16.0; $P = .03$).

Patients seen on the dedicated palliative RO service at Center 1 had a documented analgesic intervention rate of 31.6%, whereas the patients not seen on a palliative RO service (ie, those seen on a nonpalliative RO service at Center 1 plus all patients at Center 2) had a documented analgesic intervention rate of 9.2% ($P = .01$; Figure 2). There was no statistically significant difference between rates of documentation of an analgesic regimen intervention between patients seen at Center 2 and patients seen within nondedicated palliative RO services at Center 1 (0% vs 17.2%, respectively; $P = .07$).

Looking at only patients seen at Center 1, patients with a PIR of ≥4 seen on the dedicated palliative RO service had a nearly significant higher rate of documented analgesic interventions in the time period after implementation of the dedicate service (31.6% if seen on the dedicated service vs 12% if seen on a nondedicated service, $P = .06$).

Discussion

Multiple studies demonstrate the undertreatment of cancer pain in the outpatient setting.[2,9,14,15] At 2 cancer centers, we found that about half of patients who present for consideration of palliative RT for bone metastases had a PIR of ≥4, yet only 17% of them had documentation of analgesic intervention as recommended by NCCN guidelines for cancer pain. Underlying this low rate of appropriate intervention may be the assumption of rapid pain relief by RT. However, RT often does not begin at time of consulta-

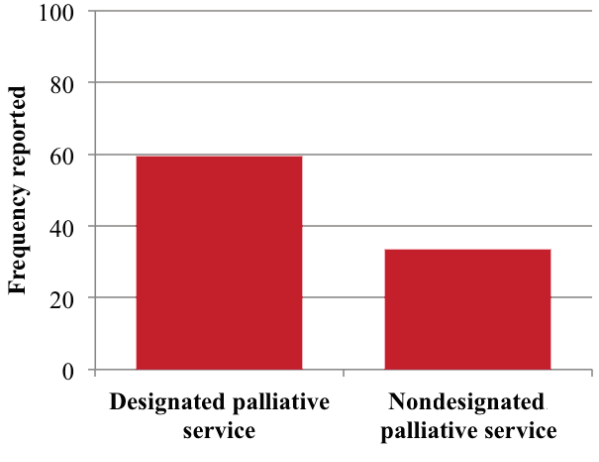

FIGURE 1 Analgesic regimen assessment documentation rates among patients seen on a designated palliative service and nondesignated palliative services.

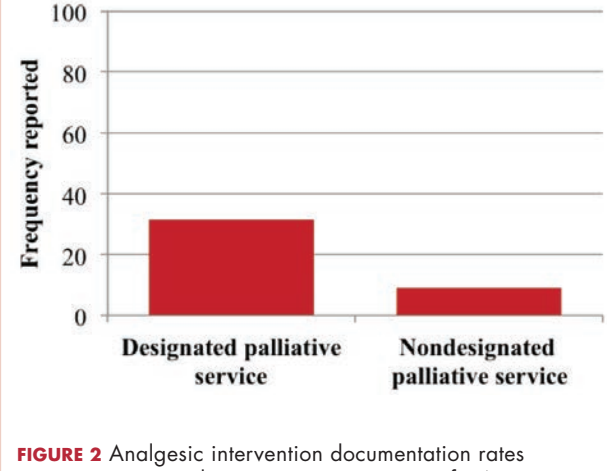

FIGURE 2 Analgesic intervention documentation rates among patients with a pain intensity rating of ≥4 seen on a designated palliative service and nondesignated palliative services.

tion,[16] and maximal pain relief may take days to weeks after commencement of RT.[17] It is estimated that a quarter of all patients with cancer develop bone metastases during the course of their disease,[12] and most of those patients suffer from pain. Thus, inherent delay in pain relief before, during, and after RT results in significant morbidity for the cancer patient population if adequate analgesic management is not provided.

The low rate of appropriate analgesic intervention at the time of RO consultation may also be related to the low incidence of proper analgesic assessment. In our cohort, 80% of symptomatic patients had an opioid or nonopioid analgesic listed in their medications within the electronic medical record at time of consultation, but only 38% had the analgesic regimen and/or its effectiveness described in the History of the Present Illness section of the record. Inattentiveness to analgesic type, dosing, and effectiveness during consultation may result in any inadequacies of the analgesic regimen going unnoticed. Consistent with this notion, we found that the rate of appropriate intervention for patients with a PIR of ≥4 was higher among patients who had analgesic regimen reported in the consultation note. Thus, interventions to implement routine review and documentation of the analgesic regimen, for example within the electronic medical record, may be one way to improve pain management.

Another possible reason for low rates of acute pain management within the RO clinic is low provider confidence in regard to analgesic management. In a recent national survey, 96% of radiation oncologists stated they were at least moderately confident with assessment of pain, yet only 77% were at least moderately confident with titrating opioids, and just 56% were at least moderately confident with rotating opioids.[10] Educational interventions that improve providers' facility with analgesic management may increase the frequency of pain management in the RO clinic.

Patients seen on the dedicated palliative RO service had significantly higher rates of documented analgesic regimen assessment and appropriate intervention during RO consultation, compared with patients seen at Center 2 and those not seen on the dedicated palliative RO service at Center 1. The improvements we observed in analgesic assessment and intervention at Center 1 for patients seen on the palliative RO service are likely owing to involvement of palliative RO and not to secular trends, because there were not similar improvements for patients at Center 1 who were not seen by the palliative RO service and those at Center 2, where there was no service.

At Center 1, the dedicated palliative RO service was created to provide specialized care to patients with metastatic disease undergoing palliative radiation. Within its structure, topics within palliative RO, such as technical aspects of palliative RT, symptom management, and communication are taught and reinforced in a case-based approach. Such palliative care awareness, integration, and education within RO achieved by the palliative RO service likely contribute to the improved rates of analgesic management we found in our study. We do note that rate of analgesic intervention in the palliative RO cohort, though higher than in the nonpalliative RO group, was still low, with only a third of patients receiving proper analgesic management. These findings highlight the importance of continued effort in increasing providers' awareness of the need to assess pain and raise comfort with analgesic initiation and titration and of having dedicated palliative care clinicians embedded within the RO setting.

Since the data for this study was acquired, Center 2 has implemented a short palliative RO didactic course for residents, which improved their comfort levels in assessing analgesic effectiveness and intervening for uncontrolled pain.[18] The impact of this intervention on clinical care will need to be evaluated, but the improved provider comfort levels may translate into better-quality care.

Limitations

An important limitation of this retrospective study is the reliance on the documentation provided in the consultation note for determining frequencies of analgesic regimen assessment and intervention. The actual rates of analgesic management that occurred in clinic may have been higher than reported in the documentation. However, such discrepancy in documentation of analgesic management would also be an area for quality improvement. Inadequate documentation limits the ability for proper follow-up of cancer pain as recommended by a joint guidance statement from the American Society of Clinical Oncology and the American Academy of Hospice and Palliative Medicine.[19,20] The results of our study may also partly reflect a positive impact in documentation of analgesic management by a dedicated palliative RO service.

Given the multi-institutional nature of this study, it may be that general practice differences confound the impact of the dedicated palliative RO service at Center 1. However, with excluding Center 2, the dedicated service was still strongly associated with a higher rate of analgesic assessment within Center 1 and was almost significantly associated with appropriate analgesic intervention within Center 1.

We used a PIR of ≥4 as a threshold for appropriate analgesic regimen intervention because it is what is recommended by the NCCN guidelines. However, close attention should be paid to the impact that any amount of pain has on an individual patient. The functional, spiritual, and existential impact of pain is unique to each patient's experience, and optimal symptom management should take those elements into account.

Conclusion

In conclusion, this study indicates that advanced cancer patient pain assessment and intervention according to NCCN cancer pain management guidelines is not common in the RO setting, and it is an area that should be targeted for quality improvement because of the positive implications for patient well-being. Pain assessment and intervention were greater in the setting of a dedicated structure for palliative care within RO, suggesting that the integration of palliative care within RO is a promising means of improving quality of pain management.

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Hospitalizations for fracture in patients with metastatic disease: primary source lesions in the United States

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Background Breast, lung, thyroid, kidney, and prostate cancers have high rates of metastasis to bone in cadaveric studies. However, bone metastasis at time of death may be less clinically relevant than occurrence of pathologic fracture and related morbidity. No population-based studies have examined the economic burden from pathologic fractures.

Objectives To determine primary tumors in patients hospitalized with metastatic disease who sustain pathologic and nonpathologic (traumatic) fractures, and to estimate the costs and lengths of stay for associated hospitalizations in patients with metastatic disease and fracture.

Methods The Healthcare Cost and Utilization Project's National (Nationwide) Inpatient Sample was used to retrospectively identify patients with metastatic disease in the United States who had been hospitalized with pathologic or nonpathologic fracture during from 2003-2010. Patients with pathologic fracture were compared with patients with nonpathologic fractures and those without fractures.

Results Of 674,680 hospitalizations of patients with metastatic disease, 17,313 hospitalizations were for pathologic fractures and 12,770 were for nonpathologic fractures. The most common primary cancers in patients hospitalized for fractures were lung (187,059 hospitalizations; 5,652 pathologic fractures; 3% of hospitalizations were for pathologic fractures), breast (124,303; 5,252; 4.2%), prostate (79,052; 2,233; 2.8%), kidney (32,263; 1,765; 5.5%), and colorectal carcinoma (172,039; 940; 0.5%). Kidney cancer had the highest rate of hospitalization for pathologic fracture (24 hospitalizations/1,000 newly diagnosed cases). Patients hospitalized for pathologic fracture had higher billed costs and longer length of stay.

Limitations Hospital administrative discharge data includes only billed charges from the inpatient hospitalization.

Conclusion Metastatic lung, breast, prostate, kidney, and colorectal carcinoma are commonly seen in patients hospitalized with pathologic fracture. Pathologic fracture is associated with higher costs and longer hospitalization.

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It has been well established that metastatic disease to bone has major significance in the morbidity associated with the diagnosis of cancer.[1] More than 75% of patients with metastatic cancer will have bone involvement at the time of death.[2-4] Moreover, there is a reported 8% incidence of a pathologic fracture in patients who carry the diagnosis of cancer.[5] Common sites of involvement include the spine, ribs, pelvis, and long bones such as humerus and femur.[6] Pathologic fracture is fracture caused by disease rather than injury or trauma (referred to here as nonpathologic). In any bone, pathologic fracture will be associated with increased morbidity for the patient, but it is the spine and long bones that frequently require surgical intervention and are associated with high mortality and morbidity. Advanced cancer can also increase fracture risk through increasing falls; in one prospective study of patients with advanced cancer, more than half the patients experienced a fall.[7]

Based on historical studies of patients who have died from common cancers,[4,6] it is commonly

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believed that breast, lung, thyroid, kidney, and prostate cancers are the most common sources of metastasis to bone, and that other common cancers, such as colorectal carcinoma (CRC), have lower rates of metastasis to bone.[6,8,9] It has been inferred from this data that cancers such as CRC thereby have lower rates of pathologic fracture.

Presence of bone metastasis at time of death may be less clinically relevant than occurrence of pathologic fracture and, especially, pathologic fracture requiring hospitalization. The authors are aware of no studies that have determined the number of patients hospitalized as a result of pathologic fracture from common tumors. Despite cadaveric findings, clinical experience dictates that colorectal carcinoma is not an uncommon primary tumor in patients presenting with metastatic disease and pathologic fracture, whereas thyroid carcinoma is more rare.

Despite lower rates of metastasis to bone from CRC, progression to advanced disease is common, with projected 50,000 deaths in the United States in 2014, and tumor progression is associated with metastasis to bone.[10] Patterns of health care use and costs associated with skeletal-related events in more common metastatic prostate and breast cancer are well documented.[11-13] The authors are aware of no population-based studies examining the burden from metastatic fractures or hospitalization incidence attributed to CRC.

Methods

This is a retrospective study of patients hospitalized in the United States with metastatic disease. Data for this study were obtained from the 2003-2010 National (Nationwide) Inpatient Sample (NIS), the Healthcare Cost and Utilization Project (HCUP), and the Agency for Healthcare Research and Quality.[14] The NIS is a stratified sample of approximately 20% of inpatient hospitalization discharges in the United States with more than 7 million hospital stays each year. The dataset contains basic patient demographics, dates of admission, discharge, and procedures, as well as diagnosis and procedure codes for unique hospitalizations. The numbers of new cases of each type of cancer diagnosed in the United States during 2003-2010 were determined from fact sheets published by the American Cancer Society.[15]

In all, 1,008,641 patients with metastatic disease in the NIS database, were identified by the presence of International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis codes 196.0-199.1. Patients were then classified by primary cancer type based on the presence of additional ICD-9-CM codes for a specific cancer type (140.x-189.x) or for a history of a specific cancer type (V10.00 – V10.91). The analysis was limited to the 10 most common types of cancer. Multiple myeloma, leukemia, lymphoma, and primary cancers of bone also cause pathologic fractures,

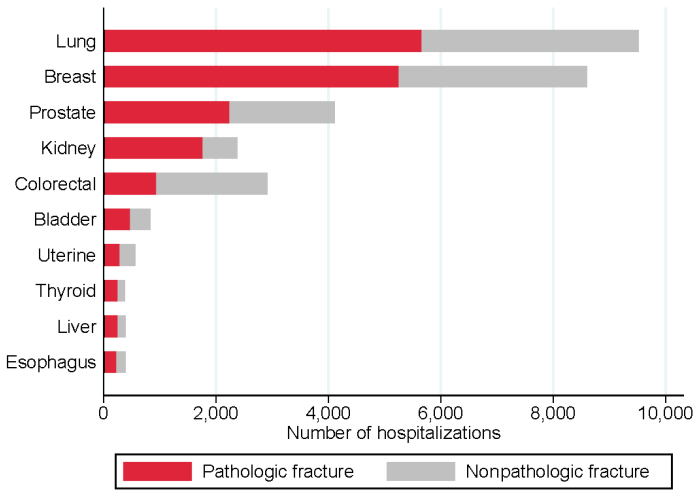

FIGURE 1 Pathologic and nonpathalogic fractures by tumor type in patients hospitalized with metastatic disease during 2003-2010.

but they were purposefully excluded from the analysis because they do not represent truly metastatic disease. Patients were excluded if they were younger than 18 years (n = 9,425), had been admitted with major significant trauma (Major Diagnostic Category 24; n = 287), or if the cancer type was either not listed in discharge billing data or not one of the 10 most common types (n = 324,249). Therefore, the final study sample consisted of 674,680 hospitalizations.

The primary outcome assessed was pathologic fracture, identified with ICD-9-CM codes 733.10-733,19. Fractures not due to bone metastasis can occur in patients with metastatic disease owing to falls and general debility; therefore, the secondary outcome was nonpathologic fracture, identified with ICD-9-CM codes for fracture (805.0-829.0) in the absence of a code for pathologic fracture. Fractures classified as a "stress fracture" (ICD-9-CM code 733.9x) or where there was a concomitant diagnosis of osteoporosis (ICD-9-CM cod 733.0x) were also considered nonpathologic for the purpose of this study. Thus there were 3 groups of hospitalized patients identified: metastatic disease without fracture (No Fracture); Pathologic Fracture; and Nonpathologic Fracture. The study was limited to the 10 types of cancer with the highest numbers of pathologic fracture, leaving 647,680 hospitalizations for analysis.

Univariate analyses comparing the Pathologic, Nonpathologic, and No Fracture groups were performed with the Student *t* test for continuous characteristics and chi-square test for categorical characteristics. All analyses were performed with use of Stata 13.1 (StataCorp, College Station, TX).

This study protocol (RSRB00055625) was reviewed by the Office for Human Subject Protection Research

TABLE 1 Hospitalizations and fractures in patients with metastatic disease in the United States, 2003-2010

Cancer type	No. of hospitalizations	No. of fractures		% hospitalizations for pathologic fracture	Estimated new cases of cancer in US 2003-2010[a]	Hospitalizations for fracture per 1,000 new cases[b]
		Pathologic	Nonpathologic			
Lung	187,059	5,652	3,870	3.0	1,563,070	18.1
Breast	124,303	5,252	3,352	4.2	1,625,910	16.2
Prostate	79,052	2,233	1,882	2.8	1,732,780	6.4
Kidney	32,263	1,765	611	5.5	364,240	24.2
Colorectal	172,039	940	1,977	0.5	1,181,450	4.0
Bladder	25,275	475	356	1.9	519,750	4.6
Uterine	16,596	280	286	1.7	415,800	3.4
Thyroid	15,258	249	125	1.6	254,230	4.9
Liver	9,427	246	140	2.6	159,550	7.7
Esophagus	13,408	221	171	1.6	122,360	9.0

[a]American Cancer Society. Cancer facts & figures. Atlanta: American Cancer Society; 2003-2010. [b]Extrapolated based on National (Nationwide) Inpatient Sample approximated 20% stratified sample of all US hospital discharges and total number of new cases of each primary tumor from the American Cancer Society statistics.

Subjects Review Board at the University of Rochester and was determined to meet exemption criteria.

Results

From 2003-2010 there were 674,680 hospitalizations in patients with metastatic cancer that met the inclusion criteria. Hospitalization was most frequent for lung cancer (187,059 admissions), colorectal cancer (172,039), and breast cancer (124,303; Table 1).

There were 17,303 hospitalizations with pathologic fracture and 12,770 hospitalizations with nonpathologic fracture (Figure 1). Among the most commonly occurring primary cancers in hospitalizations with pathologic fracture were lung, breast, prostate, kidney, and colorectal cancers (Table 1). Relative to the annual incidence,[15] kidney, lung, and breast cancer had the highest rates of hospital admission for pathologic fracture during the study period. Hospital admission with pathologic fracture was more common than nonpathologic fracture for every type of metastatic disease except colorectal and uterine cancer. Pathologic fracture in patients with metastatic disease was most likely to occur in the spine, hip, and femur (Table 2), and ratio of anatomic sites fractured was relatively consistent across each of the 10 primary malignancies (Table 3).

Demographic characteristics of patients in the 3 study groups are shown in Table 4. Patients with pathologic fracture were more likely than those in the no-fracture group to be white (63.0% vs 60.3%, respectively; $P < .001$) and female (55.5% vs 49.8%; $P < .001$), but were similar in age (66.4 years; $P = 0.7$). In-hospital mortality was lower in the pathologic fracture group compared with the no-fracture group (6.4% vs 8.8%; $P < .001$). People in the pathologic fracture group were more likely than others to be treated at a teaching hospital ($P < .001$) with ≥450 beds ($P < .001$), and reside in a zip code with higher income ($P < .01$).

Pathologic fracture hospitalizations, on average, had higher billed costs and longer length of stay ($62,974, 9.1 days; Table 4), compared with the no-fracture group ($39,576, 6.9 days; both $P < .001$) and the nonpathologic fracture group ($42,029, 7.2 days; both $P < .001$). Pathologic

TABLE 2 Number and costs of pathologic fractures by site

Fracture site	Pathologic fractures, n (%)	Mean billed costs [95% CI][a]
Spine	7,055 (40.8)	$72,067 [8,549-223,480]
Hip	4,121 (23.8)	$58,843 [13,575-149,449]
Femur	2,153 (12.4)	$59,636 [14,701-160,293]
Humerus	1,944 (11.2)	$53,849 [9,765-151,916]
Other/ unspecified	1,778 (10.3)	$52,830 [7,336-165,794]
Tibia/fibula	204 (1.2)	$53,201 [10,484-136,893]
Forearm	58 (0.3)	$54,236 [9,807-159,303]

CI, confidence interval
[a]In US$, for pathologic fractures only.

TABLE 3 Percentage of fractures at each skeletal site by primary malignancy

Skeletal site	Primary malignancy									
	Lung	Breast	Prostate	Kidney	CRC	Bladder	Uterine	Thyroid	Liver	EEsophagus
Femur	11	15.0	9.5	17.5	8.4	9.9	13.2	12.1	9.4	12.7
Forearm	0.3	0.5	0.4	0.4	0.1	0.6	0	0.4	0.4	0.9
Hip	20.9	29.2	25.6	23.2	16.7	20.4	23.2	21.7	19.9	19.5
Humerus	10.5	10.9	9.1	18.1	8.7	9.9	10.7	14.1	21.1	11.3
Other or Unspecified	12.1	9.6	10.1	8.5	9.9	14.1	11.1	9.2	10.2	11.8
Spine	44.4	34.1	44.4	30.3	55.1	42.5	38.6	42.2	38.6	43.4
Tibia/fibula	0.9	1.2	0.9	2.2	1.1	2.5	3.2	0.4	0.4	0.5

fracture in patients with thyroid, liver, and kidney cancer was associated with the highest costs of hospitalization.

In patients with metastatic disease, differences were found between those with pathologic and nonpathologic fractures: those with pathologic fracture were younger (66.4 vs 74.3 years; $P < .001$), less likely to be white (63.0% vs 69.0%; $P < .001$), and more commonly treated at a large hospital (68.4% vs 62.1%; $P < .001$) or a teaching hospital (53.5% vs 41.0%; $P < .001$).

Discussion

Other investigators have looked at risk factors for pathologic fracture, such as degree of bone involvement, location, and the presence of lytic versus blastic disease, as well as the optimal management of such patients.[16-20] In those analyses, there is an emphasis on large, lytic lesions with cortical destruction in weight-bearing long bones, and on functional pain as a key determinant of fracture risk. Although the guidelines outlined by Mirel and others are helpful in predicting fractures, they are not widely applied by practicing oncologists.[18] Oncologists and surgeons lack foolproof criteria to predict impending pathologic fracture despite evidence that the pathologic fracture event greatly increases mortality and morbidity.[1,4,21,22] As far as we know, this is the first study to determine which types of primary carcinomas were most associated with pathologic fracture requiring hospitalization. This finding will hopefully raise awareness among doctors who care for these patients to be particularly conscientious with patients who present with symptoms of bone pain with activity (functional bone pain) or with lytic disease in the long bones. The results of the present study are similar to those from cadaveric studies, which emphasize the importance of lung, breast, prostate, and kidney cancers as primary tumors that metastasize to bone and lead to pathologic fracture. A novel finding is the nearly 4-fold greater number of pathologic fractures from colorectal carcinoma than thyroid carcinoma.

The importance of detecting patients at risk for pathologic fracture is now more relevant than ever because there are treatment modalities that are readily available to patients with metastatic bone involvement. Two classes of medications, the RANK-ligand inhibitors and bisphosphonates, reduce the number of skeletal events, such as pathologic fracture, in patients with metastatic disease to bone.[23-26] However, most of those studies focused on the 3 most common carcinomas (breast, lung, and prostate) to metastasize to bone and cause pathologic fracture. There is greater variability in the prophylactic treatment of other forms of cancer that have metastasized to bone amongst oncologists.

Despite a lower proportion of hospitalizations for fracture in patients with CRC than for thyroid carcinoma (0.5% vs 1.6%, respectively), there were more pathologic fractures from CRC than from thyroid carcinoma because there are far more cases of CRC. SEER data estimate that in 2014 there were 62,000 cases of thyroid cancer and 1,890 deaths, compared with 136,000 cases of CRC and 50,000 deaths.[10] Previous findings have shown that bone metastasis from CRC is more common than originally thought, based on autopsies of CRC patients.[3] However, the lower rate of bone metastasis in CRC compared with other malignancies has led to a decreased focus on skeletal-related events in CRC. Our results suggest vigilance to bone health is warranted in patients with metastatic CRC. A novel finding is that patients with metastatic CRC also have a high number of hospital admissions for nonpathologic fracture. In establishing that patients with metastatic CRC with bone involvement have a real and significant risk of developing both pathologic and nonpathologic fractures, it may alter the treatment practice for these patients going forward, with greater consideration for an antiresorptive therapy, fall prevention education, or other preventive modalities, such as external-beam radiation therapy after it has been established that patients have metastatic bone disease.

There were some demographic differences between patients with metastatic disease who sustain pathologic

TABLE 4 Characteristics of patients with metastatic disease requiring hospital admission

Characteristic	Study group	Comparators		
	Pathologic fracture (n = 17,313)	No fracture (n = 644,597)	Nonpathologic fracture (n = 12,770)	*P*-value[a]
Age, y	66.4	66.4	74.3	.7, <.001
Female, %	55.5	49.8	62.2	<.001, <.001
Race, %				
White	63.0	60.3	69.0	<.001, <.001
Black	7.5	10.0	3.7	<.001, <.001
Hospital size (no. of beds)				<.001, <.001
Small (1-249)	10.0	12.0	12.3	
Medium (250-449)	21.7	23.1	25.5	
Large (≥450)	68.4	64.9	62.1	
Teaching hospital	53.5	47.7	41.0	<.001, <.001
Income in zip code, quartile				.007, .001
1st	24.0	24.7	21.9	
2nd	24.0	25.5	26.9	
3rd	25.5	25.0	25.7	
4th	26.5	24.8	25.5	
Died during hospitalization (%)	6.4	8.8	6.5	<.001, .02
Length of stay, days	9.1	6.9	7.2	<.001, <.001
Mean billed costs, $	62,974	39,576	42,029	<.001, <.001
Lung	63,088	41,132	43,285	<.001, .02
Breast	60,630	31,811	39,516	<.001, <.001
Prostate	54,862	32,214	39,389	<.001, <.001
Kidney	74,224	39,683	48,990	<.001, <.001
Colorectal	66,735	45,896	42,245	<.001, .007
Bladder	61,734	41,037	45,340	<.001, .1
Uterine	61,607	39,257	40,824	<.001, .6
Thyroid	78,418	35,295	47,588	<.001, .006
Liver	77,581	44,718	45,853	<.001, .8
Esophagus	61,248	$46,099	52,372	<.001, .3

[a]The 2 sets of *P*-values are for the study group compared with no fracture, and the study group compared with nonpathologic fracture.

fractures and those who do not fracture or sustain nonpathologic fractures. Patients with pathologic fracture were younger than those with nonpathologic fractures, and patients who sustained any fracture were more likely to be white than were patients in the no-fracture group. Known osteoporosis risk factors including older, female, and white with Northern European descent.[27] Those findings emphasize the importance of osteoporosis screening and fracture prevention in patients with metastatic disease in general, regardless of the presence of bony metastasis.

The present study found that patients who reside in zip codes areas with higher incomes were at slightly increased risk of hospitalization for pathologic fracture. Economic disparities in access to health care and cancer care are well documented,[28] and the basis for this finding is a direction for future research.

Both mean billed costs and length of stay were greatest in the pathologic fracture group. The large number of admissions for no-fractured patients may be a final opportunity for intervention and preventative measures

in this fragile population. Improved surveillance for bony lesions and attention to pain, especially at night, or unexplained hypercalcemia may help with early diagnosis and prevent some pathologic fractures. Patients with pathologic fracture often undergo additional treatments such as radiation therapy or chemotherapy. These additional treatments may partially explain the higher billed costs associated with inpatient hospitalization; future studies may be able to elucidate treatment differences or other reasons for the increased costs associated with pathologic fractures and identify targets to reduce expenditures.

Limitations

This study is subject to the limitations of a retrospective analysis based on hospital administrative discharge data. It evaluates only billed charges and does not account for costs associated with rehabilitation stays. However, it represents a stratified cross-sample of hospitalizations in the United States, in both teaching and nonteaching hospitals, and is the largest study to date that the authors are aware of looking at the burden of pathologic fractures in patients with metastatic disease.

This study specifically included only patients with metastatic disease, which therefore limits comparisons with the rate of hospitalization for nonpathologic fracture in patients without metastatic disease. Patients with metastatic disease who were not hospitalized during the study period are nevertheless at risk for fracture but would not have been captured in this study. It is also likely that some patients with metastatic disease had multiple hospitalizations, including some that were not for fracture; therefore, this study likely underestimates the percentage of patients with metastatic disease who sustain pathologic and nonpathologic fracture.

Some patients were excluded because we were not able to identify a primary cancer from hospital discharge records. The lack of an included diagnosis may be a result of indeterminate primary during the fracture admission or may represent a failure to accurately code a primary, known cancer. Although the NIS does not permit identification of these patients to determine if a primary cancer was subsequently identified, future studies using other databases may target patients presenting with pathologic fracture and an unknown primary tumor to evaluate subsequent cancer diagnosis.

Summary

The significance of bone metastasis in causing pathologic fractures in lung, breast, prostate, and kidney cancers was confirmed. Colorectal carcinoma has been established as the fifth most common primary cancer in patients with metastatic disease who are hospitalized with pathologic fracture, and a large number of patients with metastatic CRC sustain nonpathologic fractures requiring hospitalization. In patients with metastatic CRC or new skeletal pain, education on fall prevention and increased vigilance should be considered. Further studies are needed to determine the best method for prevention of pathologic fractures in all highly prevalent cancers, with previous hospitalizations without fracture as an appropriate target. Previous paradigms about which cancers metastasize to bone should be reconsidered in the context of which lead to clinically important fractures and hospitalization.

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Measurement of physical activity and sedentary behavior in breast cancer survivors

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Background Breast cancer survivors' self-perceived physical activity (PA) and sitting time (ST) may differ significantly from the general population and other survivor groups, so it is important that PA and ST measurement tools are compared within the breast cancer survivor population.
Objective To compare accelerometer and self-report estimates of PA and ST in breast cancer survivors.
Methods 414 breast cancer survivors (age, 56.8 years [SD, 9.2 years]; BMI, 26.2 kg/m^2 [5.4 kg/m^2]) wore an accelerometer for 7 consecutive days and completed a modified Godin Leisure-Time Exercise Questionnaire (GLTEQ), the International Physical Activity Questionnaire (IPAQ), and the Sitting Time Questionnaire (STQ) which all measured hours/minutes of activity/sitting per day. Mean differences and correlations of ST, light PA (LPA; ≤1.5 metabolic equivalents [METs]), and moderate and vigorous PA (MVPA; ≥3 METs) were compared using random-intercept mixed-effects regression models and the Spearman rank correlation coefficient (Spearman's rho [r_s], where r_s = 1 means a perfect positive correlation, and r_s = -1 means a perfect negative correlation).
Results Mean daily durations of MVPA were: accelerometer, 20.2 minutes; GLTEQ, 23.6 minutes (P_{diff} = .02); and IPAQ, 87.4 minutes (P_{diff} < .001). Correlations between accelerometer-estimated MVPA were moderate for the GLTEQ (r_s = 0.56) and poor for the IPAQ (r_s = 0.02*)*. Mean daily durations of LPA were 239.5 minutes for the accelerometer and 15.4 minutes for the GLTEQ (P_{diff} < .001); the measures were not correlated (r_s = 0.004). Mean daily durations of ST were: accelerometer, 603.9 minutes; STQ, 611.8 minutes (P_{diff} = 0.9); and IPAQ, 303.8 minutes (P_{diff} < 0.001). Correlations with the accelerometer were fair (STQ: r_s = 0.26; IPAQ: r_s = 0.30). Differences in estimates varied by disease stage, age, presence of chronic conditions, and race.
Limitations Participants were predominantly white, highly educated, and high earners, which reduced generalizability.
Conclusions Congruency of measurement was dependent on tool, intensity of activity, and participant characteristics. Target outcome, implementation context, and population should be considered when choosing a measurement for physical activity or sitting time in breast cancer survivors.
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Physical activity has numerous physical, mental, and psychosocial benefits for cancer survivors, such as a reduction in the risk of mobility disability, depression, and anxiety, and improved patient quality of life.[1,2] In addition, higher levels of physical activity are associated with reduced cancer-specific and all-causes mortality as well as cancer-specific outcomes including reduced risk of cancer progression and recurrence and new primary cancers.[3-5] However, fewer than one-third of cancer survivors are meeting government and cancer-specific recommendations of 150 minutes a week of moderate to vigorous physical activity (MPVA; ≥3 metabolic equivalents [METs]).[6,7] Growing evidence also demonstrates a significant association between higher levels of sedentary behavior and many deleterious health effects after cancer, including an increased risk for decreased physical functioning and development of other chronic diseases such as cardiovascular disease or diabetes.[8] Distinct from physical activity, sedentary behavior is defined as any waking activity resulting in low levels of energy expenditure (≤1.5 METs) while in a seated or reclined position.[9] Increased sedentary behavior, even when controlling for moderate and vigorous physical activity (MVPA), is associated with poor quality of life and increased all-cause mortality in cancer survivors.[10,11] Given the associations

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observed between higher levels of physical activity, lower levels of sedentary behavior, and improved health and disease outcomes among the large and increasing number of cancer survivors in the United States, it is important to identify low-cost methods that can be used in a in a variety of settings (ie, research, clinical, community) to accurately and efficiently measure survivors' lifestyle behaviors to identify high-risk survivors for early intervention, better understand the effects of these behaviors on survivors' health outcomes and disease trajectories, and ultimately, improve survivors' health and quality of life.[12,13]

Two methods commonly used to capture physical activity and sedentary behavior across the lifespan are accelerometry (Actigraph, Pensacola, FL) and self-report questionnaires such as the Godin Leisure-Time Questionnaire (GLTEQ), International Physical Activity Questionnaire (IPAQ), and Sitting Time Questionnaire (STQ).[14-17] Each method has unique strengths and weaknesses. Sending accelerometers to multiple individuals at a single time point can be costly, particularly in large-scale epidemiological studies, and the accelerometer's waist-worn, nonwaterproof design may prevent researchers from capturing certain activities such as swimming and resistance training. However, the accelerometer provides objective, precise assessments of most physical activities and may help remove response bias.[18] Conversely, self-report questionnaires rely solely on individuals' memories and often result in recall bias, inaccurate reporting, and under- or overestimation of physical activity engagement.[19,20] Nevertheless, these questionnaires can be widely disseminated at low cost in a variety of settings (eg, clinical, research, community) and are less of a burden to participants.

Recent studies comparing objective (eg, accelerometer) with subjective (eg, self-report) methods of measuring physical activity and sedentary behavior in healthy middle-aged adults and older adults have demonstrated mixed findings with no distinct trends in the degree to which these methods differ.[19,21,22] To date, little consideration has been given to the measurement of these lifestyle behaviors in cancer survivors. Boyle and colleagues recently investigated the concurrent validity of an accelerometer to the GLTEQ in colon cancer survivors, finding significant differences in estimated MVPA (~11 minutes). However, no studies, to our knowledge, have compared accelerometer and self-report measures in breast cancer survivors, so it remains unclear how these different measurement tools relate to each another in this population.

It is particularly important to compare these measurement tools among breast cancer survivors because evidence indicates this population's behavioral habits, self-perceived activity, and sitting time and movement patterns may differ significantly from the general population and other survivor groups across the lifespan.[23,24] Further, previous studies examining these behaviors in cancer survivors focused primarily on sitting time and MVPA.[15,25,26] Examining other lower-intensity intensities (eg, light activity or lifestyle) in cancer survivors may also be important given that increased levels of activity are associated with health benefits, ranging from reduced disability and fatigue to improved cardiovascular health and quality of life, and that breast cancer survivors engage in fewer of these activities compared with noncancer controls.[23] These lower levels of physical activity may be more prevalent among cancer survivors of their high levels of fatigue and propensity toward increased sitting time during the first year of treatment,[11] so it is important to be able to accurately assess these activities in this population. The purpose of the present study was to compare estimates of time spent in light physical activity (LPA), MVPA, and sitting time (ST) obtained from an accelerometer and 3 self-report measurement tools (GLTEQ, IPAQ, STQ) in a large, US-based sample of breast cancer survivors. A secondary purpose was to determine whether estimate comparisons among measurements changed by participant characteristics.

Methods

Participants and procedures

This study consisted of a subsample of women who participated in a larger study whose findings have been reported elsewhere by Phillips and McAuley.[27] In that study, breast cancer survivors (n = 1,631) were recruited nationally to participate in a 6-month prospective study on quality of life. Eligibility criteria included being aged 18 years or older, having had a diagnosis of breast cancer, being English speaking, and having access to the internet. Once consented to participate in the study, 500 women were randomly selected to wear the accelerometer.

Participants in this group were mailed an accelerometer, an activity log, instructions for use, and a self-addressed stamped envelope to return the monitor. They were asked to wear the accelerometer during all waking hours for 7 consecutive days of usual activity. They were also sent a secure link to complete 3 activity questionnaires online. The questionnaires were to be completed by the end of the 7-day monitoring period. Only women with $\geq$3 valid days of accelerometer data and complete data on variables of interest (n = 414) were included in the present analyses. All of the participants consented to the study procedures approved by the University of Illinois Institutional Review Board.

Measures

Demographics. The participants self-reported their age, level of education, height, and weight. Their body mass index (BMI; kg/m^2) was estimated using the standard equation. They also self-reported their health and cancer history, detailing breast cancer disease stage, time since diagnosis, treatment type, and whether they had had a cancer recurrence. They were also asked to report whether they

had ever been diagnosed (Yes/No) with 18 chronic conditions (eg, diabetes, arthritis).

Godin Leisure-Time Exercise Questionnaire.[16] The GLTEQ assessed participants' weekly frequency and mean amount of time performing MVPA (moderate exercise, such as fast walking, combined with vigorous exercise, such as jogging), and LPA (light/mild exercise, eg, easy walking) during the previous 7 days. The mean daily duration (in minutes) for each intensity category (MVPA, LPA) was calculated using activity frequencies and the amount of time spent in each activity presented as minutes/day.

The International Physical Activity Questionnaire.[14] The IPAQ evaluated participants' physical activity of at least moderate intensity in 4 domains of everyday life: job-related physical activity, transportation, housework/caring for family, and leisure-time activity. Within each domain, participants were asked the number of days per week and time per day (hours and minutes) spent performing MVPA. To estimate sitting time, the questionnaire asks participants to report the total amount of time spent sitting per day in 2 conditions, during weekdays and during weekends. The present analysis averaged sitting time for a typical 7-day (5 week days, 2 weekend days) period. We multiplied reported minutes per day and frequency per week of each activity category (MVPA and ST) to calculate the mean number of minutes per day.[29,30]

Sitting Time Questionnaire.[17,28] The STQ estimated the mean time (hours and minutes) participants spent sitting each day on weekdays and at weekends within 5 domains: while traveling to and from places, at work, watching television, using a computer at home, and at leisure, not including watching television (eg, visiting friends, movies, dining out). Mean minutes per day of ST were calculated using all sitting domains.

Actigraph accelerometer (model GT1M, Health One Technology, Fort Walton Beach, FL). The Actigraph GT1M is a reliable and objective measure of physical activity.[31-33] Participants wore the monitor on the right hip for 7 consecutive days during all waking hours, except when bathing or swimming. Activity data was analyzed in 1-minute intervals. A valid day of accelerometer wear time was defined as ≥600 minutes with no more than 60 minutes of consecutive zero-values, with allowance of ≤2 minutes of observations <100 counts/minute within the nonwear interval.[34] Each minute of wear time was classified according to intensity (counts/min) using the following cut-points:[34] sedentary, <100 counts/min; LPA, 100-2,019 counts/min; and MVPA, ≥2,020 count/min. Mean daily durations (min/day) spent in each behavior were estimated by dividing the number of minutes in each category by the number of valid days.

Statistical analysis

All statistical analyses were completed in SPSS Statistics 23 (IBM, Chicago, IL). Descriptive statistics were used to define participant characteristics. Rank-order correlation between the methods was assessed using Spearman's rho (r_s) and results were interpreted as follows: r_s = 0.10, small; 0.30, moderate; and 0.50, strong.[35] Within each activity intensity group, we jointly modeled daily minutes of self-report and accelerometer data using a random-intercept mixed-effects regression model. Differences between measurement tools were assessed based on regression coefficients with accelerometer as the reference category. Finally, we did a post hoc analysis of leisure-time–only MVPA from the IPAQ to compare with other estimates of MVPA.

We calculated the measurement tool difference scores for each estimated intensity category (ST, LPA, MVPA), that is, accelerometer estimated ST minus STQ estimated ST, and GLTEQ estimated MVPA minus IPAQ estimated MVPA. We used these data in an exploratory analysis to examine whether there were statistically significant differences between measurement difference scores by demographic or disease characteristics using linear regression stratified analyses. For example, we were interested in whether there was a significant difference in measurement tool estimates for sitting time in older compared with younger survivors. Analyses were stratified by age (<60/≥60 years), body mass index (<25 kg/m^2/≥25 kg/m^2), race (white/people of color), disease stage (I and II/III and IV), years since diagnosis (≤5 years/>5 years), recurrence (Yes/No), received chemotherapy (Yes/No), received radiation (Yes/No), and the presence of 1 or more chronic diseases (Yes/No).

Results

Participants

The mean age of the participants was 56.8 years [9.2], they were overweight (BMI, 26.2 kg/m^2 [5.4]), and pre-

TABLE 1 Participant characteristics (N = 441)

Characteristic	Value
Mean age, y (SD)	56.8 (9.2)
Mean body mass index, kg/m^2 (SD)	26.2 (5.4)
Race, % persons of color	7.5
Disease stage, % late stage	12.2
Time since diagnosis, % ≤5 y	45.6
Received chemotherapy, % Yes	54.9
Received radiation, % Yes	64.9
Recurrence, % Yes	11.1
Presence of chronic disease, (% reporting ≤1)	68.5

TABLE 2 Mean daily duration (min/d) in intensity category by measurement tool

Measurement tool	Intensity category, mean min/d (SD)		
	Sedentary	Light	Moderate and vigorous
Accelerometer	603.9 (78.0)	239.5 (61.7)	20.2 (17.8)
GLTEQ	NA	15.4 (22.3)	23.6 (23.4)
STQ	605.2 (296.2)	NA	NA
IPAQ	303.8 (163.4)	NA	87.4 (120.5)
Measurement estimate mean difference: M_{diff} [95% CI] *P*-value			
Acclerometer-GLTEQ	NA	224.5 [218.2, 230.7] $P < .001$	2.8 [-4.9, -0.9] $P = .02$
Accelerometer-IPAQ	300.1 [283.6, 317.0) $P < .001$	NA	67.4 [-78.6, -55.8] $P < .001$
Accelerometer-STQ	8.1 [-35.5, 19.4) $P = .56$	NA	NA
GLTEQ-IPAQ	NA	NA	64.6 [-76.6, -52.5] $P < .001$
IPAQ-STQ	301.5 [-330.1, -272.8] $P < .001$	NA	NA

GLTEQ, Godin Leisure-Time Exercise Questionnaire; IPAQ, International Physical Activity Questionnaire; NA, not applicable; STQ, Sitting Time Questionnaire

dominantly white (96.7%; Table 1). Table 2 provides a summary of mean daily duration of activity estimates for ST, LPA, and MVPA and the estimate mean difference scores between measurements. Also shown are the results of the stratified analyses to investigate whether congruence among the questionnaires and accelerometer measures were different based on participant characteristics for physical activity (Table 3) and ST (Table 4) estimates.

Moderate and vigorous physical activity

Accelerometer–GLTEQ. The mean difference in MVPA estimates between the accelerometer and GLTEQ was less than 5 minutes ($M_{accelerometer}$ = 20.2 minutes; M_{GLTEQ} = 23.6 minutes), even though the difference was statistically significant ($P = .02$). Estimates of MVPA from the accelerometer and GLTEQ (r_s = 0.564, $P < .001$) showed a strong relationship. Stratified analyses showed that the difference

TABLE 3 Stratified analysis of mean difference scores of physical activity minutes (Accelerometer–questionnaire) by participant characteristics

Characteristic	Measurement tool					
	GLTEQ				IPAQ	
	Level of intensity					
	Light		Moderate and vigorous		Moderate and vigorous	
	D	*P*-value	D	*P*-value	D	*P*-value
Age (≥60 y)	-18.3[a]	.005[a]	-6.8[a]	**.001[a]**	-21.9	.064
Body mass index (≥25 kg/m²)	-9.7	.127	3.9	.062	-4.7	.688
Race (person of color)	9.0	.54	4.1	.394	**47.5[a]**	**.033[a]**
Disease stage (late)	-1.8	.849	1.0	.739	**-41.8[a]**	**.018[a]**
Time since diagnosis (≤5 y)	3.6	.62	1.2	.563	16.4	.159
Treatment						
Chemotherapy (Yes)	-5.2	.422	2.5	.225	-4.9	.67
Radiation (Yes)	-6.3	.355	-0.3	.878	-14.1	.245
Recurrence (Yes)	13.8	.254	-0.04	.989	-16.8	.366
Chronic disease present (Yes, ≤1)	-12.0	.084	0.4	.849	1.7	.89

GLTEQ, Godin Leisure-Time Exercise Questionnaire; IPAQ, International Physical Activity Questionnaire

[a]Significant ($P < .05$) difference score by participant characteristic group.

scores between the GLTEQ and accelerometer were lower for older survivors (≥60 years) compared with younger survivors such that older survivors reported significantly less time in MVPA on the GLTEQ compared with accelerometer estimates (difference score [D] = 6.8 minutes less, P = .001).

Accelerometer–IPAQ. The accelerometer estimated significantly fewer minutes of MVPA per day when compared with the IPAQ (M_{diff} = -67.4; 95% confidence interval [CI], -78.6, -55.8; P < .001). Estimates of MVPA from the accelerometer and IPAQ (r_s = 0.011, P = .680) were poorly related. Differences between the IPAQ and accelerometer were greater for later-stage breast cancer, compared with early-stage diagnoses such that participants with late-stage disease reported significantly less MVPA on the IPAQ compared with accelerometer estimates (D = 41.8 minutes less than early-stage disease, P = .018). Finally, participants of color reported a greater difference in MVPA between the accelerometer and the IPAQ than did their white counterparts (D = 47.5 minutes, P = .033).

TABLE 4 Stratified analysis of mean difference score of sedentary time (Accelerometer–questionnaire) by participant characteristics

	Measurement tool			
	STQ		IPAQ	
Characteristic	**D**	**P-value**	**D**	**P-value**
Age (≥60 y)	39.8	.164	**47.6**[a]	**.006**[a]
Body mass index (≥25 kg/m²)	-53.2	.058	-27.0	.112
Race (person of color)	1.1	.984	-30.3	.502
Disease stage (late)	**-158.3**[a]	**<.001**[a]	-0.5	.985
Time since diagnosis (≤5 y)	39.9	.719	91.0	.136
Treatment				
Chemotherapy (Yes)	-18.1	.519	-12.2	.474
Radiation (Yes)	-6.6	.821	-1.3	.942
Recurrence (Yes)	33.4	.463	17.3	.515
Chronic disease present (Yes, ≤1)	7.5	.804	-19.0	.303

IPAQ, International Physical Activity Questionnaire; STQ, Sitting Time Questionnaire

[a]Significant (P < .05) difference score by participant characteristic group.

GLTEQ–IPAQ. GLTEQ estimated significantly fewer minutes of MVPA per day compared with the IPAQ (M_{diff} = -64.6; 95% CI, -76.6, -52.5; P < .001). The estimates of MVPA from the GLTEQ had a small correlation with IPAQ estimates (r_s = 0.128, P = .011).

IPAQ estimates showed almost triple the MVPA minutes per day as were estimated by the accelerometer and GLTEQ. As the MVPA estimate for the IPAQ include nonleisure activities, we conducted a post hoc analyses that only included the leisure-time items from the IPAQ. Leisure-time only IPAQ items, estimates indicated survivors spent a mean 18.5 [SD, 14.2] min/day in MVPA. Although the magnitude of the difference between the accelerometer and GLTEQ estimates (~10 minutes) was much smaller using the leisure-time only IPAQ items, a repeated measures analysis of variance revealed there was still a significant difference between these estimates (P < .05 for both) and negligible correlation.

Light intensity physical activity

Accelerometer–GLTEQ. There was a large and significant difference between LPA estimates from the GLTEQ and accelerometer (M_{diff} = 224.5; 95% CI, 218.2, 230.7; P < .001) with estimates from the accelerometer being higher than those for the GLTEQ. Additionally, the measurements showed a negligible correlation (r_s = 0.004, P = .94). Difference scores for GLTEQ and accelerometer estimated LPA were significantly different by age, with survivors aged 60 years or older demonstrating a difference that was 18.3 minutes shorter (P = .005) than the difference in younger survivors (<60 years).

Sitting time

Accelerometer–IPAQ. Mean IPAQ estimates were significantly lower (M = 303.8 [63.4]) than accelerometer estimates (M = 603.9 [78.0]). Rank-order correlations between IPAQ and accelerometer estimated ST was small (r_s =0.26, P < .001). Difference scores between IPAQ and accelerometer estimates were significantly greater for survivors who were 60 years or older, compared with those younger than 60 years (D = 47.6 minutes, P = .006), indicating that older survivors tended to self-report significantly more ST than estimated by the accelerometer.

Accelerometer–STQ. There was no significant difference in estimated mean ST minutes per day between the STQ and the accelerometer, but the correlation between estimates was low (r_s = 0.30, P < .001). Stratified analyses revealed estimates for the difference scores for mean daily ST between the STQ and accelerometer were greater for participants who were diagnosed with later-stage breast cancer (D= -158.3 minutes, P < .001) and those who had received chemotherapy (D= -61.7 minutes, P = .028; Table 2) than for those who were diagnosed with early-

stage breast cancer or had not received chemotherapy. Women who had later-stage disease reported significantly less ST than did women diagnosed with early-stage disease, when compared with estimates by the accelerometer.

IPAQ-STQ. The estimated mean ST was significantly lower for IPAQ (M = 303.8 minutes [163.4]) than for the STQ (M = 605.2 minutes [296.2]). There were no significant estimate differences among the stratified groups.

Discussion

The purpose of the present study was to compare 4 measurement tools, an accelerometer-based activity monitor and 3 self-report questionnaires, to estimate ST, LPA, and MVPA in breast cancer survivors. Developing and evaluating accurate and precise measurement tools to assess physical activity and ST in breast cancer survivors remains a critical step toward better understanding the role of physical activity in cancer survivorship. Our results indicate that the congruency of the measurement tools examined was highly dependent on the activity intensity of interest and participants' demographic or disease characteristics. Overall, the accelerometer estimated a greater amount of time spent sitting and engaging in LPA and less time in MVPA than was estimated on the STQ, GLTEQ, and IPAQ. In addition, our findings suggest significant subgroup differences that will be important in future development and implementation of physical activity measurement for breast cancer survivors.

MVPA has been the most commonly measured activity intensity among cancer survivors to date.[15,25,26] The present results indicate mean daily MVPA estimates were significantly higher for the GLTEQ compared with the accelerometer (M_{diff} = 2.8 min/d, P = .019), although the magnitude of these differences was relatively small. This difference is lower than in another study that compared these measures in colon cancer survivors and found the GLTEQ over-estimated MVPA by 10.6 min/day compared with the accelerometer (P < .01).[15] However, the correlation between the 2 tools in our study was similar to that of Boyle and colleagues (r_s = 0.56 and r_s = 0.51, respectively). A possible explanation for the equivocal findings across these studies may lie in the difference in study sample demographics; a previous study results finding breast cancer survivors may be better at recalling their physical activities because they may be more attentive to activities they perform daily.[26]

The IPAQ significantly estimated more than an hour more of MVPA minutes per day compared with the accelerometer and GLTEQ. There are a number of limitations to the reporting of MVPA on the IPAQ. These limitations have been previously reported in the literature and include cross-cultural differences as well as overreporting of nonleisure-time MVPA (eg, occupational or household activities). However, the IPAQ has consistently been shown to be a valid and reliable tool for physical activity surveillance in different populations across the world.[29,36,37] This shows that although MVPA was overestimated in our population, we do not mean to undermine the IPAQ value in other populations in which it has shown great utility for overall physical activity surveillance. When we excluded nonleisure-time MVPA, MVPA equated to about 18 min/day, which was closer in magnitude to the GLTEQ and accelerometer. These data highlight the importance of identifying the specific activity parameters of interest when selecting a measurement tool to ensure congruency between the tool and construct of interest.

The differences in MVPA estimation from the 3 tools have significant translational consequences, notably the potential for misclassification of meeting physical activity guidelines. For example, the percentage of women in the present sample that met physical activity guidelines ranged from 0% (using the accelerometer) to 19.5% (using the IPAQ), depending on the measurement tool used. These findings have meaningful implications for future physical activity assessment because multiple measurement tools are currently being used to estimate physical activity in breast cancer survivors and would provide useful information regarding how breast cancer survivors report their physical activity time.

For example, scores from the IPAQ may result in a survivor being classified as meeting physical activity guidelines when in fact they are not, and thereby missing the opportunity for intervention; or the accelerometer may classify an active survivor as inactive, which could result in using time and resources for a behavior change intervention that is not necessary. The clinical significance of these findings is to provide providers with data-based information on the strengths and limitations of the measurement tools so that they can accurately estimate physical activity and ST and appropriately optimize resources and treatments.

The degree of measurement tool congruence is likely influenced by a number of factors. First, survivors' perceptions of the intensity of their activity are relative and subjective to their state of feeling during the activity. For example, breast cancer survivors with lower functional capacity may perceive activities with lower absolute intensity as having a higher relative intensity (ie, they think they are working at a moderate intensity so record an activity as such, but the activity is classified as light by the accelerometer). Second, although our self-report measures asked survivors to record the time they had spent active over the previous 7 days, survivors might report on what they consider a "usual" week, which may reflect the ideal rather than the reality. Third, the accelerometer cut-points used were derived from young, healthy adults on a treadmill. Thus, generalization to an older, sick, less active population that could be experiencing treatment-related side effects could lead to underestimation of time spent in MVPA. To bet-

ter understand measurement congruency in breast cancer survivors, future research should investigate how functional capacity and activity intensity perceptions are influenced by a breast cancer diagnosis and how those factors may influence subjective and objective physical activity measurement. If those factors were found to have significant influence on activity in breast cancer survivors, it would warrant future development of breast-cancer–specific accelerometer reduction techniques.

The comparison of LPA presented another interesting significant contrast between self-report (GLTEQ) and accelerometry. Results indicated the GLTEQ underestimated LPA by 224.5 [3.2] min/day compared with the accelerometer. This equates to over 3.5 h/day of active time (or about 280 kcal/day) that was potentially unaccounted for by the GLTEQ. The difference between these estimates could be due to the fact that the GLTEQ was designed to measure exercise time and therefore may not be as sensitive as the accelerometer to nonexercise-related LPA. Light intensity activities typically span a large range of domains (ie, occupational, leisure time, household) and tend to occur in higher volumes than MVPA, which may lead to some challenges with recall. Expanding existing LPA questionnaires to encompass these domains would likely provide increased congruency between self-reported and accelerometer-derived estimates for LPA, as it may provide a better trigger for recalling these high volume activities. With increasing literature advocating the important role of LPA in adults' health in concert with data suggesting survivors may engage in lower levels of LPA than healthy controls,[23], accurately accounting for these lower intensity activities to provide a "whole picture" of a survivor's active day remains an important future research direction. Combining accelerometer and self-report data using ecological momentary assessment to capture these behaviors in real-time in the real world could provide a better understanding of the context in which LPA occurs as well as survivors' perceptions of intensity to build more accurate and scalable measurement tools for LPA.

Our ST results indicate nonsignificant difference estimates from the accelerometer and the STQ (M_{diff} = 1.3 [15.3] min/day) with slightly higher estimates for the STQ versus accelerometer. This finding is consistent with the one other study that has examined these relationships in cancer survivors.[15] However, our findings also indicate the IPAQ significantly underestimated ST compared with the accelerometer and the STQ by about half (Table 1). These differences may be because both the STQ and Marshall questionnaire used in the previous study measure multiple domains of sitting (ie, computer, television, travel) on both weekdays and weekends whereas the IPAQ uses only two recall items of overall sitting time (for weekday and weekend separately). The domain-specific, structured approach has been shown to improve recall and may help to prevent underestimation and general underreporting of the high volume, ubiquitous behavior of sitting.[17,38] Finally, we would be remiss to not acknowledge the known limitations to estimating ST using the count-based approach on the waist-worn accelerometer. Due to the monitor's orientation at the hip, the accelerometer may misrepresent total ST by misclassifying standing still as sitting. However, Kozey-Keadle and colleagues have previously examined estimation of ST using waist-worn accelerometers and have shown the 100 count per minute cut off yields ST estimates within 5% range of accuracy for a seated position compared with direct observation.[39]

Of further interest are our exploratory results indicating that age and disease stage may modify the congruency between activity and ST measures. Specifically, older survivors and those with more advanced disease stage generally reported more PA and less ST than were measured by the accelerometer. These differences raise the question of whether these subgroups are systematically reporting more time physically active, overestimating their intensity, or the accelerometer is misclassifying their activity intensity. These misclassifications could be due to their age, disease stage, fatigue status, functional status, cognitive function, occupational status, etc. and would be important next steps for exploration of measurement of physical activity in breast cancer survivors. Finally, the difference score for MVPA was greater for survivors of color than for white survivors, with survivors of color overreporting MVPA compared with accelerometer-derived estimates. This may be due in part to cultural differences between white survivors and survivors of color. Previous research has suggested that people of color may accumulate a majority of their activity in occupational or household-related domains, thus explaining lower levels of leisure-time MVPA but high levels of reported total MVPA from other nonleisure domains.[20] However, given the small number of survivors of color in the present study, these results should be interpreted with caution.

With the multitude of physical activity and ST measurement tools available, many factors including cost, sample size, primary outcome of interest, and activity characteristics of interest (eg, duration, intensity, energy expenditure) need to be considered[40] when choosing a tool. Our findings may help inform these decisions for breast cancer survivors. For example, if LPA is of interest, an accelerometer may provide a more comprehensive assessment of these activities than the GLTEQ. In contrast, if MVPA is the activity of interest, our results suggest the GLTEQ and accelerometer were more congruent than the IPAQ was with either measure, therefore, if budgetary constraints are a concern, the more cost-efficient GLTEQ could provide similar results to an accelerometer. In addition to considering measurement congruency, it is also critically important to carefully consider the population (breast cancer survi-

vors) and subsequent burden that accompanies the measurement tool of choice. Overall, our results indicate, when choosing a questionnaire for ST or LPA for breast cancer survivors, the more comprehensive the questions, to encompass multiple domains or time of day, the greater amount of time that will be captured within that activity category. Conversely, since the majority of MVPA is completed in leisure-time, dependent on the age and race of the population, a shorter questionnaire may be sufficient. Additionally, dependent on time since diagnosis and treatment received, activity recall or body movement patterns may be affected which could influence measurement tool selection.[23,24] Finally, it is also important to consider the setting in which measurement is taking place. In busy clinical settings, shorter, self-report measures may have a greater chance of being implemented than accelerometers or longer self-report measures and would still provide useful information regarding an overall snapshot of survivors' MVPA or ST that could be used to initiate a conversation or referral for a program to help survivors positively change one or both of these behaviors.

Limitations

There were a few limitations within the current study that should be taken into account. First, the accelerometer cut-points used were developed with healthy, young adults; therefore using different cut-points may have yielded different results.[34] Given the large age range in our participants (23-84 years), we believe the use of these cut-points was justified, in lieu of population-specific (ie, older adults) cut-points. In addition, limitations to estimating activity from an accelerometer include the inability to capture certain activities such as swimming and cycling and the aforementioned inability to distinguish between body postures (ie, sitting vs standing).[41] The participants were predominantly white, highly educated, and high earners (85.2% earned ≥$40,000 per year), therefore, the present results may not be generalizable to survivors from more diverse backgrounds. However, as far as we know, this is the first study to report the congruency of estimated ST, LPA, and MVPA across multiple measurement tools in a nationwide sample of breast cancer survivors who were heterogeneous in terms of disease characteristics (ie, stage, treatment, time since diagnosis).

Conclusions

Our findings suggest that physical activity and ST estimates in breast cancer survivors may be dependent on the measurement tool used. In addition, congruency of measurement tools was dependent on activity intensity of interest, and participant age, race, and disease history may also influence these factors. Therefore, researchers should consider the intended outcomes of interest, the context in which the tool is being used (ie, clinical versus research), the available resources, and the participant population before they select a measurement tool for estimating physical activity and sitting time in breast cancer survivors.

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Concurrent ipilimumab and CMV colitis refractory to oral steroids

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Immune checkpoint inhibitors, including anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA4) and anti-programmed cell death protein-1 (anti-PD-1) antibodies, have demonstrated clinical and survival benefits in a variety of malignancies, which has led to an expansion in their role in oncology. In melanoma, the anti-CTLA-4 antibody, ipilimumab, has demonstrated a survival benefit in patients with advanced metastatic melanoma and in patients with resectable disease with lymph node involvement.[1,2]

Ipilimumab exerts its effect by binding CTLA-4 on conventional and regulatory T cells, thus blocking inhibitory signals on T cells, which leads to an antitumor response.[3] The increased immune response counteracts the immune-evading mechanisms of the tumor. With increased use of these agents, immune-related adverse events (irAEs) have become more prevalent. The most common irAEs secondary to ipilimumab are skin rash, colitis/diarrhea, hepatitis, pneumonitis, and various endocrinopathies.[4] In a phase 3 trial of adjuvant ipilimumab in patients with resected stage III melanoma, grade 3 or 4 adverse events occurred in 54.1% of participants in the ipilimumab arm, the most common being diarrhea and colitis (9.8% and 6.8%, respectively).[2]

Recognition and management of irAEs has led to the implementation of treatment guidelines.[4,5] Management of irAEs includes checkpoint inhibitor discontinuation and reversal of the immune response by institution of immunosuppression with corticosteroids. Here we present the case of a patient with stage IIIB, BRAF V600E-positive melanoma, who developed colitis refractory to standard therapy after treatment with ipilimumab and whose clinical course was complicated by cytomegalovirus (CMV) reactivation and bowel perforation.

Case presentation and summary

A 40-year-old white woman with stage IIIB BRAF V600E-positive melanoma presented with diarrhea refractory to high-dose prednisone (1 mg/kg BID). She had recently undergone wide local excision and sentinel node biopsy and received her inaugural dose of ipilimumab (10 mg/kg).

The patient first presented with loose, watery stools that had begun 8 days after she had received her first dose of adjuvant ipilimumab. She was admitted to the hospital, and intravenous methylprednisolone was initiated along with empiric ciprofloxacin (400 mg, IVPB Q12h) and metronidazole (500 mg, IVPB Q8h) as infectious causes were concurrently ruled out. During this initial admission, the patient's stool was negative for *Clostridium difficile* toxin, ova, and parasites, as well as enteric pathogens by culture. After infectious causes were excluded, she was diagnosed with ipilimumab-induced colitis. Antibiotics were discontinued, and the patient ultimately noted improvement in her symptoms. On hospital day 7, she was experiencing only 2 bowel movements a day and was discharged on 80 mg of prednisone twice daily.

After discharge the patient noted persistence of her symptoms. At her follow-up, 9 days after discharge, the patient noted continued symptoms of low-grade diarrhea. She failed a trial of steroid tapering due to exacerbation of her abdominal pain and frequency of diarrhea. Further investigation was negative for *C. diff* toxin and a computed-tomography scan was consistent with continuing colitis. The patient's symptoms continued to worsen, with recurrence of grade 3 diarrhea, and she was ultimately readmitted 17 days after her earlier discharge (36 days after her first ipilimumab dosing).

On re-admission, the patient was again given intravenous methylprednisolone and experienced

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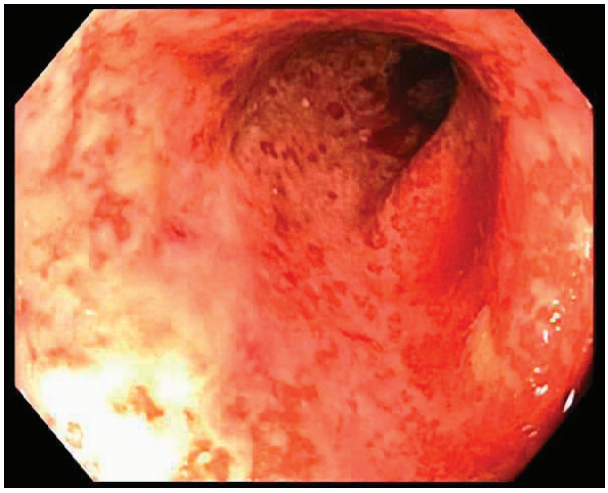

FIGURE 1 Representative image taken from sigmoidoscopy demonstrating severe inflammation by its edematous, erythematous, friable, and granulation tissue. Biopsy returned with immunohistochemical staining positive for cytomegalovirus.

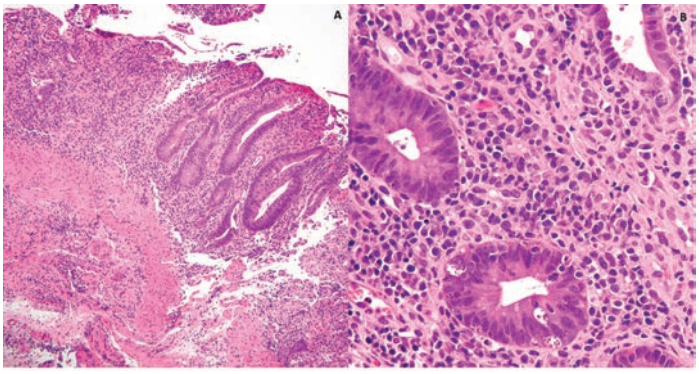

FIGURE 2 **A,** Lymphoplasmacytic expansion of the lamina propria with mild architectural disarray is present (hematoxylin and eosin, 100x). **B,** Increased intraepithelial lymphocytes and prominently increased crypt apoptosis are also identified (hematoxylin and eosin, 400x).

interval improvement in the frequency of diarrhea. A gastroenterology expert was consulted, and the patient underwent a flexible sigmoidoscopy that demonstrated findings of diffuse and severe inflammation and biopsies were obtained (Figure 1). After several days of continued symptoms, the patient received infliximab 5 mg/kg for treatment of her adverse autoimmune reaction. After administration, the patient noted improvement in the frequency and volume of diarrhea, however, her symptoms still persisted.

Biopsy results subsequently revealed findings compatible with ipilimumab-induced colitis, and immunohistochemical staining demonstrated positivity for cytomegalovirus (CMV). Specifically, histologic examination showed lymphoplasmacytic expansion of the lamina propria, some architectural distortion, and increased crypt apoptosis. Scattered cryptitis and crypt abscesses were also noted, as were rare stromal and endothelial cells with characteristic CMV inclusions (Figure 2 and Figure 3).

Serum CMV polymerase chain reaction (PCR) was also positive at 652,000 IU/mL (lower limit of detection 100 IU/mL). Induction dosing of ganciclovir (5 mg/kg IV Q12h) was initiated. The combined treatment with intravenous methylprednisone and ganciclovir led to an improvement in diarrhea frequency and resolution of blood in the stool. She was transitioned to oral prednisone, but it resulted in redevelopment of grade 3 diarrhea. The patient was therefore resumed on and discharged on daily intravenous methylprednisolone.

After discharge, the patient was started on budesonide 9 mg daily. Her serum CMV PCR level reduced and she was transitioned to oral valgancyclovir (900 mg daily) for maintenance. Another unsuccessful attempt was made to switch her to oral prednisone.

About 14 weeks after the initial ipilimumab dosing, the patient underwent another flexible sigmoidoscopy that again demonstrated severe colitis from the rectum to sigmoid colon. Biopsies were negative for CMV. Patient was readmitted for recurrence of diarrhea the following week. Treatment with IV methylprednisone (1mg/kg BID) and infliximab (5 mg/kg) again led to an improvement of symptoms. She was again discharged on IV methylprednisone (1 mg/kg BID) with a taper.

In the 15th week after her initial ipilimumab dose, the patient presented with a perforated bowel, requiring a subtotal colectomy and end ileostomy. She continued on a slow

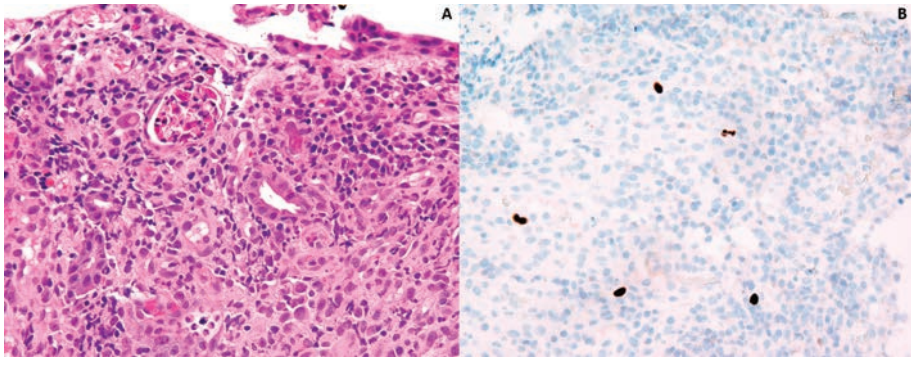

FIGURE 3 **A**, Focal crypt abscess and stromal cells with characteristic viral cytopathic effect (enlargement and cytoplasmic inclusions) are focally identified (hematoxylin and eosin, 400x). **B**, Immunohistochemical stain for cytomegalovirus highlights several scattered stromal/endothelial cells (immunohistochemical stain for CMV, 400x).

taper of oral prednisone (50 mg daily and decrease by 10 mg every 5 days).

At her last documented follow-up, 8 months after her first ipilimumab dose, she was having normal output from her ileostomy. She developed secondary adrenal insufficiency because of the long-term steroids and continued to take prednisone 5 mg daily.

Discussion

Diarrhea and colitis are common irAEs attributable to checkpoint-inhibitor therapy used for the treatment of melanoma. This case of ipilimumab-induced colitis refractory to high-dose oral steroids demonstrates the risks associated with management of anti-CTLA-4 induced colitis. In particular, the high-dose corticosteroids required to treat the autoimmune component of this patient's colitis increased her susceptibility to CMV reactivation.

The diagnosis of colitis secondary to ipilimumab is made primarily in the appropriate clinical setting, and typically onsets during the induction period (within 12 weeks of initial dosing) and most resolve within 6-8 weeks.[6] Histopathologically, there is lymphoplasmacytic expansion of lamina propria, increased intraepithelial lymphocytes, and increased epithelial apoptosis of crypts. One can also see acute cryptitis and crypt abscesses. Reactive epithelial changes with mucin depletion are also often seen in epithelial cells.

Findings from immunohistochemical studies have shown the increased intraepithelial lymphocytes to be predominantly CD8-positive T cells, while the lamina propria contains an increase in the mixture of CD4- and CD8-positive T cells. In addition, small intestinal samples show villous blunting. There is an absence of significant architectural distortion and well-developed basal lymphoplasmacytic infiltrates characteristic of chronic mucosal injury, such as idiopathic inflammatory bowel disease.[7] Granulomas are also absent in most series, though they have been reported in some cases.[8] The features are similar to those seen in autoimmune enteropathy, but goblet and endocrine cells remain preserved. Graft-versus-host disease has similar histologic features, however, the clinical setting usually makes the distinction between these obvious.

Current treatment algorithms for ipilimumab-related diarrhea, begin with immediate treatment with intravenous methylprednisolone (125 mg once). This is followed with oral prednisone at a dose of 1-2 mg/kg tapered over 4 to 8 weeks.[4] In patients with persistent symptoms despite adequate doses of corticosteroids, infliximab (5 mg/kg every 2 weeks) is recommended until the resolution of symptoms, and a longer taper of prednisone is often necessary.

Institution of high-dose corticosteroids to treat grade 3 or 4 irAEs can increase the risk for infection, including opportunistic infections. One retrospective review of patients administered checkpoint inhibitors at a single institution revealed that 7.3% of 740 patients developed a severe infection that lead to hospitalization or treatment with intravenous antibiotics.[9] In that patient cohort, only 0.6% had a serious infection secondary to a viral etiology, and 1 patient developed CMV enterocolitis. Most patients who developed an infection in this cohort had received corticosteroids (46/54 patients, 85%) and/or infliximab (13/54 patients, 24%).[9]

CMV is a member of the Herpesviridae family. After a primary infection, which can often go unrecognized in an immunocompetent host, CMV can persist in a latent state.[10] In a study by Bate and colleagues, the age-adjusted seropositivity of CMV was found to be 50.4%.[11] Based on those results, immunosuppression in a patient who has previously been infected with CMV can lead to a risk of reactivation or even reinfection. In the era of checkpoint-inhibitor therapy, reactivation of CMV has been described previously in a case of CMV hepatitis and a report of CMV colitis.[12,13] Immunosuppression, such as that caused by corticosteroids, is a risk factor for CMV infection.[14] Colitis caused by CMV usually presents with abdominal pain, diarrhea, and bloody diarrhea.[15] In suspected cases of CMV colitis, endoscopy should be pursued with biopsy for tissue examination. A tissue diagnosis is required for CMV colitis because serum PCR can be negative in isolated cases of gastrointestinal CMV infection.[15]

Conclusion

Despite appropriate treatment with ganciclovir and the noted response in the patient's serum CMV PCR, symptom exacerbation was observed with the transition to oral prednisone. The requirement for intravenous corticosteroids in the present case demonstrates the prolonged effects exerted by irAEs secondary to checkpoint-inhibitor therapy. Those effects are attributable to the design of the antibody – ipilimumab is a fully humanized monoclonal antibody and has a plasma half-life of about 15 days.[1,4]

By the identification of CMV histopathologically, this case, along with the case presented by Lankes and colleagues,[13] illustrates the importance of considering CMV colitis in patients who are being treated with ipilimumab and who develop persistent or worsening diarrhea after initial treatment with high-dose steroids.

Early recognition of possible coexistent CMV colitis in patients with a history of treatment with ipilimumab can have important clinical consequences. It can lead to quicker implementation of proper antiviral therapy and minimization of immune suppression to levels required to maintain control of the patient's symptoms.

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Recurrent head and neck cancer presenting as a large retroperitoneal mass

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Worldwide, head and neck cancers account for more than half a million cases annually and nearly 400,000 deaths.[1] Although the exact incidence of metastatic disease of these primarily squamous cell tumors is difficult to determine, the incidence is thought to be much lower than that of other solid tumors.[2] When the different sites of metastatic disease of these tumors have been studied previously, the most common have been (in descending order of frequency) the lungs, bones, liver, skin, mediastinum, and bone marrow.[2,3] It is extremely rare area for head and neck squamous cell cancers to metastasize to the retroperitoneum. To our knowledge, only 2 other such cases have been reported in the literature.[4,5] In those two cases, the metastatic recurrence occurred at 6 and 13 months after definitive treatment of the primary cancer.

Case presentation and summary

The patient in this case is a 60-year-old man with a history of stage IV moderately differentiated invasive squamous cell carcinoma (p16 negative, Bcl-2 negative, EGFR positive) of the hypopharynx that had been initially diagnosed in 2012. At that time, he underwent a total laryngectomy, partial pharyngectomy, and total thyroidectomy. A 2-centimeter mediastinal mass was also identified on a computed-tomography scan of the thorax and resected during the initial curative surgery. Final surgical pathology on the primary hypopharyngeal tumor revealed a 4.1-cm moderately differentiated squamous cell carcinoma with negative margins, but positive lymphovascular invasion (Figure 1). The 2-cm mediastinal mass also revealed the same squamous cell carcinoma as the hypopharyngeal primary. Final surgical margins were negative.

The patient went on to receive adjuvant treatment in the form of concurrent chemoradiation with cisplatin (100 mg/m^2 every 21 days for 3 doses, with 70 Gy of radiation]. After his initial treatment, he was followed closely by a multidisciplinary team, including otolaryngology, radiation oncology, and medical oncology specialists. He underwent a positron-emission tomography–CT scan 1 year after the conclusion of adjuvant therapy that showed no evidence of local or distant disease. The patient underwent 12 fiberoptic pharyngoscopy procedures over the course of 4 years without any evidence of local disease recurrence. He underwent a CT scan of the neck in October of 2016 without any evidence of local disease recurrence.

In early 2017, the patient presented with fatigue, abdominal pain, and back pain during the previous month. CT imaging revealed a left retroperitoneal mass of 8.8 x 4.0 x 6.6 cm, with bony destruction of L3-L4 causing left hydronephrosis (Figure 2 and Figure 3). Other staging work-up and imaging did not reveal any other distant disease or locoregional disease recurrence in the head and neck. Lab work was significant for an acute kidney injury that was likely secondary to mass effect from the tumor.

The mass was biopsied, with pathology revealing squamous cell carcinoma consistent with metastatic, recurrent disease from the previously known head and neck primary, and it was also p16 negative, Bcl-2 negative, and EGFR positive (Figure 4). After a multidisciplinary discussion it was determined that the best front-line treatment option would be to treat with definitive concurrent chemoradiation. However, due to the size and location of the mass, it was not possible to deliver an effective therapeutic dose of radiation without unacceptable toxicity to the adjacent structures. Therefore, palliative systemic therapy was the only option. These

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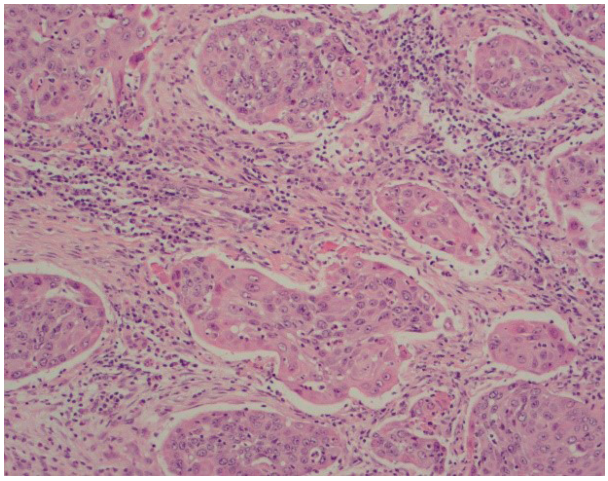

FIGURE 1 The original squamous cell carcinoma, showing invasive hypopharyngeal squamous cell carcinoma (H&E stain, 400x). Reproduced with permission from the Department of Pathology at the University of Texas Medical Branch.

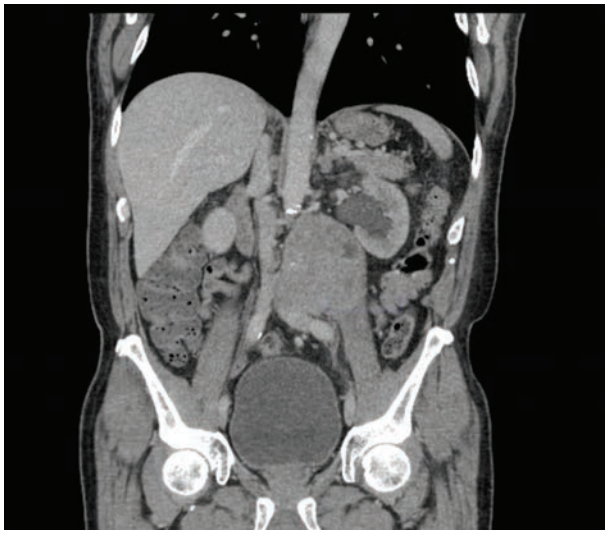

FIGURE 3 A computed-tomography scan, coronal view, show the left retroperitoneal mass, with mass effect on adjacent structure.

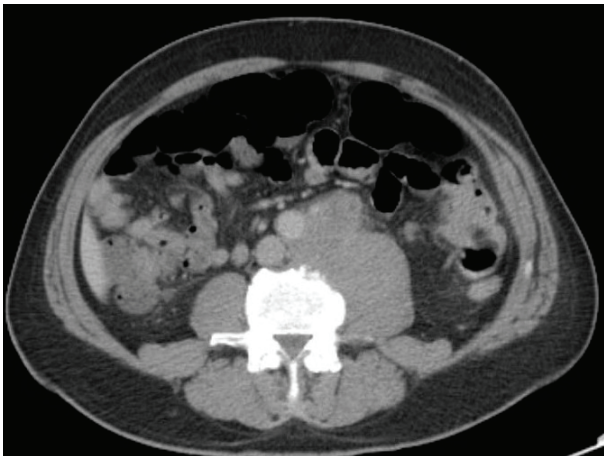

FIGURE 2 A computed-tomography scan, transverse view, showing a large left retroperitoneal mass of 8.8 x 4.0 x 6.6 cm.

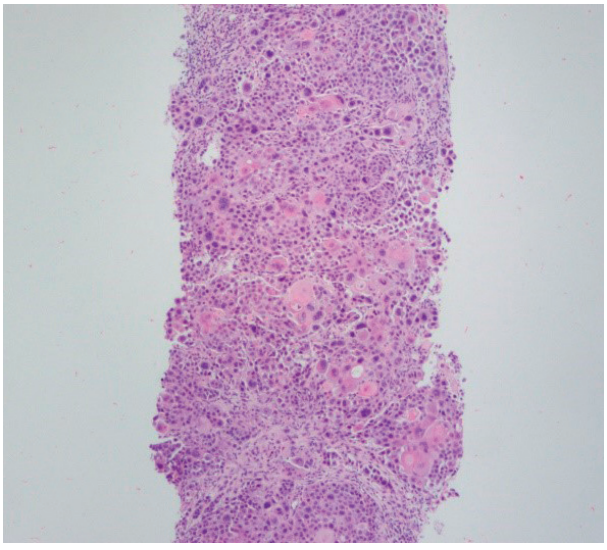

FIGURE 4 Metastatic recurrent squamous cell carcinoma from the retroperitoneal mass (H&E stain, 200x). Reproduced with permission from the Department of Pathology at the University of Texas Medical Branch.

treatment options, including systemic chemotherapy and immunotherapy, were discussed with the patient. However, he did not want to pursue any further cancer treatment and wanted instead to focus on palliation (pain control, antiemetics and nephrostomy to relieve obstruction) and hospice. He passed away 3 months later.

Discussion

Masses of the retroperitoneum have a wide differential diagnosis.[6] Primary malignancies including lymphomas, sarcomas, neurogenic tumors, and germ cell tumors may all present primarily as retroperitoneal masses.[6,7] Nonmalignant processes such as retroperitoneal fibrosis may also present in this manner.[7] Certain tumors are known to metastasize to the retroperitoneum, namely carcinomas of the gastrointestinal tract and ovary as well as lung cancer or melanoma.[5,8] Some primary retroperitoneal masses in women have been described in the literature as being HPV-associated squamous cell cancers of unknown primaries.[9]

When head and neck cancers metastasize they typically metastasize to the lungs, bone, liver, mediastinum, skin, and bone marrow. Most metastasis is pulmonary in origin, with the literature indicating it accounts for 52%-66% of head

and neck cancer metastases, with bone metastases next in frequency at 12%-22%.[2,3,10] In general, the incidence of distant metastatic disease in head and neck cancers is not as common as its other solid tumor counterparts, and even metastasis to other lymph node groups other than locoregional cervical nodes is rare.[11] Furthermore, late metastasis occurring more than 2 years after definitive treatment is also an infrequent occurrence.[12]

When discussing distant metastatic disease in head and neck cancer, previous literature has described an increasing likelihood of distant metastases when there is locoregional disease recurrence.[13] Moreover, the retroperitoneum is an exceedingly rare site of distant metastatic disease for head and neck cancer. There have been only 2 previous cases that have described this phenomenon, and in both cases the metastases occurred within or close to 1 year of definitive locoregional treatment.[4,5]

Conclusion

We present our case to present an exceedingly rare case of distant metastatic, recurrent disease from head and neck cancer to the retroperitoneum (without locoregional recurrence) that occurred 4 years after definitive treatment. We believe this to be the first case of its kind to be described when taking into consideration the site of metastases, when the metastatic recurrence occurred and that it happened without loco-regional disease recurrence. This case highlights the importance of keeping a wide differential diagnosis when encountering a retroperitoneal mass in a patient with even a remote history of head and neck cancer.

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Massive liver metastasis from colon adenocarcinoma causing cardiac tamponade

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Colorectal cancer is the third most commonly diagnosed cancer in the United States.[1] About 5% of Americans will be diagnosed with colorectal cancer in their lifetime, of which 20% will present with distant metastasis.[2] The most common sites of metastasis are regional lymph nodes, liver, lung and peritoneum, and patients may present with signs or symptoms related to disease burden at any of these organs. In this case, we present a patient with metastatic colorectal cancer to liver who developed cardiac tamponade due to extrinsic compression from an enlarging liver lesion. We are not aware of this unusual complication being reported elsewhere in the literature and we discuss our approach to this challenging case.

Case presentation and summary

A 55-year-old man had presented to an outside hospital in August of 2014 with 6 months of hematochezia and a 40-lb weight loss. He was found to be severely anemic on admission (hemoglobin, 4.9 g/dL [normal, 13-17 g/dL], hematocrit, 16% [normal, 35%-45%]). A computed-tomography (CT) scan of the abdomen and pelvis with contrast revealed a mass of 6.9 x 4.7 x 6.3 cm in the rectosigmoid colon and a mass of 10.0 x 12.0 x 10.7 cm in the right hepatic lobe consistent with metastatic disease. The patient was taken to the operating room where the rectosigmoid mass was resected completely. The liver mass was deemed unresectable because of its large size, and surgically directed therapy could not be performed. Pathology was consistent with a T3N1 moderately differentiated adenocarcinoma 11 cm from the anal verge. Further molecular tumor studies revealed wild type *KRAS* and *NRAS*, as well as a *BRAF* mutation.

About 4 weeks after the surgery, the patient was seen at our institution for an initial consultation and was noted to have significant anasarca, including 4+ pitting lower extremity edema and scrotal edema. He complained of dyspnea on exertion, which he attributed to deconditioning. His resting heart rate was found to be 123 beats per minute (normal, 60-100 bpm). Jugular venous distention was present. The patient was sent for an urgent echocardiogram, which showed external compression of the right atrium and ventricle by his liver metastasis resulting in tamponade physiology without the presence of any pericardial effusion (Figure 1). A CT of the abdomen and pelvis at that time showed that the liver mass had increased to 17.6 x 12.1 x 16.1 cm, exerting pressure on the heart and causing atelectasis of the right middle and lower lung lobes (Figure 2).

Treatment plan

The patient was evaluated by surgical oncology for resection, but his cardiovascular status placed him at high risk for perioperative complications, so such surgery was not pursued. Radioembolization was considered but not pursued because the process needed to evaluate, plan, and treat was not considered sufficiently timely. We consulted with our radiation oncology colleagues about external beam radiotherapy (EBRT) for rapid palliation. They evaluated the patient and recommended the EBRT, and the patient signed consent for treatment. We performed a CT-based simulation and generated an external beam, linear-accelerator–based treatment plan. The plan consisted of three 15-megavoltage photon fields delivering 3,000 cGy in 10 fractions to the whole liver, with appropriate multileaf collimation blocking to minimize dose to adjacent heart, right lung, and bilateral kidneys (Figure 3).

Before initiation of the EBRT, the patient received systemic chemotherapy with a dose-adjusted FOLFOX regimen (5-FU bolus 200 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, with infusional 5-FU 2,400 mg/m^2 over 46 hours).

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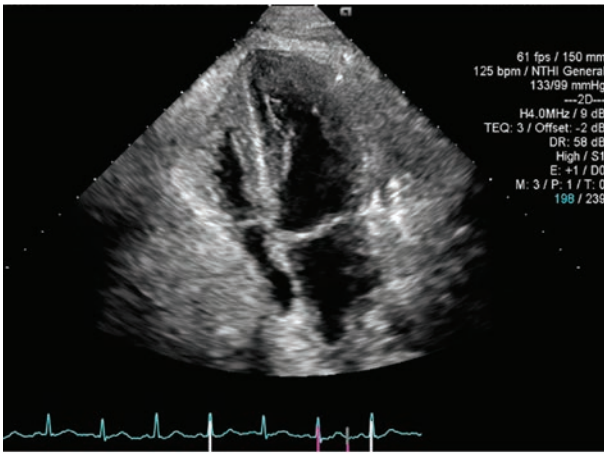

FIGURE 1 Echocardiogram showing extrinsic compression of the heart resulting in tamponade physiology.

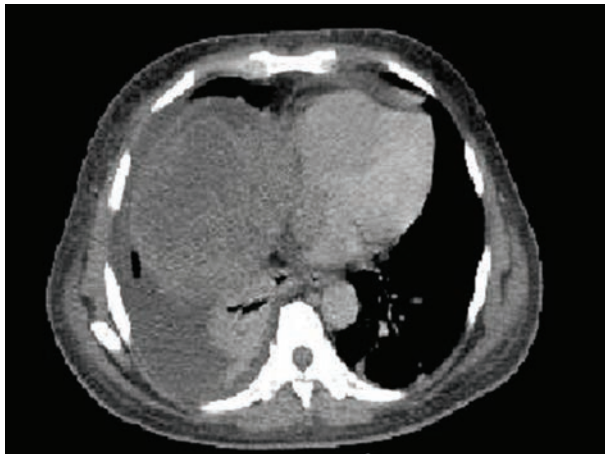

FIGURE 2 Computed-tomography scan demonstrating right middle and lower lobe atelectasis and right ventricular compression by liver mass.

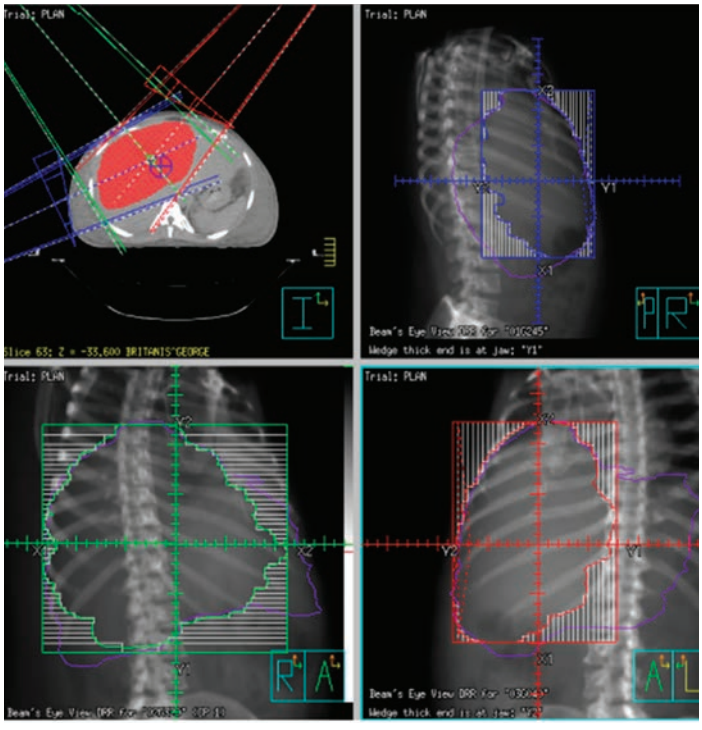

FIGURE 3 Three-field radiation treatment plan, including beam's eye views from one posterior oblique and two anterior oblique fields with blocking to minimize adjacent heart, lung, and kidney dose.

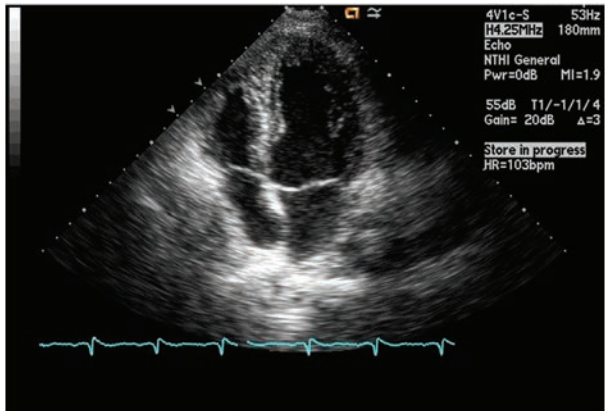

FIGURE 4 Follow-up echocardiogram showing resolution of tamponade.

After completing 1 dose of modified FOLFOX, he completed 10 fractions of whole liver radiotherapy with the aforementioned plan. He tolerated the initial treatment well and his subjective symptoms improved. The patient then proceeded to further systemic therapy. After recent data demonstrated improved median progression-free survival and response rates with FOLFOXIRI plus bevacizumab (infusional 5-FU 3200 mg/m^2, leucovorin 200 mg/m^2, irinotecan 165 mg/m^2, and oxaliplatin 85 mg/m^2, bevacizumab 5 mg/kg) versus FOLFIRI plus bevacizumab,[3] we decided to modify his systemic therapy to FOLFOXIRI with bevacizumab to induce a better response.

Treatment response

After 2 doses of chemotherapy and completion of radiotherapy, the edema and shortness of breath improved. A follow-up echocardiogram performed a month after completion of EBRT, 1 dose of FOLFOX, and 1 dose of FOLFOXIRI showed resolution of the cardiac compression (Figure 4). A CT scan of the abdomen and pelvis obtained after 3 cycles of FOLFOXIRI showed marked decrease in the size of the right lobe hepatic mass from 17.6 x 12.1 cm to 12.0 x 8.0 cm. Given the survival benefit of VEGF inhibition in colon cancer, bevacizumab (5 mg/kg) was added to the FOLFOXIRI regimen with cycle 4.

Unfortunately, after the 5th cycle, a CT scan of the abdomen showed an increase in size of the hepatic lesions. At this time, FOLFOXIRI and bevacizumab were stopped, and given the tumor's *KRAS/NRAS* wild type status, systemic therapy was changed to panitumumab (6 mg/kg). The patient initially tolerated treatment well, but after 9 cycles, the total bilirubin started to increase. CT abdomen at this point was consistent with progression of disease. The patient was not eligible for a clinical trial targeting *BRAF* mutation given the elevated bilirubin. Regorafanib (80 mg daily for 3 weeks on and 1 week off) was started. After the first cycle, the total bilirubin increased further and the regorafanib was dose reduced to 40 mg daily. Unfortunately, a repeat CT scan of the abdomen demonstrated progression of disease, and given that he developed a progressive transaminitis and hyperbilirubinemia, hospice care was recommended. The patient died shortly thereafter, about 15 months after his initial diagnosis.

Discussion

Massive liver metastasis in the setting of disseminated cancer is not an uncommon manifestation of advanced cancer that can have life-threatening consequences. In te present case, a bulky liver metastasis caused extrinsic compression of the right atrium, resulting in obvious clinical and echocardiogram-proven cardiac tamponade physiology. To our knowledge, this is the first reported case of the treatment of a bulky hepatic metastasis causing cardiac tamponade. In this patient's case, both radiotherapy and chemotherapy were given safely in rapid sequence resulting in quick resolution of the patient's symptoms and echocardiogram findings. The presence of a *BRAF* mutation conferred a poor prognosis and poor response to systemic chemotherapy. Nevertheless, the patient showed good response to a FOLFOXIRI regimen, chosen in this emergent situation given its significantly higher response rates compared with the standard FOLFIRI regimen, which was tolerated well with minimal adverse effects.

Findings from randomized controlled trials examining the role of palliative radiotherapy for metastatic liver disease have suggested that dose escalation above 30 Gy to the whole liver may lead to unacceptably high rates of radiation-induced liver disease, which typically leads to mortality.[4-8] Two prospective trials comparing twice daily with daily fractionation have shown no benefit to hyperfractionation, with possibly increased rates of acute toxicity in the setting of hepatocellular carcinoma.[9,10] There is emerging evidence that partial liver irradiation, in the appropriate setting in the form of boost after whole-liver RT or stereotactic body radiotherapy, may allow for further dose escalation while avoiding clinical hepatitis.[11] Although there is no clear consensus about optimal RT dose and fractionation, the aforementioned studies show that dose and fractionation schemes ranging between 21 Gy and 30 Gy in 1.5 Gy to 3 Gy daily fractions likely provide the best therapeutic ratio for whole-liver irradiation.

In conclusion, this case demonstrates the resolution of cardiac tamponade from a massive liver colorectal metastasis after chemoradiation and illustrates the potential utility of adding radiotherapy to chemotherapy in an urgent scenario where the former might not typically be considered.

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Cardiac pleomorphic sarcoma after placement of Dacron graft

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Primary cardiac tumors, either benign or malignant, are very rare. The combined incidence is 0.002% on pooled autopsy series.[1] The benign tumors account for 63% of primary cardiac tumors and include myxoma, the most common, and followed by papillary fibroelastoma, fibroma, and hemangioma. The remaining 37% are malignant tumors, essentially predominated by sarcomas.[1]

Although myxoma is the most common tumor arising in the left atrium, we present a case that shows that sarcoma can also arise from the same chamber. In fact, sarcomas could mimic cardiac myxoma.[2] The cardiac sarcomas can have similar clinical presentation and more importantly can share similar histopathological features. Sarcomas may have myxoid features.[2] Cases diagnosed as cardiac myxomas should be diligently worked up to rule out the presence of sarcomas with myxoid features. In addition, foreign bodies have been found to induce sarcomas in experimental animals.[3,4] In particular, 2 case reports have described sarcomas arising in association with Dacron vascular prostheses in humans.[5,6] We present here the case of a patient who was diagnosed with cardiac pleomorphic sarcoma 8 years after the placement of a Dacron graft.

Case presentation and summary

A 56-year-old woman with history of left atrial myxoma status after resection in 2005 and placement of a Dacron graft, morbid obesity, hypertension, and asthma presented to the emergency department with progressively worsening shortness of breath and blurry vision over period of 2 months. Acute coronary syndrome was ruled out by electrocardiogram and serial biomarkers. A computed-tomography angiogram was pursued because of her history of left atrial myxoma, and the results suggested the presence of a left atrial tumor. She underwent a transesophageal echocardiogram, which confirmed the presence of a large left atrial mass that likely was attached to the interatrial septum prolapsing across the mitral valve and was suggestive for recurrent left atrial myxoma (Figure 1). The results of a cardiac catheterization showed normal coronaries.

The patient subsequently underwent an excision of the left atrial tumor with profound internal and external myocardial cooling using antegrade blood cardioplegia under mildly hypothermic cardiopulmonary bypass. Frozen sections showed high-grade malignancy in favor of sarcoma. The hematoxylin and eosin stained permanent sections showed sheets of malignant pleomorphic spindle cells focally arranged in a storiform pattern. There were areas of necrosis and abundant mitotic activity. By immunohistochemical (IHC) stains, the tumor cells were diffusely positive for vimentin, and negative for pancytokeratin antibody (AE1/AE3), S-100 protein, Melan-A antibody, HMB45, CD34, CD31, myogenin, and MYOD1. IHC stains for CK-OSCAR, desmin, and smooth muscle actin were focally positive, and a ki-67 stain showed a proliferation index of about 80%. The histologic and IHC findings were consistent with a final diagnosis of high-grade undifferentiated pleomorphic sarcoma (Figure 2).

A positron emission tomography scan performed November 2013 did not show any other activity. The patient was scheduled for chemotherapy with adriamycin and ifosfamide with a plan for total of 6 cycles. Before her admission for the chemotherapy, the patient was admitted to the hospital for atrial fibrillation with rapid ventricular response and had multiple complications requiring prolonged hospitalization and rehabilitation. Repeat imaging 2 months later showed diffuse metastatic disease.

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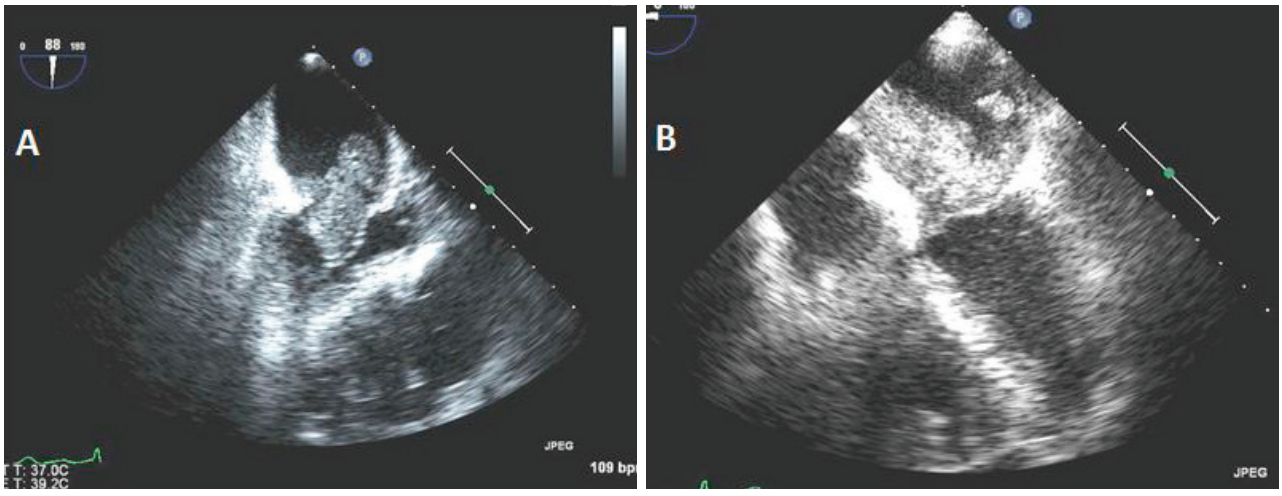

FIGURE 1 A transesophageal echocardiogram confirmed the presence of a large left atrial mass: **A,** 2 chamber view, and **B,** 4 chamber view.

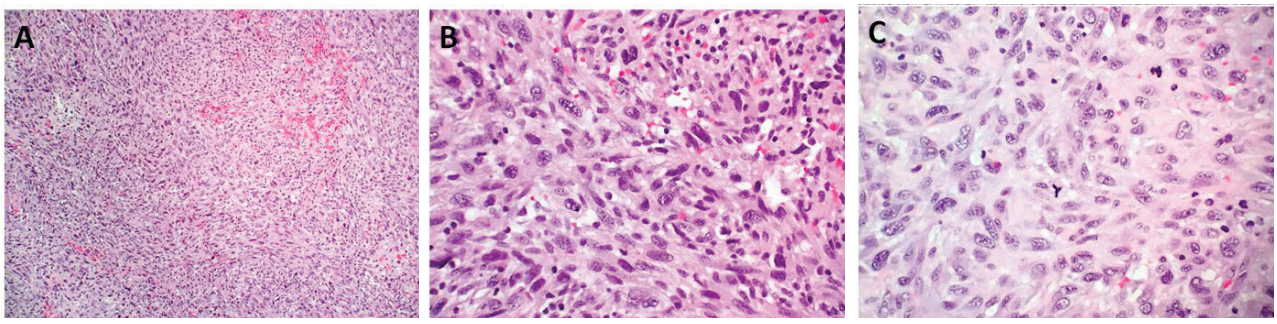

FIGURE 2 Undifferentiated pleomorphic sarcoma showing: **A,** pleomorphic spindle cells arranged in a storiform pattern (H&E, x100); **B,** markedly pleomorphic spindle cells at high magnification (H&E, x400); **C,** an atypical mitotic figure in the center (H&E, x400).

However, her performance status had declined and she was not eligible for chemotherapy. She was placed under hospice care.

Discussion

This case demonstrates development of a cardiac pleomorphic sarcoma, a rare tumor, after placement of a Dacron graft. Given that foreign bodies have been found to induce sarcomas in experimental animals,[3,4] and a few case reports have described sarcomas arising in association with Dacron vascular prostheses, [5-10] it seems that an exuberant host response around the foreign body might represent an important intermediate step in the development of the sarcoma.

There is no clearly defined pathogenesis that explains the link between a Dacron graft and sarcomas. In 1950s, Oppenheimer and colleagues described the formation of malignant tumors by various types of plastics, including Dacron, that were embedded in rats. [3,4] Most of the tumors were some form of sarcomas. It was inferred that physical properties of the plastics may have some role in tumor development. Plastics in sheet form or film that remained in situ for more than 6 months induced significant number of tumors compared with other forms such as sponges, films with holes, or powders.[3,4] The 3-dimensional polymeric structure of the Dacron graft seems to play a role in induction of sarcoma as well. A pore diameter of less than 0.4 mm may increase tumorigenicity.[11] The removal of the material before the 6-months mark does not lead to malignant tumors, which further supports the link between Dacron graft and formation of tumor. A pocket is formed around the foreign material after a certain period, as has been shown in histologic studies as the site of tumor origin.[9,10]

At the molecular level, the MDM-2/p53 pathway has been cited as possible mechanism for pathogenesis of intimal sarcoma.[12,13] It has been suggested that endothelial dysplasia occurs as a precursor lesion in these sarcomas.[14] The Dacron graft may cause a dysplastic effect on the

endothelium leading to this precursor lesion and in certain cases transforming into sarcoma. Further definitive studies are required.

The primary treatment for cardiac sarcoma is surgical removal, although it is not always feasible. Findings in a Mayo clinic study showed that the median survival was 17 months for patients who underwent complete surgical excision, compared with 6 months for those who complete resection was not possible.[15] In addition, a 10% survival rate at 1 year has been reported in primary cardiac sarcomas that are treated without any type of surgery.[16]

There is no clear-cut evidence supporting or refuting adjuvant chemotherapy for cardiac sarcoma. Some have inferred a potential benefit of adjuvant chemotherapy although definitive conclusions cannot be drawn. The median survival was 16.5 months in a case series of patients who received adjuvant chemotherapy, compared with 9 months and 11 months in 2 other case series.[17,18,19] Multiple chemotherapy regimens have been used in the past for treatment. A retrospective study by Llombart-Cussac colleagues, analyzed 15 patients who had received doxorubicin-containing chemotherapy, in most cases combined with ifosfamide or dacarbazine. [20] Resection was complete in 6 patients and incomplete in 9. The patients were given chemotherapy within 6 weeks of surgery. Five patients developed metastatic disease during therapy. The median interval to first relapse was 10 months and overall median survival was 12 months in these patients.[20] Other regimens that have been used for treatment are mitomycin, doxorubicin, and cisplatin (MAP); doxorubicine, cyclophosphamide, and vincristine (DCV); ifosfamide and etoposide (IE); ifostamide, doxorubicin, and decarbazine; doxorubicin and paclitaxel, and paclitaxel alone.[4] Of those, a patient with on the IE survived the longest, 32 months.

Radiation showed some benefit in progression-free survival in a French retrospective study.[21] Radiation therapies have been tried in other cases, as well in addition to chemotherapy. However, there is not enough data to support or refute it at this time.[15,17,20] Several sporadic cases reported show benefit of cardiac transplantation.[21,22]

Conclusion

In consideration of the placement of the Dacron graft 8 years before the tumor occurrence, the anatomic proximity of the tumor to the Dacron graft, and the association between sarcoma with Dacron in medical literature, it seems logical to infer that this unusual malignancy in our patient is associated with the Dacron prosthesis.

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Patient navigators' personal experiences with cancer: does it have an impact on treatment?

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Patient navigation has emerged in the past decade as a strategy to decrease cancer disparities among low-income, minority populations. Patient navigators help individuals who face personal and systemtic barriers to gaining access to care.[1] Their role is to help patients find their way through a complex health care system,[2,3] including logistic support of rescheduling appointments, assistance with transportation, and child care needs. They provide personal support, including coaching patients on their clinical visits, educating them about the cancer treatment process, and addressing their fears of diagnosis and treatment. Patient navigation has shown improvement in cancer screening rates, time to diagnostic resolution for those patients who have abnormal cancer screening tests, and quality of cancer care.[4,5]

In hiring patient navigators, it is not clear which professional training and skill sets and what personal experiences are most useful to becoming an effective navigator. Personal cancer experience can include a personal diagnosis, the experience of serving as a primary caregiver for a patient during treatment, or having a family member or close friend with cancer. Several current support programs specifically recruit cancer survivors on the assumption that their cancer treatment experience can provide helpful insights to a current patient for both emotional and logistical support.[6] In this paper, we sought to address whether patient navigation promotes more timely diagnostic care if the navigator has experience with cancer.

Methods

This is a secondary analysis of the patients with abnormal cancer screening in the navigation arm of the national Patient Navigation Research Program (PNRP) study,[1, 5] a collaborative effort across 10 centers to investigate the efficacy of patient navigation on improving patient-level outcomes for those who have abnormal results from a breast, cervical, colorectal, or prostate cancer screening test. The study demonstrated that patient navigation was effective in reducing delays in diagnosis and treatment[5] and resulting in a higher quality of care,[4] especially among vulnerable populations.[7] The Institutional Review Board of each respective institution approved the research.

All of the patient navigators were paid employees with a minimum high-school diploma or equiv-

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Correspondence: Carolyn L Rubin, EdD; Carolyn.Rubin@tufts.edu. Disclosures: The authors report no disclosures or conflicts of interest. ClinicalTrials.gov identifiers: NCT00613275, NCT00496678, NCT00375024, NCT01569672. JCSO 2018;16(1):e43–e46. doi: https://doi.org/10.12788/jcso.0266.

alent. Navigators' activities were standardized across centers through a national training program.[8] Navigators used the care management model to identify and address barriers to care and to track participants throughout the course of their diagnostic evaluation,[9] with the primary aim of timely diagnostic resolution. Most navigation programs were embedded within the clinical care system and interacted with patients through mail, by phone, and face-to-face contact.[1]

Data collection

Each center used agreed-upon inclusion and exclusion criteria and collected and coded the same patient-level data. Medical records were abstracted for pertinent clinical data on patients. Demographic data were collected through a patient survey or extracted from medical record registration. The central data coordinating center collected navigator information including demographic characteristics and experience with cancer.

We created a new variable, *Personal experience with cancer*. Personal experience with cancer was based on three questions asked of navigators: whether they were a cancer survivor; whether they were the primary caregiver to a family member or close friend with cancer; and whether they had a family member with cancer. Because of the small sample size, responses from navigators who were cancer survivors (n = 6) or primary caregivers to a family member with cancer (n = 4) were collapsed into a single category, referred to as personal experience with cancer, to compare with navigators who had no personal experience with cancer, which included those who reported a family member with cancer but who were not serving as a primary caregiver.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Each clinical center received approved from their institution's human subjects review board. Informed consent was obtained from all patient navigator participants included in the study. Participating patients completed informed consent at some centers. At other centers where the study design was an implementation of a system intervention, a waiver of informed consent was approved by the Institutional Review Board.

Data analysis

The primary outcome variable was time to diagnostic resolution. We included only participants supported by a single navigator. A Fisher exact test by cancer type was used to compare the two groups (personal experience vs none) in the proportion of patients who achieved diagnostic resolution by 365 days. We reviewed the percentage of patients resolved for the total population as well as stratified by cancer site (breast, cervical, prostate, and colorectal), owing to the known mean differences in time to diagnostic resolution by type of cancer.

TABLE 1 Characteristics of patients – Patient Navigation Research Program (N = 3,975)

Characteristic	No. of patients (%)
Sex	
Female	3,700 (93)
Male	275 (7)
Race/ethnicity	
White	967 (24)
Black/African American	984 (25)
Hispanic	1,861 (47)
Other	161 (4)
Missing	2 (<1)
Primary language	
English	2,393 (60)
Spanish	1,309 (33)
Vietnamese	82 (2)
Portuguese Creole	15 (<1)
Albanian	32 (1)
Other/missing	144 (4)
Insurance status	
Public	1,498 (38)
Private	861 (22)
None	1,573 (40)
Missing	43 (1)

Cox proportional hazard models and adjusted hazard ratios were developed and calculated to examine the impact of navigator's personal experience with cancer on time to resolution, controlling for patient gender, race, age, and cancer type in the models. The analysis controlled for the individual effect of navigators through clustering. We used $P < .05$ as the cut-off for significance, and used Stata 10.1 (StataCorp, College Station Texas 77845) for all analyses.

Results

Our analytic sample included the 3,975 patients with only 1 navigator over the course of the study, 79% of the navigation (n = 5,063) arm. Most of the patients were women (93%), and most were from racial and ethnic minority communities. Most patients spoke English (60%), with Spanish (33%) as the next most common language. Most patients were publically insured (38%) or uninsured (40%) (Table 1).

Of the total 49 navigators, 6 were cancer survivors and 4 were primary caregivers to a family member with can-

cer; an additional 19 reported that they had family members with cancer (Table 2). Most of the navigators were women. The racial/ethnic distribution mirrored the populations they served: white (29%); black or African American (31%); and Hispanic (37%). English was the only spoken language of 67% of the navigators; 27% spoke Spanish, and 6% reported speaking another language. Most had a college degree (63%).

TABLE 2 Characteristics of patient navigators by personal experience with cancer – Patient Navigation Research Program

Patient navigator characteristic	Personal experience with cancer		Total (N = 49)
	Cancer survivor/ primary caregiver (n = 10)	No personal cancer experience (n = 39)	
Sex			
Female	9 (90)	36 (92)	45 (92)
Race/ethnicity			
White	3 (30)	11 (28)	14 (29)
Black/African American	2 (20)	13 (33)	15 (31)
Hispanic	4 (40)	14 (36)	18 (37)
Other/missing	1 (10)	1 (3)	1 (2)
Languages spoken			
English only	6 (60)	27 (69)	33 (67)
Spanish	3 (30)	10 (26)	13 (27)
Other	1 (10)	2 (5)	3 (6)
Education			
College graduate	6 (60)	25 (64)	31 (63)
Insurance status before position as navigator			
Uninsured	1 (10)	3 (8)	4 (8)
Private	5 (60)	31 (79)	36 (73)
Missing	4 (40)	5 (13)	9 (18)

The unadjusted bivariate comparison of patients who achieved diagnostic resolution within 365 days, by navigator experience with cancer, are shown in Table 3. We found no difference in time to diagnostic resolution for those patients for whom navigators had personal experience with cancer compared with those whose navigators had no experience. When stratified by type of cancer screening abnormality (breast, cervical, prostate, or colorectal), the results also did not reveal a significant difference in the proportion of patients achieving diagnostic resolution by 365 days by navigator experience with cancer.

In the Cox proportional hazard model adjusting for patient gender, age, race/ethnicity, cancer type, and adjusting for navigator using clustering, there was no difference between patients whose navigators had experience with cancer care, and those who did not (adjusted hazard ratio, 1.03; 95% confidence interval, .83-1.3). The level of education of navigators was not significantly associated with time to diagnostic resolution for patients.

Discussion

Although several cancer support programs have explicitly used cancer survivors as patient navigators or other supports for patients in active cancer care, there are scant data on whether this expertise improves care. Our study was not able to identify that navigators with previous experience with cancer care, either as a patient or as the primary caregiver, was associated with improved time to diagnostic resolution.

As patient navigation has become the standard of cancer diagnostic and treatment practices, there is a need to develop competencies and standards for hiring and training navigators. Part of this hiring process is to determine what past experience and training are relevant for effective navigation. There is little previous research on relevant skills of navigators, with only one study having demonstrated that language and racial/ ethnic concordance between patients and navigators was associated with more timely care. The national PNRP program hired mostly lay navigators with minimal medical experience, but with affiliations to the communities of the patients receiving care. Our program has demonstrated that lay individuals can be trained in the logistic aspects of navigation.[5] Although it may seem intuitive that the experience of being a cancer survivor may make a navigator more empathetic, it is also possible that being too close to the experience of survivorship can also pose challenges to a navigator. Alternatively, navigation may be equally effective with proper training regardless of previous experience with cancer.

Our study is limited to addressing the outcome of timely resolution in the diagnostic phase of care after abnormal cancer screening. It is possible that past experience with cancer care will be beneficial when providing navigation for cancer care. While this study represents one of the largest groups of navigators who have been studied, the small sample may have limited our ability to detect differences. Our study has the benefit of a diverse group of navigators from a nationally representative, multi-site study. We suggest that prior experience with cancer care is not a prerequisite to

TABLE 3 Diagnostic resolution within 365 days of abnormal screening finding, by cancer type and patient navigator experience with cancer – Patient Navigation Research Program

	Total (N = 3,975)	Cancer type								
		Breast (n = 2,324)		Cervical (n = 1,256)		Prostate (n = 191)		Colorectal (n = 204)		
Navigator experience with cancer	No. of patients	n (%) reaching resolution at 365 d	No. of patients	n (%) reaching resolution at 365 d	No. of patients	n (%) reaching resolution at 365 d	No. of patients	n (%) reaching resolution at 365 d	No. of patients	n (%) reaching resolution at 365 d
Cancer survivor/ primary caregiver	576	511 (88.7)	515	467 (90.7)	0	0 (0)	4	3 (75)	57	41 (71.9)
Family member/ no experience	3,399	3,035 (89.3)	1,809	1,650 (91.2)	1,256	1,122 (89.3)	187	158 (84.5)	147	108 (73.5)
***P*-value from Fisher exact test**	.6445		.7844		NA[b]		.3993		.7844	

[a]Some numbers do not add up because of rounding. [b]Not applicable because one of the cells = 0.

supporting diagnostic care after abnormal cancer screening. Providing appropriate training to navigators may be sufficient to ensure effective and appropriate care is provided by patient navigators.

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Hallmark tumor metabolism becomes a validated therapeutic target

Jane de Lartigue, PhD

Altered cell metabolism has long been recognized as a distinctive feature of malignant cells but, until recently, research efforts had focused on a single aspect. It has become increasingly evident that many metabolic pathways are altered in cancer cells. Improved understanding has yielded the first regulatory approval in this new class of drugs. Here, we discuss the latest developments in the therapeutic targeting of the cancer metabolism hallmark.

A cancer cell's sweet tooth

The metabolism of cancer cells differs from that of normal cells, an observation that has spawned a dedicated field of research and new targeted drug development. The German physiologist Otto Warburg is credited as the father of the field with his observations about the way in which cancer cells derive energy from glucose.[1]

In normal cells, glucose is converted into pyruvate in the cytoplasm, which is then, most often, fed to the mitochondria that use oxidative phosphorylation to produce energy in the form of adenosine triphosphate (ATP). Cancer cells seem instead to favor using the pyruvate to produce lactate through glycolysis (Figure 1).

Glycolysis is usually reserved for conditions of poor oxygen availability, but although the tumor microenvironment is often hypoxic, cancer cells have been shown to use glycolysis even when oxygen is plentiful. As a result, the phenomenon is known as aerobic glycolysis, although it is most often referred to as the Warburg effect.[2]

Glycolysis is much less efficient than oxidative phosphorylation at producing energy, yielding only 2 ATP. In order to meet their energy demands in this way, cancer cells ramp up their glucose intake, an effect that has been exploited for the detection of cancer with positron-emission tomography.

Warburg postulated that this metabolic shift was a result of mitochondrial damage and defective oxidative phosphorylation, even going so far as to suggest that cancer was a mitochondrial disease. It has subsequently been shown that the mitochondria are mostly intact in cancer cells and that oxidative phosphorylation can still occur.[3]

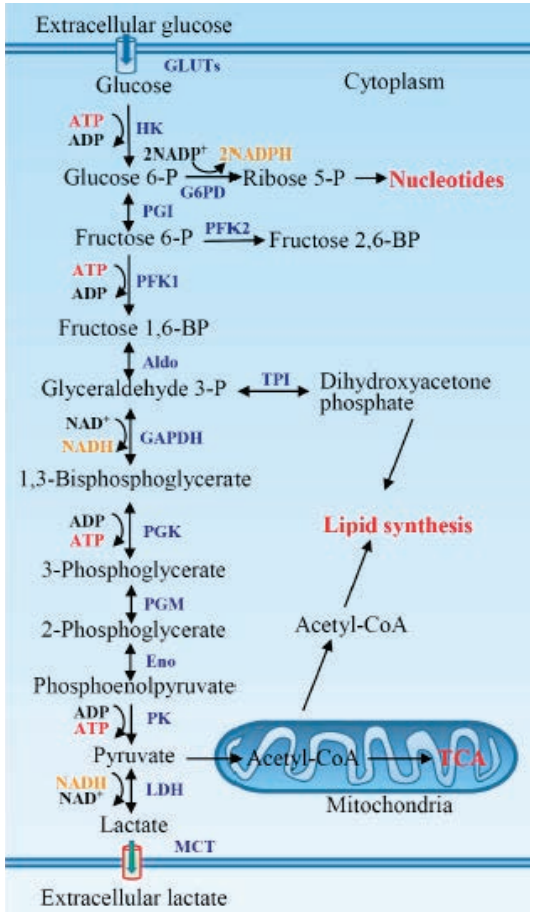

FIGURE 1 The glycolytic pathway and its association with other metabolic pathways. Reproduced under a creative commons license. Yu L, et al. The sweet trap in tumors: aerobic glycolysis and potential targets for therapy. Oncotarget 2016;7(25):38908-38926.

Aldo, aldolase; Eno, enolase; G6PD, glucose-6-phosphate dehydrogenase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GLUTs, glucose transporters; HK, hexokinase; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; PFK, phosphofructokinase; PGI, phosphoglucose isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; TCA, tricarboxylic acid cycle; TPI, triose phosphate isomerase

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TABLE 1 Select drugs targeting tumor cell metabolism

Drug	Developer	Mechanism of action	Approved indication/clinical testing
Enasidenib (AG-221)	Agios	IDH inhibitor	FDA approved August 2017 for the treatment of relapsed/refractory *IDH2*-mutant AML Phase 3 vs SOC in *IDH2*-mutant AML (IDHENTIFY; NCT02577406)
Ivosidenib (AG-120)	Agios	IDH inhibitor	Phase 3 + azacitidine in *IDH*-mutant AML (AGILE; NCT03173248) Phase 3 in *IDH*-mutant cholangiocarcinoma (ClarIDHy; NCT02989857) Phase 1 + AG-881 in *IDH*-mutant low-grade glioma (NCT03343197)
IDH305	Novartis	IDH inhibitor	Phase 2 in *IDH*-mutant glioma (NCT02977689)
AG-881	Agios	IDH inhibitor	Phase 1 in advanced solid tumors (NCT02481154[a]) and hematologic malignancies (NCT02492737[a])
Metformin	MD Anderson Cancer Center	Antidiabetic drug	Phase 3 in CRC (NCT02614339) Phase 2/3 endometrial cancer (NCT02065687) Phase 2 + gemcitabine in pancreatic cancer (NCT02005419) Phase 2 in NSCLC (NCT02285855) Phase 2 colon cancer (MECORA; NCT03359681) Phase 2 + simvastin in bladder cancer (NCT02360618)
AZD3965	AstraZeneca	MCT1 inhibitor	Phase 1 in advanced cancer (NCT01791595)
Ritonavir	AbbVie	GLUT-1 inhibitor	Phase 2 + docetaxel in mCRPC (NCT03136640) Phase 1 + metformin in relapsed/refractory multiple myeloma or CLL (NCT02948283)
CB-839	Calithera	Glutaminase inhibitor	Phase 2 + paclitaxel in TNBC (NCT03057600) Phase 2 + everolimus in RCC (NCT03163667) Phase 1/2 + azacitidine in MDS (NCT03047993) Phase 1/2 + capecitabine in solid tumors and fluoropyrimidine-resistant *PIK3CA*-mutant CRC (NCT02861300) Phase 1/2 + nivolumab in ccRCC and other solid tumors (NCT02771626)
AZD5363	AstraZeneca	AKT inhibitor	P2 + enzalutamide mCRPC (RE-AKT; NCT02525068) P1/2 + paclitaxel advanced gastric adenocarcinoma (NCT02451956, NCT02449655) P1/2 + chemotherapy in mCRPC (ProCAID; NCT02121639) P1 in advanced solid tumors with AKT mutations (NCT03310541)
Ipatasertib (GDC0068)	Genentech	AKT inhibitor	P2 + fluoropyrimidine and oxaliplatin in gastric/GEJ cancer (NCT01896531)[a] P2 + paclitaxel in TNBC (LOTUS; NCT02162719)[a] P1/2 + abiraterone acetate mCRPC (NCT01485861)[a]
GSK2141795	GSK	AKT inhibitor	P2 + trametinib in multiple myeloma (NCT01989598)[a] P2 + trametinib in uveal melanoma (NCT01979523)[a] P2 + trametinib in TNBC (NCT01964924)[a] P1 + trametinib in endometrial cancer (NCT01935973)[a]
MK-2206	Merck	AKT inhibitor	P2 + bicalutamide in prostate cancer (NCT01251861)[a] P1 + anastrozole, fulvestrant or both in mBC (NCT01344031)[a] P1 +hydroxychloroquine in advanced solid tumors (NCT01480154)[a]

IDH, isocitrate dehydrogenase; MCT1, monocarboxylate transporter 1; GLUT1, glucose transporter 1; FDA, United States Food and Drug Administration; AML, Acute myelogenous leukemia; SOC, standard of care; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; mCRPC, metastatic castration-resistant prostate cancer; TNBC, triple-negative breast cancer; RCC, renal cell carcinoma; MDS, myelodysplastic syndrome; ccRCC, clear cell renal cell carcinoma; TNBC, triple negative breast cancer; mBC, metastatic breast cancer

[a]Trial is active, but no longer recruiting participants.

The Warburg effect has been the subject of significant investigative efforts as researchers have attempted to better understand how this phenomenon comes about. Studies have shown that it is driven in large part by the transcription factors hypoxia inducible factor 1 alpha (HIF-1α) and c-Myc. In addition, numerous other signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway, and the activation of oncogenes and inactivation of tumor suppressors, are thought to play a central role.

HIF-1α is an oxygen-sensing transcription factor that coordinates cellular responses to reduced oxygen levels by binding to specific regions, known as hypoxia response elements, on target genes in the nucleus and regulating their subsequent expression. Oxygen levels and metabolism are tightly linked, and HIF-1α sits at the intersection of the

2 since many of its target genes are involved in metabolic pathways, including many glycolytic enzymes, but it also directly inhibits oxidative phosphorylation by suppressing key enzymes in this metabolic pathway.

The expression of HIF-1α and numerous glycolytic enzymes, including lactate dehydrogenase (LDH), phosphofructokinase (PFK), hexokinase II (HKII), and pyruvate dehydrogenase kinase (PDK) is increased in many tumor types. Other molecules associated with glucose uptake and metabolism are also dysregulated, such as the GLUT-1 glucose transporter.[2,4-6]

Targeting glycolysis and glucose uptake

According to one study, glucose transporters and glycolytic enzymes are overexpressed in 24 different types of cancer, representing more than 70% of all cancer cases.[7] This enables cancer cells to respond metabolically as though they are experiencing hypoxia, even when oxygen is plentiful and, indeed, when hypoxia is a concern, to mount a faster response. It also provides a tempting avenue for anticancer drug design by exploiting the dependency of cancer cells on glycolysis to survive and thrive.

Inhibitors of HKII, LDH, PFK, PDK, and GLUT-1 have been and continue to be developed. For example, 2-deoxy-D-glucose is a glucose molecule in which the 2-hydroxyl group has been replaced by hydrogen, preventing further glycolysis; it acts as a competitive inhibitor of HKII. Dichloroacetate (DCA) activates the pyruvate dehydrogenase complex and inhibits the actions of the PDKs. Although development of DCA itself was unsuccessful, DCA derivatives continue to be pursued. WZB117 and STF-31 are novel small-molecule inhibitors of GLUT-1-mediated glucose transport. To date, where inhibitors of glycolysis have progressed into clinical trials, they have not proved successful, often limited by off-target effects and low potency.[8-11]

A variety of cell signaling pathways are implicated in metabolism by tightly regulating the ability of cells to gain access to and use nutrients. Through aberrations in these pathways, cancer cells can essentially go rogue, ignoring regulatory signals and taking up nutrients in an autonomous manner. One of the most frequently altered signaling pathways in human cancer, the PI3K-Akt-mTOR pathway, is also an important regulator of metabolism, coordinating the uptake of multiple nutrients, including glucose.

Akt in particular is thought to have a critical role in glucose metabolism and increased Akt pathway signaling has been shown to correlate with increased rates of glycolysis in cancer cells. Thus, Akt inhibitors could double as glycolytic or glucose transport inhibitors.[12,13]

A number of Akt inhibitors are being evaluated in clinical trials (Table) and results from the phase 2 LOTUS trial of ipatasertib (GDC-0068) were recently published. Among 124 patients randomly assigned to paclitaxel in combination with either ipatasertib or placebo, there was a modest improvement in progression-free survival (PFS) in the ipatasertib arm in patients with triple-negative breast cancer (TNBC; 6 months vs 4.2 months, respectively; hazard ratio [HR], 0.60; P = .037). The effect was more pronounced, though not statistically significant, in patients with phosphatase and tensin homolog (PTEN)-low tumors (6.2 months vs 3.7 months; HR, 0.59; P = .18). The most common grade 3 and higher adverse events (AEs) were diarrhea, reduced neutrophil count, and neutropenia.[14]

The Warburg paradox

Although the molecular mechanisms underlying the Warburg effect have been revealed to some extent, why cancer cells would choose to use such an energy-inefficient process when they have such high energy demands, remains something of a paradox. It's still not entirely clear, but several explanations that are not necessarily mutually exclusive have been proposed and relate to the inherent benefits of glycolysis and might explain why cancer cells favor this pathway despite its poor energy yield. First, ATP is produced much more rapidly through glycolysis than oxidative phosphorylation, up to 100 times faster. Thus, using glycolysis is a trade-off, between making less energy and making it more quickly.

Second, cancer cells require more than just ATP to meet their metabolic demands. They need amino acids for protein synthesis; nucleotides for DNA replication; lipids for cell membrane synthesis; nicotinamide adenine dinucleotide phosphate (NADPH), which helps the cancer cell deal with oxidative stress; and various other metabolites. Glycolysis branches off into other metabolic pathways that generate many of these metabolites. Among these branched pathways is the pentose phosphate pathway (PPP), which is required for the generation of ribonucleotides and is a major source for NADPH. Cancer cells have been shown to upregulate the flux of glucose into the PPP to meet their anabolic demands and counter oxidative stress.

Third, the lactic acid produced through glycolysis is actively exported from tumor cells by monocarboxylate transporters (MCTs). This creates a highly acidic tumor microenvironment, which can promote several cancer-related processes and also plays a role in tumor-induced immunosuppression, by inhibiting the activity of tumor-infiltrating T cells, reducing dendritic cell maturation, and promoting the transformation of macrophages to a protumorigenic form.[2,4,6]

Beyond the Warburg effect

Although the focus has been on glucose metabolism and glycolysis, it has been increasingly recognized that many different metabolic pathways are altered. Fundamental changes to the metabolism of all 4 major classes of macromolecules – carbohydrates, lipids, proteins, and nucleic acids – have been observed, encompassing all aspects of

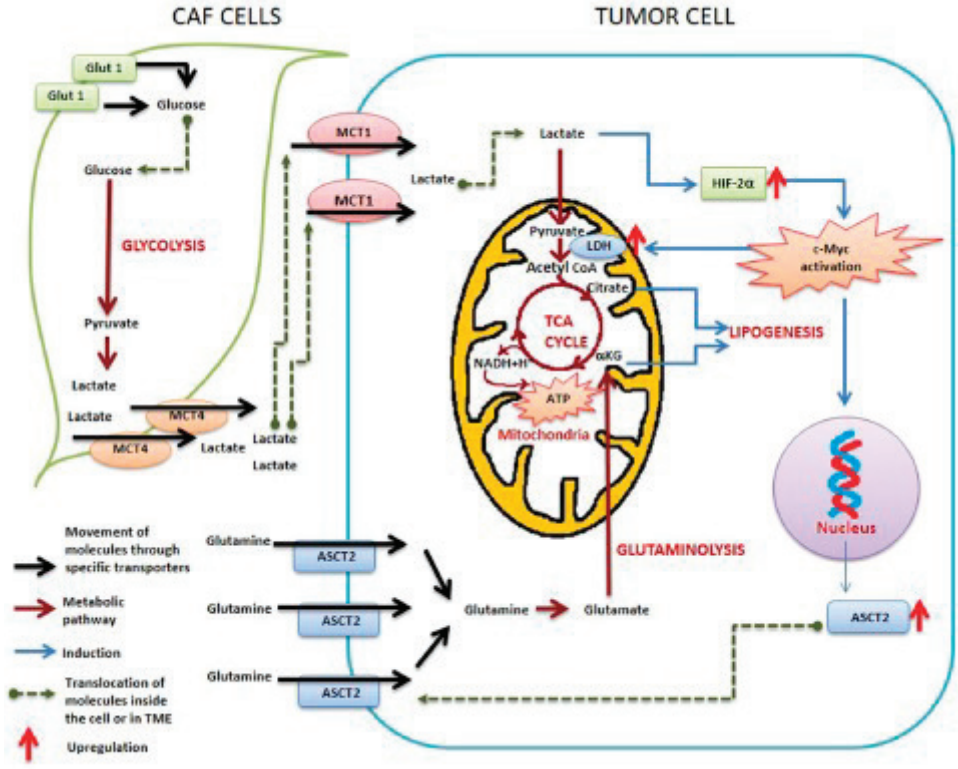

FIGURE 2 The 'reverse' Warburg effect. Cancer cells induce oxidative stress in neighboring stromal fibroblasts, triggering aerobic glycolysis and the production of lots of lactate. Via the 'lactate shuttle' mechanism, the lactate is exported from the stromal cell through MCTs and transported to the cancer cells where it is imported via different MCTs. In the cancer cell, it is oxidized back into pyruvate and used to fuel oxidative phosphorylation. Reproduced under a creative commons license. Gupta S, et al. Metabolic cooperation and competition in the tumor microenvironment: implications for therapy. Front Oncol. 2017;7:68.

MCT, monocarboxylate transporter

cellular metabolism and enabling cancer cells to meet their complete metabolic requirements. There is also evidence that cancer cells are able to switch between different metabolic pathways depending on the availability of oxygen, their energetic needs, environmental stresses, and many other factors. Certainly, there is significant heterogeneity in the metabolic changes that occur in tumors, which vary from tumor to tumor and even within the same tumor and across the lifespan of a tumor as it progresses from an early stage to more advanced or metastatic disease.

The notion of the Warburg effect as a universal phenomenon in cancer cells is now being widely disregarded. Many tumors continue to use oxidative phosphorylation, particularly slower growing tumors, to meet their energy needs. More recently a "reverse" Warburg effect was described, whereby cancer cells are thought to influence the metabolism of the surrounding stromal fibroblasts and essentially outsource aerobic glycolysis to these cells, while performing energy-efficient oxidative phosphorylation themselves (Figure 2).[5,15,16]

There is thought to be a "lactate shuttle" between the stromal and cancer cells. The stromal cells express high levels of efflux MCTs so that they can remove the subsequently high levels of lactate from the cytoplasm and avoid pickling themselves. The lactate is then shuttled to the cancer cells that have MCTs on their surface that are involved in lactate uptake. The cancer cells oxidize the lactate back into pyruvate, which can then be used in the tricarboxylic acid (TCA) cycle to feed oxidative phosphorylation for efficient ATP production. This hypothesis reflects a broader appreciation of the role of the microenvironment in contributing to cancer metabolism.[17,18]

An improved holistic understanding of cancer cell metabolism has led to the recognition of altered cancer metabolism as one of the hallmark abilities required for transformation of a normal cell into a cancerous one. It is categorized as "deregulation of bioenergetics" in the most up to date review of the cancer hallmarks.[19] It has also begun to shape the therapeutic landscape as new drug targets have emerged.

IDH inhibitors first to market

A number of new metabolically-targeted treatment strategies are being developed. Most promising are small molecule inhibitors of the isocitrate dehydrogenase (IDH) enzymes. These enzymes play an essential role in the TCA cycle, catalyzing the conversion of isocitrate to alpha-ketoglutarate, generating carbon dioxide and NADPH. Recurrent mutations in the *IDH1* and *IDH2* genes have been observed in several different types of cancer, including glioma, acute myeloid leukemia (AML), and cholangiocarcinoma.

IDH mutations are known as neomorphic mutations because they confer a new function on the altered gene product. In this case, the mutant IDH enzyme converts alpha-ketoglutarate further into D-2-hydroxyglutarate (D-2HG). This molecule has a number of different effects that promote tumorigenesis, including fostering defective DNA repair (Figure 3).[20,21]

Intriguing research presented at the American Association of Cancer Research Annual Meeting revealed that *IDH* mutations may make cancer cells more vulnerable to poly (ADP-ribose) polymerase (PARP) inhibition,

likely as a result of defects in homologous recombination pathways of DNA repair.[22]

The pursuit of IDH as a potential therapeutic target has yielded the first regulatory approval for a metabolically targeted anticancer therapy. In August 2017, the United States Food and Drug Administration (FDA) approved enasidenib, an IDH2 inhibitor, for the treatment of relapsed or refractory AML with an *IDH2* mutation. It was approved in combination with a companion diagnostic, the RealTime IDH2 Assay, which is used to detect *IDH2* mutations.

The approval was based on a single-arm trial in which responses occurred in almost a quarter of the 199 patients treated with 100 mg oral enasidenib daily. After a median follow-up of 6.6 months, 23% of the patients experienced a complete response or a complete response with partial hematologic recovery lasting a median of 8.2 months. The most common AEs were nausea, vomiting, diarrhea, elevated bilirubin levels, and reduced appetite.[23]

Several other IDH inhibitors are also showing encouraging efficacy. Ivosidenib is an IDH1 inhibitor and the results of a phase 1 study in patients with cholangiocarcinoma were recently presented at a leading conference. Escalating doses of ivosidenib (100 mg twice daily to 1,200 mg once daily) were administered to 73 patients (as of December 2016). The confirmed partial response (PR) rate was 6%, the rate of stable disease was 56%, and PFS at 6 months was 40%. There were no dose-limiting toxicities (DLTs) and treatment-emergent AEs included fatigue, nausea, vomiting, diarrhea, decreased appetite, dysgeusia, and QT prolongation.[24]

Another study of ivosidenib was presented at the 2017 annual meeting of the Society for Neuro-Oncology. In that study, patients with glioma received daily doses of ivosidenib ranging from 300 mg to 900 mg. Two patients had a minor response, 83% had stable disease, and the median PFS was 13 months. There were no DLTs and most AEs were mild to moderate and included, most commonly, headache, nausea, diarrhea, and vomiting.[25]

Pursuing alternative targets and repurposing drugs

Other metabolic targets that are being pursued include glutaminase, given the observation of significantly enhanced glutamine uptake in cancer cells. CB-839 is a glutaminase inhibitor that is currently being evaluated in phase 1 and 2 clinical trials. Updated clinical trial data from a phase 1 trial of CB-839 in combination with paclitaxel in patients with advanced/metastatic TNBC were presented at the San Antonio Breast Cancer Symposium last year.[26]

As of October 2017, 49 patients had been treated with 400 mg, 600 mg, or 800 mg CB-839 twice daily in combination with 80 mg/m^2 intravenous paclitaxel weekly. Among the 44 patients evaluable for response, the rate of PR was 22% and of disease control, 59%. The one DLT was grade 3 neutropenia at the 400 mg dose. Overall AEs were mostly low grade and reversible.

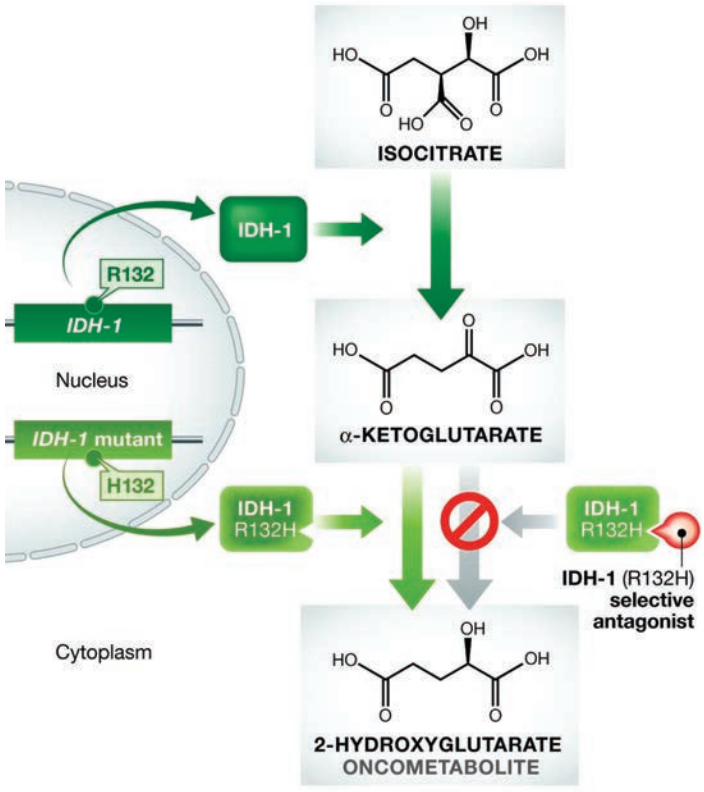

FIGURE 3 IDH inhibitors: mechanism of action. Mutant IDH enzymes convert α-ketoglutarate, the usual product of IDH enzymatic action, into the unusual oncometabolite 2-hydroxyglutarate. IDH inhibitors block this conversion and prevent the oncogenic effects of the IDH mutant. Reproduced from a creative commons license. Carlsson SK, et al. Emerging treatment strategies for glioblastoma multiforme. EMBO Mol Med. 2014;6:1359-1370.

IDH, isocitrate dehydrogenase

In recent years, lactate has emerged as more than just a by-product of altered cancer cell metabolism. It is responsible, at least in part, for the highly acidic tumor microenvironment that fosters many of the other hallmarks of cancer. In addition, lactate promotes angiogenesis by upregulating HIF-1α in endothelial cells. Depriving tumor cells of the ability to export lactate is a potentially promising therapeutic strategy. An MCT-1 inhibitor, AZD3965, is being evaluated in early stage clinical trials.

Finally, several drugs that are renowned for their use in other disease settings are being repurposed for cancer therapy because of their potential effects on cancer cell metabolism. Ritonavir, an antiretroviral drug used in the treatment of HIV, is an inhibitor of GLUT-1 and is being evaluated in phase 1 and 2 clinical trials. Meanwhile, long-term studies of metformin, a drug that has revolu-

tionized the treatment of diabetes, have revealed a reduction in the emergence of new cancers in diabetic patients treated who are treated with it, and the drug has been shown to improve breast cancer survival rates. Its precise anticancer effects are somewhat unclear, but it is thought to act in part by inhibiting oxidative phosphorylation. Numerous clinical trials of metformin in different types of cancer are ongoing.[27,2]

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New myeloma drugs improve response and extend survival

David H Henry, MD,[a] interviews Kenneth C Anderson, MD[b]

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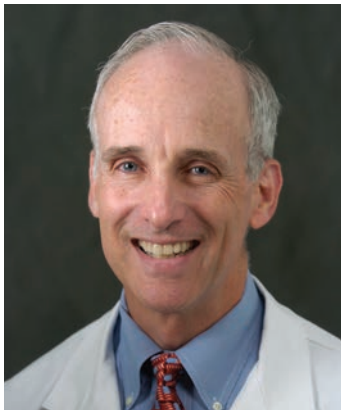
In this interview, Dr David Henry, the Editor-in-Chief of The Journal of Community and Supportive Oncology, and Dr Ken Anderson, the Kraft Family Professor of Medicine at Harvard Medical School and an international thought leader and investigator in myeloma, discuss three cases of patients with myeloma that are indicative of the remarkable therapeutic advances in oncology in general, and in myeloma in particular. In the last 10-15 years, numerous approvals by the US Food and Drug Administration have transformed the treatment landscape for multiple myeloma by providing patients and oncologists with many new options and combination possibilities for treating the disease. And since many of the agents have been tested in advanced myeloma, their use has edged the disease toward initial management. The encouraging news is that in the new classes of drugs, and especially the second-generation drugs, response rates, progression-free disease, and overall survival are significantly better, with some combinations yielding response rates of up to 70%-80%, and overall and progression-free survival of up to 10 years.

DR HENRY I thought we might discuss some cases of patients with myeloma, starting with a relatively simple case and ending with one that is a little more complicated. For the first case, we have a 56-year-old healthy man with IgG kappa myeloma whose work-up shows he has multiple lytic bone lesions. He has normal renal function, normal calcium, and he's transplant-eligible by other health issues. I'll leave the cytogenetics up to you if that changes your approach. How would you develop or pose some options for this man's treatment to begin with?



Dr Henry

Dr Anderson

DR ANDERSON It's important to start out by saying that we, in myeloma, have many new classes of drugs and many new opportunities to choose from to treat this patient.[1] As you know, we have proteasome inhibitors, the first-generation bortezomib, then carfilzomib and ixazomib. We have the immunomodulatory drugs (IMiDs), thalidomide, and now lenalidomide and pomalidomide. We have a histone deacetylase (HDAC) inhibitor approved called panobinostat, and we have 2 monoclonal antibodies approved, elotuzumab and daratumumab. These classes of medicine have made it possible for 20 different Food and Drug Administration (FDA) approvals in the last 10-15 years. These agents, having been tested in advanced myeloma, have moved toward initial management.

This person is 50 years old. He has adequate liver, heart, lung, and kidney function, so he would be eligible for high-dose therapy and stem-cell transplantation. In terms of initial management, there are many options (Figure 1). We strongly recommend that triplet therapy be used initially. The most common triplets would be lenalidomide, bortezomib, and dexamethasone (RVD)[2,3] or cyclophosphamide, bortezomib, and dexamethasone (CyBorD).[4] If this man had neuropathy, perhaps carfilzomib, the second-generation pro-

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teasome inhibitor, with lenalidomide and dexamethasone could have been used. Why do we use these? The extent and frequency of response with these triplets is nearly universal overall response rate, with three-quarters very good partial and half-complete responses, including minimal residual disease negative responses. In this patient, we would therefore recommend treatment with either RVD or CyBorD for several cycles to maximal response.

He would then have autologous stem cells collected, and it is still the standard of care to proceed to high-dose melphalan and a single high-dose therapy and stem-cell transplantation. The cytogenetics are important: if this patient has standard-risk multiple myeloma, then lenalidomide maintenance would be given after transplant. It is now FDA-approved for this purpose because it can prolong both progression-free and – most importantly – overall survival.[5] Standard-risk cytogenetics might, for example, include hyperdiploidy or translocation 11;14. On the other hand, if his myeloma were high-risk and characterized, for example, by 17p deletion, we would carry out the same induction and transplantation, but we would alter the maintenance to incorporate a proteasome inhibitor. Lenalidomide and bortezomib, for example, could be combined. Early data show that using combined maintenance therapy with lenalidomide and bortezomib, can overcome the early relapses that are characteristic of high-risk disease.[6]

Because of the extent and frequency of response to combination novel therapies, we have undertaken with our French colleagues a clinical trial of RVD in newly diagnosed patients – such as this patient – followed by stem-cell collection in all patients (Figure 2). Then there is a randomization to either early high-dose therapy, melphalan, and autologous stem-cell transplantation, followed by lenalidomide maintenance; or in the other cohort, harvesting of stem cells, additional RVD, and then maintenance with lenalidomide, saving the stem-cell transplant for later.

The French portion of this trial was reported in the New England Journal of Medicine earlier in 2017.[7] It showed that patients who received RVD, high-dose melphalan, stem-cell transplant, and had 1 year of lenalidomide maintenance, had a progression-free survival advantage of about 1 year, without an overall survival advantage; compared with those patients who received RVD and lenalidomide maintenance, saving the transplant for later. I would hasten to add that lenalidomide maintenance was given for only 1 year in this trial, and patients in the RVD-only or RVD-and-transplant arms of this trial relapsed after the lenalidomide maintenance was discontinued.

The American portion of this trial is identical. That is, RVD induction is being given and all patients have a stem-cell collection. Half of the patients then go to high-dose melphalan and stem-cell transplant early, and half of them have the transplant only later at the time of relapse. A major difference, however, is that in both the RVD-only and RVD-and-transplant cohorts, patients receive lenalidomide maintenance until progression. This trial has been ongoing since 2009 and is still ongoing, which tells us that patients in both arms – the RVD-only as well as the RVD-and-transplant arms – are doing well.

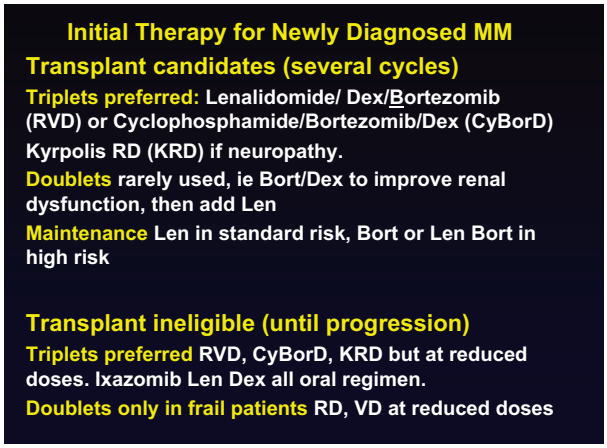

FIGURE 1 Initial therapy for newly diagnosed multiple myeloma for transplant eligible and ineligible patients. Reprinted with permission from Kenneth C Anderson, MD.

In the recent STAMINA trial, all patients underwent a single high-dose therapy and transplant. Then there was a randomization to lenalidomide maintenance only in 1 cohort; a randomization to consolidation with RVD post-transplant followed by lenalidomide maintenance in the second cohort; or a randomization to a second high-dose melphalan and stem-cell transplant followed by lenalidomide maintenance in the third cohort.[8] I mention this because the outcomes in all 3 cohorts was similar.

I believe this tells us strongly that high-dose therapy and stem-cell transplantation twice – so-called tandem transplant – is no longer a major option in multiple myeloma. For now, however, in this patient, the standard of care would be to undergo induction therapy with triplet, novel combination treatment. Then, stem cells would be collected and high-dose therapy stem-cell transplant would be done, followed either by lenalidomide maintenance for standard disease or lenalidomide and bortezomib maintenance for high-risk disease. We won't really know if we can delay transplant until the trials I've mentioned totally read out. In my clinical practice, if patients have had a major response to their induction therapy and have stem cells harvested, we can then offer them the opportunity to use maintenance therapy and save the transplant as a potential option for later, when myeloma relapses.

DR HENRY In summary then, this would be, in 2017, off-protocol while the data is pending: it's reasonable to get a deep induction response, collect stem cells, have a discussion with the patient, and then consider high-dose therapy or not.

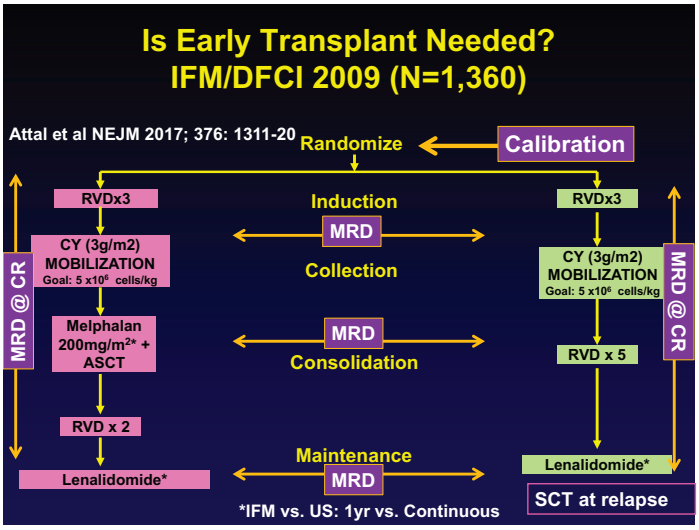

FIGURE 2 Assessing the need for early stem-cell transplant. Reprinted with permission from Kenneth C Anderson, MD.

DR ANDERSON Yes. I think it's reasonable to discuss it. We need to be open and honest with patients that the standard of care remains transplant, that you incorporate novel treatments before the transplant and novel treatments as maintenance after the transplant. The happy news is that the outcome, especially for patients who have standard-risk myeloma, is at least a decade or longer progression-free survival. It's an optimistic picture. The data in terms of transplant being needed or not, will come within the next several years.

For now, it is a standard of care to use 1 high-dose melphalan and stem-cell transplant in this setting. I will add into our discussion with patients – besides the opportunity to harvest stem cells and think about whether one needs to do a transplant early on or not – is the issue of toxicity. High-dose melphalan by itself has a small but real secondary incidence of cancer, myelodysplasia, or leukemia. If one uses lenalidomide maintenance after melphalan transplantation treatment, that risk of secondary cancer is slightly increased.

In my experience, if patients have achieved a complete response with induction therapy only, it's not unreasonable to offer early transplant and be clear that's the standard of care. The alternative is maintenance with lenalidomide, knowing once the stem cells have been harvested, that transplantation can be an option to treat relapsed myeloma. We have many other options available as well. Time will tell in terms of the ongoing randomized trials as to whether transplant remains central to our treatment paradigm.

DR HENRY This leads us to our second patient. Here we have an older man of 74 years. He's a professional piano player, so we want to try to avoid peripheral neuropathy in him. He has some mild renal insufficiency and some coronary artery disease, so he's deemed transplant-ineligible. He has IgG kappa myeloma, and he's brand new. What would you consider to be options for him for treatment?

DR ANDERSON This brings up the issue of a transplant-ineligible patient. He has significant comorbidity that would make transplantation an increased risk. What we would recommend in such a patient is still triplet induction therapy incorporating novel agents (Figure 1). Lenalidomide, the immunomodulatory drug, can safely be given in the context of neuropathy because it does not cause significant neuropathy. It would need to be dose modified, depending on the degree of renal insufficiency. We would recommend also including proteasome inhibitors. Bortezomib, the first-generation proteasome inhibitor, would be contraindicated because it does have a small but real attendant neuropathy. If, however, it is given weekly and subcutaneously, the risk of attendant neuropathy is quite low. In this patient, therefore, one could start with lenalidomide and bortezomib weekly and subcutaneously,[1,2] with a very early and vigilant follow-up for the earliest signs of neuropathy, so as not to allow it to develop and compromise his career.

Alternatively, one could use a proteasome inhibitor that does not have attendant neuropathy. Carfilzomib, the second-generation proteasome inhibitor, does not have neuropathy.[9] But we would need to have caution here, because this patient has a history of coronary artery disease, and carfilzomib has a very small, but real, incidence of cardiac toxicity so would need to be used judiciously in this setting. The third proteasome inhibitor, ixazomib, is the next-generation bortezomib-class proteasome inhibitor, and it's oral.[10] It has less neuropathy than does bortezomib, so in my view is a very realistic option for him together with lenalidomide. It does have a small incidence of neuropathy, so close monitoring for neuropathy would be indicated. We could use lenalidomide–dexamethasone as a doublet and avoid neuropathy,[11] but usually doublets are reserved only for frail patients.

My recommendation, therefore, would be RVD with the bortezomib weekly or subcutaneously, or alternatively, lenalidomide, ixazomib, dexamethasone as an all-oral regimen as induction therapy. In my view, this 74-year-old patient with comorbidity is not a transplant candidate. However, one can be very optimistic with this patient. The likelihood that he could have myeloma as a chronic illness and die from something else is quite high. Initial induction triplet therapy would achieve a very high response extent and frequency. The durability would be long, especially with lenalidomide maintenance if it's standard-risk myeloma or lenalidomide and a proteasome inhibitor, probably ixazomib in this setting, if he were to have high-risk myeloma.

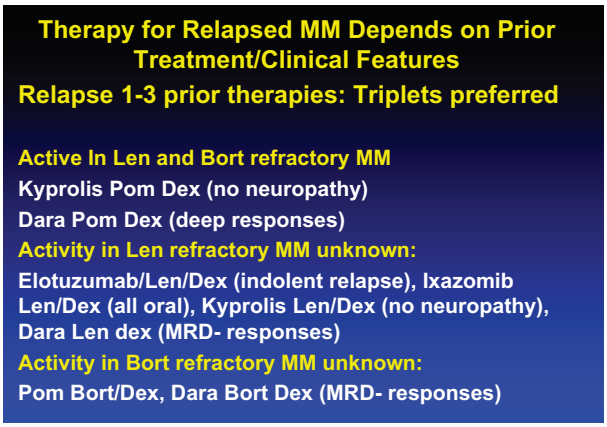

FIGURE 3 Therapy for relapsed multiple myeloma in relation to previous treatment and clinical features of the disease: triplets are preferred for relapsed patients with 1-3 previous therapies. Reprinted with permission from Kenneth C Anderson, MD.

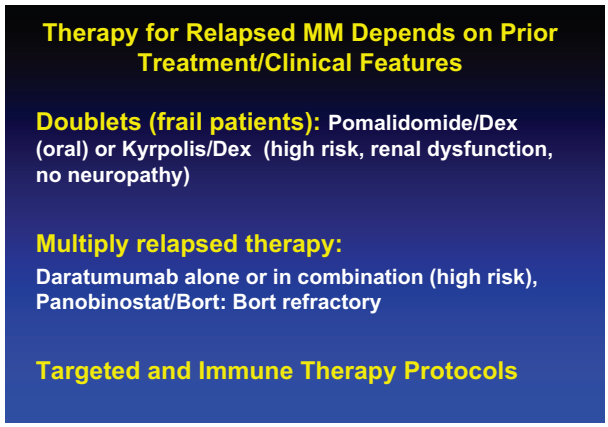

FIGURE 4 Therapy for relapsed multiple myeloma in relation to previous treatment and clinical features of the disease: doublets are preferred for frail patients. Reprinted with permission from Kenneth C Anderson, MD.

If myeloma relapses, then there are many options that could be used in this patient and achieve years of progression-free and overall survival. Indeed, he is 74 years old and will respond very well to induction triplet therapy, with many years' duration of response due to continuous lenalidomide or lenalidomide and proteasome inhibitor maintenance. Then there are many effective options to treat relapsed therapy using triplet novel agents. Therefore, his lifespan is unlikely to be shortened by multiple myeloma.

DR HENRY It's so incredible compared with what it was when I trained. The next patient, a 45-year-old woman with IgG lambda myeloma, has had RVD induction and responded. She had lenalidomide maintenance, but then she progressed, and she got her stem-cell transplant, and she's progressing after that. I guess we're looking here to fold in some of the newer agents. How you would you do that in this patient?

DR ANDERSON Yes. I think one of the most remarkable and exciting developments with myeloma is the rapid approval of the novel classes of agents that I mentioned earlier – the proteasome inhibitors, the immunomodulatory drugs, the HDAC inhibitor, and the monoclonal antibodies.[1] They're particularly relevant in a patient such as this one, whose myeloma has relapsed after what would be considered standard therapy for a young person with standard-risk myeloma. This patient had RVD and maintenance therapy, and then progressed. The transplant was given for relapsed myeloma. The opportunity to use stem-cell transplant in patients when myeloma becomes active after maintenance should not be forgotten as it can be very effective. In all the trials done to date in which early versus late transplant are compared, there have been similar outcomes. Therefore, if the transplant isn't done early, don't forget that it's an option at the time the myeloma progresses. I do want to mention, that there are lots of options for relapsed myeloma (Figures 3 and 4). I mentioned RVD or CyBorD as initial triplet therapies.[2-4] In North America, those are the 2 most common regimens. If myeloma then relapses and is resistant to RVD or to CyBorD, then we need to identify alternatives.

We also need to think about the comorbidities in the patient – issues such as age, neuropathy, presence of renal dysfunction, and other clinical factors. And we need to think about what treatment they've had in the past. This patient has had RVD, maintenance with lenalidomide, and a stem-cell transplant. We can offer patients a variety of therapies, but in the context of resistance to the first-generation proteasome inhibitor bortezomib and the first-generation immunomodulatory drug lenalidomide, we would strongly recommend the second-generation immunomodulatory drug pomalidomide[12] together with a second-generation proteasome inhibitor, be that carfilzomib[13] or ixazomib.[14] When one uses the second-generation IMiDs and proteasome inhibitors together, there's a very high frequency of response in the order of 70%-80%, which lasts years.

Besides carfilzomib and ixazomib proteasome inhibitors, we also have elotuzumab and daratumumab, the monoclonal antibodies.[15-17] These agents have been FDA approved to treat patients such as this one who has had 1-3 previous therapies for their myeloma. All of them have been approved in randomized phase 3 trials compared with lenalidomide-dexamethasone in the control arm.[13-15,17] They've all been found to be superior. Although lenalidomide-dexamethasone combined with daratumumab, ixazomib, elotuzumab, or carfilzomib is superior to lenalidomide

in relapsed myeloma, the situation in North America, as in this patient, is usually that patients have had lenalidomide-dexamethasone as part of their initial treatment and their myeloma is refractory to lenalidomide.

Hence, we recommend, that we go to the second-generation pomalidomide and second-generation proteasome inhibitors, either carfilzomib or ixazomib. Having said that, the treatment paradigm is evolving. For example, the monoclonal antibody daratumumab was initially approved by the FDA in multiply relapsed disease as a single agent because it achieves a 30% response rate.[16] It now has been moved earlier into the first relapse of multiple myeloma, where it achieves much higher response rates when combined with lenalidomide–dexamethasone or combined with bortezomib–dexamethasone.[17,18] Response rates of 70%-80% can be achieved, including minimal residual disease negative complete responses.

Today, in a patient who has had RVD transplant and myeloma has returned, we would recommend second-generation IMiDs, pomalidomide, and second-generation proteasome inhibitors, either carfilzomib or ixazomib. Data for daratumumab combined with lenalidomide-dexamethasone or with bortezomib-dexamethasone, look very promising. We need, however, to see more experience of daratumumab together with lenalidomide-dexamethasone or daratumumab together with bortezomib-dexamethasone in patients whose myeloma is refractory to RVD, that is, patients whose myeloma has returned after RVD induction treatment. Of note, pomalidomide, dexamethasone, and daratumumab have just been approved by the FDA and may also be active even in myeloma recurring after RVD treatment.[19]

Daratumumab in combination will be moving earlier and earlier and may be appropriate to treat the first relapse. I do want to stress, however, that at present I save daratumumab for the second or greater relapse. Daratumumab is active even when relapse occurs after treatment with second-generation IMiDs and proteasome inhibitors.

DR HENRY Before we close, I have a couple practical questions with these antibodies. Daratumumab has the track record of first-treatment severe reactions and long infusion times. How long are you anticipating the first daratumumab treatment takes? There has been some talk that maybe splitting it in half and going over 2 days is easier on the patient and the infusion center. Have you done that?

DR ANDERSON Yes, I think that's a very important point. We need to be thinking – first and foremost – about efficacy of our therapy. Equally important, however, are the safety profile and the user-friendliness for the patient. Daratumumab infusions are quite long – on the order of 8 hours or longer on day 1 of infusion. And to date, all the clinical trials have used daratumumab infusions weekly for 8 treatments, followed by 8 treatments given every 2 weeks. Then monthly daratumumab is given as a maintenance therapy. Thus, there is a requirement for multiple outpatient clinic visits that can be prolonged.

One of the opportunities that's being tested is to give daratumumab subcutaneously. While this is being evaluated in protocols now, the results that have been reported at our national meetings look to be quite promising in terms of efficacy, similar to results with the intravenous administration. Obviously, this would allow for a much more convenient clinic visit and shorter time for the patients being treated.

I should mention that the other antibody, elotuzumab, has been approved in combination with lenalidomide and dexamethasone.[15] The infusions with lenalidomide, dexamethasone, and the antibody elotuzumab are much shorter, on the order of 2- or 3-hour visits. The place for elotuzumab in the management of relapsed myeloma is yet to be totally defined. We tend to use it now in the setting of more indolent relapses, where patients might have a slowly rising monoclonal protein. Elotuzumab-lenalidomide-dexamethasone has maintained an overall survival advantage at 4 years compared with lenalidomide-dexamethasone when used in relapsed myeloma.

We are quite excited about both antibodies. Daratumumab tends to get most of the activity, as it achieves responses as a single agent,[16] and the depth of the responses are markedly increased when it's combined with lenalidomide-dexamethasone or bortezomib-dexamethasone.[17,18] However, one shouldn't forget elotuzumab[15] based on its tolerability and the survival advantage I mentioned at 4 years.

The final point is that we think about myeloma genetically at the time of diagnosis and relapse in terms of standard or high-risk disease. One of the hallmarks of high-risk disease has been 17P deletion or P53 dysfunction. One of the most exciting outcomes of the development of monoclonal antibodies has been the responses observed even in the context of P53 deletion. Clearly, antibody-mediated cellular cytotoxicity, complement-mediated cytotoxicity, and other mechanisms of action of these antibodies do not require normal P53 function. The important point, therefore, is that what has previously been thought of as high-risk disease can nowadays be effectively treated with these new immune treatments, correlating with the marked improvement in survival and overall outcome.

DR HENRY We have outlined 3 kinds of myeloma patients we see, and especially interesting is the last patient, who has relapsed and then progressed, and in whom newer drugs have a role. Thank you for such a complete and thorough discussion, Dr Anderson.

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