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

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# ASCO 2018: Less is more as 'tailoring' takes on new meaning

Howard A Burris III, MD

A record-setting 40,000-plus oncology professionals attended this year's annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago. The outstanding education and scientific program, with the theme of *Delivering Discoveries: Expanding the Reach of Precision Medicine*, was planned and led by ASCO President Dr Bruce Johnson, professor and director of Thoracic Oncology at the Dana Farber Cancer Institute in Boston, and chaired by Sarah Cannon's Dr David Spigel and Harvard's Dr Ann Partridge. A recurring finding throughout the meeting was that "less is more" in several key areas of cancer therapy. From small molecules targeting driver mutations across various tumors to the application of immunotherapy in subsets of common cancers, it is clear that more patients are experiencing dramatic results from novel approaches.

A featured plenary session trial was TAILORx, a study of 10,273 women with hormone-receptor–positive, surgically resected breast cancer that had not spread to the lymph nodes, was less than 5 cm, and was not positive for the HER2 gene amplification. This clinical trial was sponsored by the NCI and initiated in 2006. It used the OncotypeDX genetic test to stratify patients into groups of low, intermediate, or high risk for recurrence. The low-risk patients received only hormonal therapy, and the high-risk patients were treated with hormonal therapy plus chemotherapy.

Dr Joseph Sparano, professor of Medicine and Women's Health at the Albert Einstein College of Medicine in New York, presented the results from the group of 6,700 intermediate risk women who were randomized to receive hormonal therapy alone or in combination with chemotherapy. After 9 years of follow-up, 83.3% of the volunteers, as Dr Sparano appropriately referred to them, who were treated with hormonal therapy were still cancer free, compared with 84.3% of those who also received chemotherapy, demonstrating no statistical benefit for the addition of chemotherapy. Of note, breast cancer experts discussing the trial, including Dr Lisa Carey, professor of Breast Cancer Research at the UNC Lineberger Cancer Institute in Chapel Hill, urged that younger women, under the age of 50, with recurrence scores (RS) toward the higher end of the intermediate risk group (RS, 16-25) should still discuss and consider chemotherapy with their physicians. In summary, all patients fitting the study criteria with low (<11) and lower intermediate (<16) RS can avoid chemotherapy, as well as those patients over the age of 50 with RS <26.

These landmark and practice changing results mean that each year about 60,000 women in the United States will be spared the side effects of toxic drugs. These 10,273 study volunteers are true heroes to the women who will be diagnosed with breast cancer in coming years.

In the field of lung cancer, many new trial results using immunotherapy were presented, with the most talked about being single-agent pembrolizumab, a PD1 inhibitor, improving survival over traditional chemotherapy in patients with PD-L1 positive tumors, which comprise the majority of squamous cell and adenocarcinomas of the lung. Also in the plenary, Dr Gilberto Lopes of the Sylvester Cancer Center at the University of Miami, presented these results from the KEYNOTE-042 study. In patients with PD-L1 tumor proportion score (TPS) of >1%, the benefit in overall survival (OS) of pembrolizumab compared with chemotherapy was 16.7 versus 12.1 months, respectively (HR, 0.81). In those patients with a TPS of >20%, the OS benefit was 17.7 versus 1.0 months (HR, 0.77), and in the group with a TPS of >50%, the benefit was 20.0 versus 12.2 months (HR, 0.69). Overall, the quality of life and the occurrence of side effects were substantially better for those patients receiving immunotherapy alone. Other findings presented at the meeting demonstrated the benefit of adding immunotherapy to chemotherapy and of treating with combination immunotherapy (PD-1 and CTLA-4 inhibitors). Many options now exist, much work remains to be done, and accrual to clinical trials is more important than ever.

Another plenary session trial evaluated the benefit of per-

forming a nephrectomy in patients with advanced or metastatic renal cell carcinoma (RCC), a long-held and practiced standard of care. Dr Arnaud Mejean of Paris Descartes University presented findings from the CARMENA trial, which randomized 450 patients with metastatic clear cell RCC to receive cytoreductive nephrectomy followed by sunitinib, or sunitinib alone. The OS results of 18.4 versus 13.9 months, respectively (HR, 0.89) favored sunitinib alone in this noninferiority analysis. Other endpoints lined up in favor of not removing the cancerous kidney, and the presenter and discussants were united in their opinion of the results and the resulting change in doing less surgery in these patients.

In a step away from less therapy, the European Pediatric Soft Tissue Sarcoma Study showed that adding 6 months of low-dose maintenance chemotherapy after standard intensive therapy improves survival in children with high-risk rhabdomyosarcoma. The addition of a vinorelbine and cyclophosphamide low-dose regimen improved 5-year disease-free survival from 69.8% to 77.6% (HR, 0.68) and OS from 73.7% to 86.5% (HR, 0.52) as presented by Dr Gianni Bisogno, University of Padovani, Italy. The mainte-

nance regimen showed no increase in toxicity and actually fewer infections were noted.

In the area of molecular profiling, multiple studies at the meeting demonstrated the importance of assessing cancers for mutations as outstanding results were seen with therapies for NTRK, RET, ROS, and MSI-high driven tumors. In a debate on the role of molecular profiling, I had the opportunity to declare and support our position at Sarah Cannon that all patients with relapsed or metastatic cancers should have this testing performed. It will be through better understanding of the biology of these cancers that we will advance the field for all patients while sometimes finding a target or mutation that will dramatically change the life of a patient.

In keeping with the meeting's theme, *Delivering Discoveries: Expanding the Reach of Precision Medicine,* the presentations and the discussions clearly demonstrated that through the use of precision medicine techniques such as prognostic gene assays and molecular profiling, patients can receive the best therapy, even "tailored" therapy, which may often actually be less therapy. It is an exciting time in cancer research, and I have never been more optimistic about the future of cancer treatment for our patients.

# Therapy updates and clinical challenges

The landmark US Food and Drug Administration approvals last year of tisagenlecleucel and axicabtagene ciloluecel – the first two chimeric antigen receptor (CAR) T-cell therapies for cancer – signified a new era of therapeutic possibilities (p. e124). CAR T-cells are a type of adoptive cell therapy or immunotherapy in which a patient's immune cells are genetically engineered to target a tumor-associated antigen (in the case of these first two approvals, that target is CD19). In August, tisagenlecleucel got the green light for the treatment of B-cell precursor acute lymphoblastic leukemia in patients up to age 25 years, and in the fall, axicabtagene ciloluecel was approved for the treatment of refractory, aggressive B-cell non-Hodgkin lymphoma. The earlier this year, the agency also approved tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma. As Carl June, MD, a pioneer in CAR T-cell research notes in an interview on page e175, the next approval likely will be for multiple myeloma.

But while the science and the potential of these therapies are exciting, the impact of their cost and toxicities on patients tempers some of the enthusiasm. The Centers of Medicare & Medicaid Services is working on a final rule on payment for the inpatient administration of the two therapies for fiscal year 2019 and is considering the creation of a new Medicare Severity-Diagnosis Related Group code for procedures involving the use of CAR T-cell therapies (p. e177). Walid F Gellad, MD, of the Center for Pharmaceutical Policy and Prescribing at the University of Pittsburgh, has said that some estimates for the cost of these therapies as high as $1.5 million per patient, and there is particular concern for the older adults who make up the Medicare population. These high costs would affect access to the therapy for many patients, irrespective of age, but one encouraging development on this front would be the development of lower-priced, off-the-shelf, third-party products. Another unknown with CAR T-cell therapies is the extent of side effects in real-world patients compared with those in trials, and what the long-term posttherapy recurrence rates would be.

In addition to highlighting CAR T-cell therapies in this issue, on page e167, Jane de Lartigue takes a look at tumor heterogeneity and the challenges it presents in the ongoing quest for effective cancer treatments. Dr de Lartigue describes the two key models used to explain how tumors develop – the clonal evolution model and the cancer stem cell model. She argues that although evidence suggests the models are not mutually exclusive and contribute to heterogeneity differently in different tumor types, heterogeneity and evolution, fueled by genomic alterations, are "intricately intertwined" in the development of cancer.

With cancer therapies come side effects, psychosocial effects, and sometimes challenges with posttreatment mobility, activities of daily living, and even self-care. Three articles in this issue deal with those posttreatment issues. On page e130, Kundu and colleagues report on a prospective study in which they evaluated physical and psychosocial functioning after diagnosis of prostate cancer and the factors associated with treatment satisfaction after treatment. They found that despite declines in erectile function and sexual domains, treatment satisfaction was more closely related to emotional, psychosocial, and nonsexual effects, underscoring the importance of assessing health-related quality-of-life outcomes beyond physical functioning. Forrest and colleagues (p. e138) set out to report outcomes of patients who received radiation therapy while on an inpatient rehabilitation facility and found that comprehensive care that includes radiation and rehabilitation at the inpatient rehabilitation facility level benefits appropriately selected patients. And on page e145, Ibrahim and colleagues tracked the effectiveness of a 12-week exercise program on long-term levels of upper-limb pain in young survivors of breast cancer and found that although there was some transient improvement in shoulder pain, it did not translate in to long-term benefits.

Our usual line-up of Case Reports on clinical challenges in the practice setting includes the case of a child with carcinoma of the colon (p. e152); two separate reports on patients with therapy-related skin reactions, one with radiation dermatitis (p.e156), the other with a reaction to a checkpoint inhibitor (p. e159); and a patient with recurrence of a small gastric gastrointestinal stromal tumor with high mitotic index (p. e163).

# First CAR T-cell therapy approvals bolster booming immunotherapy market

There were a number of landmark approvals by the US Food and Drug Administration (FDA) in 2017 for cancer therapies, among them, the approval of the first two chimeric antigen receptor (CAR) T-cell therapies for cancer: tisagenlecleucel (in August) and axicabtagene ciloluecel (in October).[1] CAR T-cells are a type of adoptive cell therapy or immunotherapy, in which the patient's own immune cells are genetically engineered to target a tumor-associated antigen, in this case CD19. In tisagenlecleucel, CD19 proteins on B cells are targeted in the treatment of B-cell precursor acute lymphoblastic leukemia. Axicabtagene ciloluecel, the second anti-CD19 CAR T-cell therapy, was approved for the treatment of refractory, aggressive B-cell non-Hodgkin lymphoma.

## Tisagenlecleucel

Tisagenlecleucel was approved for the treatment of pediatric patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) whose disease is refractory to treatment or who have relapsed after second-line therapy or beyond.[2] Approval was based on the pivotal ELIANA trial, a single-arm, global phase 2 trial conducted at 25 centers worldwide during April 2015 through April 2017. Patients were eligible for enrollment if they had relapsed or refractory B-cell ALL and were at least 3 years of age at screening and no older than 21 years of age at diagnosis, had at least 5% lymphoblasts in the bone marrow at screening, had tumor expression of CD19, had adequate organ function, and a Karnofsky (adult) or Lansky (child) Performance Status of ≥50 (with the worst allowable score, 50, indicating a patient who requires considerable assistance and frequent medical care [Karnofsky] and lying around much of the day, but gets dressed; no active playing but participates in all quiet play and activities [Lansky]). Exclusion criteria included previous receipt of anti-CD19 therapy, concomitant genetic syndromes associated with bone marrow failure, previous malignancy, and/or active or latent hepatitis B or C virus (HBV/HCV) infection.

The overall remission rate (ORR) was evaluated in 75 patients who were given a single dose of tisagenlecleucel (a median weight-adjusted dose of $3.1 \times 10^6$ transduced viable T cells per kg of body weight) within 14 days of completing a lymphodepleting chemotherapy regimen. The confirmed ORR after at least 3 months of follow-up, as assessed by

### What's new, what's important

The approval of tisagenlecleucel for the treatment of pediatric patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia was based on findings from the ELIANA trial in which 75 patients were given a single dose of tisagenlecleucel after completing a lymphodepleting chemotherapy regimen. The most common adverse events (AEs) associated with tisagenlecleucel treatment included cytokine release syndrome, hypogammaglobulinemia, infection, pyrexia, decreased appetite, among others. AEs were of grade 3/4 severity in 84% of patients. To combat serious safety issues, the FDA approved tisagenlecleucel with an REMS that requires health care providers who administer the drug to be trained in their management. Common toxicities include hypersensitivity reactions, serious infections, prolonged cytopenias, and hypogammaglobulinemia. Patients should be monitored for signs and symptoms of infection. Viral reactivation can occur after tisagenlecleucel treatment, so patients should be screened for HBV, HCV, and HIV before collection of cells. The administration of myeloid growth factors is not recommended during the first 3 weeks after infusion or until CRS has resolved. Patients should also be monitored for life for secondary malignancies.

Axicabtagene ciloleucel was approved for the treatment of adult patients with certain types of relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for the treatment of patients with primary central nervous system lymphoma. Approval was based on the ZUMA-1 trial. The most common grade 3 or higher AEs included febrile neutropenia, fever, and CRS, among others. Serious AEs occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias, and serious infections. Grade 3 or higher CRS or neurologic toxicities occurred in 13% and 28% of patients, respectively. Three patients died during treatment. Axicabtagene ciloleucel is also approved with an REMS. Patients should be monitored for serious infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies, and potential neurologic events affecting the ability to drive and operate dangerous machinery.

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

## Mechanism of action: tisagenlecleucel and axicabtagene ciloleucel

Reprogramming the immune system's killers. It has long been understood that there is a dynamic and complex relationship between a tumor and the host immune system. Unique antigens displayed on a cancer cell can distinguish it from a healthy cell and drive an anti-tumor immune response. However, tumors have also evolved a multitude of mechanisms to subvert that immune response.

In recent years, a new brand of cancer therapy has sought to exploit the anti-tumor immune response by redirecting its cytotoxic activity against the tumor. CAR T-cell therapy is a particularly promising form of cell-based immunotherapy, in which the patient's own immune cells are genetically engineered to endow them with tumor cell specificity.

The T cells are the main effectors of the cell-based adaptive immune response and patrol the body seeking out foreign invaders and damaged host cells that are marked by unique antigens. On encountering one of these antigens displayed on the surface of antigen-presenting cells (such as macrophages) and bound to major histocompatibility complex (MHC) molecules, the T cell is activated by engagement of the T-cell receptor (TCR) on its surface, triggering the downstream receptor signaling pathways that the TCR orchestrates.

CAR T-cells are engineered to express a different activating receptor, known as a chimeric antigen receptor (hence, CAR). The CAR is a synthetic receptor composed of the single-chain variable fragment (scFv) of an antibody that binds to a particular tumor-associated antigen – in the case of tisagenlecleucel and axicabtagene ciloleucel, the target antigen is CD19. The scFv is fused to a part of the TCR protein that is responsible for initiating downstream signaling pathways on TCR activation – the CD3 zeta chain – and a costimulatory domain that provides a secondary signal to fully activate the T cell.
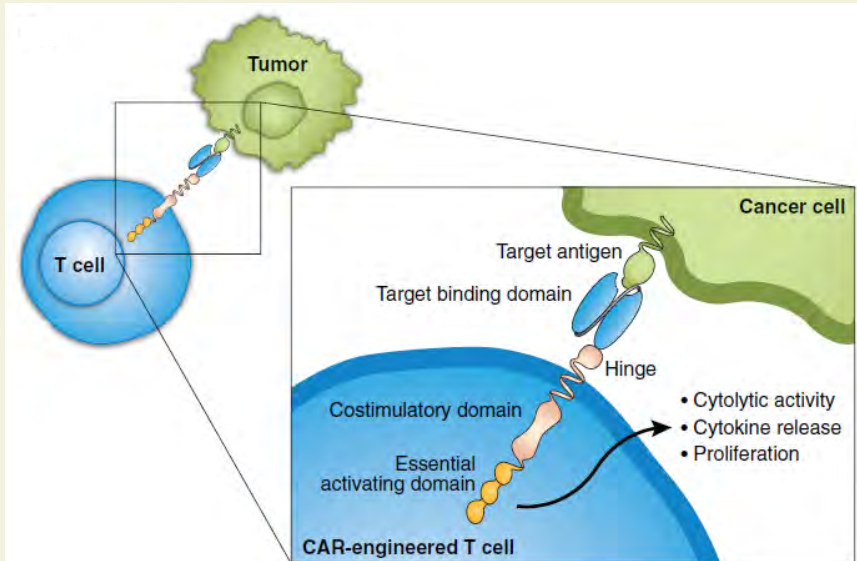


**FIGURE** CAR T-cell mechanism of action. CAR T-cells are derived from a patient's own T cells that have been genetically modified to express a synthetic immune receptor on their surface. This receptor couples the specificity of an antibody for a specific tumor-associated antigen with the T cell activating machinery and allows T cells to kill tumor cells in an MHC-independent fashion. Reproduced under a Creative Commons license: Roberts ZJ, et al. Axicabtagene ciloleucel, a first-in-class CAR T-cell therapy for aggressive NHL. Leuk Lymphoma 2017. doi: 10.1080/10428194.2017.1387905.

The CAR is designed to couple the tumor cell specificity of an antibody with the T-cell activation machinery, allowing direct activation of the T cell that expresses the CAR by a tumor-associated antigen, without the need for that antigen to be presented to the cell in a complex with MHC. Once a CAR T cell has been activated by the target antigen, it acts similarly to a normal T cell, rapidly proliferating and releasing cell-killing products, as well as cytokines that attract other immune cells to the site of the tumor.

For CAR T-cell therapy, the patient's T cells are collected via a procedure known as leukapheresis, and the CAR is introduced into the T-cell membrane through the use of a virus. The CAR-positive T cells are then infused back into the patient after a regimen of chemotherapy that is designed to deplete the patient's normal T cells, to give the CAR T-cells the best chance of success.

independent central review, was 81%, which included 60% of patients in complete remission (CR) and 21% in complete remission with incomplete hematologic recovery, all of whom were negative for minimal residual disease.

The most common adverse events (AEs) associated with tisagenlecleucel treatment were cytokine release syndrome (CRS), hypogammaglobulinemia, infection, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium. AEs were of grade 3/4 severity in 84% of patients.[3]

To combat serious safety issues, including CRS and neurologic toxicities, the FDA approved tisagenlecleucel with a Risk Evaluation and Mitigation Strategy (REMS) that, in part, requires health care providers who administer the drug to be trained in their management. It also requires the facility where treatment is administered to have immediate,

onsite access to the drug tocilizumab, which was approved in conjunction with tisagenlecleucel for the treatment of patients who experience CRS.

In addition to information about the REMS, the prescribing information details warnings and precautions relating to several other common toxicities. These include hypersensitivity reactions, serious infections, prolonged cytopenias, and hypogammaglobulinemia.

Patients should be monitored for signs and symptoms of infection and treated appropriately. Viral reactivation can occur after tisagenlecleucel treatment, so patients should be screened for HBV, HCV, and human immunodeficiency virus before collection of cells.

The administration of myeloid growth factors is not recommended during the first 3 weeks after infusion or until CRS has resolved. Immunoglobulin levels should be monitored after treatment and hypogammaglobulinemia managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement according to standard guidelines.

Patients treated with tisagenlecleucel should also be monitored for life for secondary malignancies, should not be treated with live vaccines from 2 weeks before the start of lymphodepleting chemotherapy until immune recovery after tisagenlecleucel infusion, and should be aware of the potential for neurological events to impact their ability to drive and use dangerous machinery.[4]

Tisagenlecleucel is marketed as Kymriah by Novartis Pharmaceuticals. The recommended dose is 1 infusion of 0.2-5 x $10^6$ CAR-positive viable T cells per kilogram of body weight intravenously (for patients ≤50kg) and 0.1-2.5 x $10^8$ cells/kg (for patients >50kg), administered 2-14 days after lymphodepleting chemotherapy.

### Axicabtagene ciloleucel

Axicabtagene ciloleucel was approved for the treatment of adult patients with certain types of relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.[5] It is not indicated for the treatment of patients with primary central nervous system lymphoma.

Approval followed positive results from the phase 2 single-arm, multicenter ZUMA-1 trial.[6] Patients were included if they were aged 18 years of age and older, had histologically confirmed aggressive B-cell non-Hodgkin lymphoma that was chemotherapy refractory, had received adequate previous therapy, had at least 1 measurable lesion, had completed radiation or systemic therapy at least 2 weeks before, had resolved toxicities related to previous therapy, and had an Eastern Cooperative Oncology Group Performance

Status of 0 (asymptomatic) or 1 (symptomatic), an absolute neutrophil count of ≥1000/µL, a platelet count of ≥50,000/µL, and adequate hepatic, renal and cardiac function. They were treated with a single infusion of axicabtagene ciloleucel after lymphodepleting chemotherapy.

Patients who had received previous CD19-targeted therapy, who had concomitant genetic syndromes associated with bone marrow failure, who had previous malignancy, and who had active or latent HBV/HCV infection were among those excluded from the study.

Patients were enrolled in 2 cohorts; those with DLBCL (n = 77) and those with PMBCL or transformed follicular lymphoma (n = 24). The primary endpoint was objective response rate, and after a primary analysis at a minimum of 6 months follow-up, the objective response rate was 82%, with a CR rate of 52%. Among patients who achieved CR, the median duration of response was not reached after a median follow-up of 7.9 months.

A subsequent updated analysis was performed when 108 patients had been followed for a minimum of 1 year. The objective response rate was 82%, and the CR rate was 58%, with some patients having CR in the absence of additional therapies as late as 15 months after treatment. At this updated analysis, 42% of patients continued to have a response, 40% of whom remained in CR.

The most common grade 3 or higher AEs included febrile neutropenia, fever, CRS, encephalopathy, infections, hypotension, and hypoxia. Serious AEs occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias, and serious infections. Grade 3 or higher CRS or neurologic toxicities occurred in 13% and 28% of patients, respectively. Three patients died during treatment.

To mitigate the risk of CRS and neurologic toxicity, axicabtagene ciloleucel is approved with an REMS that requires appropriate certification and training before hospitals are cleared to administer the therapy.

Other warnings and precautions in the prescribing information relate to serious infections (monitor for signs and symptoms and treat appropriately), prolonged cytopenias (monitor blood counts), hypogammaglobulinemia (monitor immunoglobulin levels and manage appropriately), secondary malignancies (life-long monitoring), and the potential effects of neurologic events on a patient's ability to drive and operate dangerous machinery (avoid for at least 8 weeks after infusion).[7]

Axicabtagene ciloleucel is marketed as Yescarta by Kite Pharma Inc. The recommended dose is a single intravenous infusion with a target of 2 x $10^6$ CAR-positive viable T cells per kilogram of body weight, preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy.

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# Psychosocial factors and treatment satisfaction after radical prostatectomy

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**Background** Sexual and urinary side effects of prostate cancer treatment have been well described in the literature, but less is known about the psychosocial effects of prostate cancer treatment.
**Objective** To prospectively evaluate physical and psychosocial functioning after diagnosis of prostate cancer and factors associated with treatment satisfaction after prostate cancer treatment.
**Methods** Patients diagnosed with prostate cancer at a university-based urology department were invited to participate in this internet-based study. Validated questionnaires were used to evaluate health-related quality of life (HRQoL) domains at pretreatment baseline following diagnosis and at 1, 3, 6, and 12 months after treatment. Domains of HRQoL included sexual, urinary, and bowel functioning; anxiety and depression; and sleep disturbance, pain, and fatigue. Linear repeated measures models were used to examine changes in self-reported measures at each time point.
**Results** Of 105 men diagnosed with prostate cancer enrolled in the study, 54 completed assessments through 12 months. Decreased erectile function and sexual HRQoL following treatment were not significantly associated with worse treatment satisfaction over time. Instead, treatment satisfaction was significantly associated ($P < .01$) with anxiety ($r$, .28-.60), depression ($r$, .32-.48), fatigue ($r$, .40-.56), pain ($r$, .32-.61), sleep disturbance ($r$, .51-.59), and bladder problems ($r$, .41-.63).
**Limitations** Not all patients were enrolled or completed all longitudinal questionnaires, which may bias the results because of unmeasurable factors. We were not able to identify improvements or declines in HRQoL more than 12 months after treatment.
**Conclusions** Despite declines in erectile function and sexual domains, treatment satisfaction was more closely related to emotional, psychosocial, and nonsexual effects. The findings underscore the importance of assessing HRQoL outcomes beyond physical functioning, which can yield opportunities to improve satisfaction.

More than 164,690 men are expected to be diagnosed with prostate cancer in the United States in 2018.[1] Men with prostate cancer face not only stress associated with the diagnosis but also decisional conflict regarding different treatment options.[2] Most men diagnosed with clinically localized prostate cancer receive 1 or more of the following treatments: radical prostatectomy, external-beam radiation therapy, and/or brachytherapy, all of which are associated with posttreatment urological or sexual side effects including bowel, urinary, or erectile dysfunction.[3-5] Men who choose active surveillance may experience increased anxiety associated with the constant vigilance and monitoring of their tumor status along with the uncertainty of not definitively removing or radiating their prostate.[6] In addition to direct functional limitations of sexual and urological side effects, treatment can also lead to secondary psychosocial effects, including depression, self-blame, embarrassment, guilt, lower masculine self-esteem, increased reticence to participate socially or engage in sexual activity, and relationship distress.[7-9] Therefore, health-related quality of life (HRQoL) and treatment satisfaction are important for this population.

Urological and sexual side effects of prostate cancer treatments are often a primary focus during treatment decision making between patients and providers. However, little prospective empirical data exist regarding the role of HRQoL and other nonurological physical and psychosocial outcomes on overall treatment satisfaction. The purpose of this study was to prospectively evaluate the role of both urological and nonurological outcomes on overall treatment satisfaction in men diagnosed with prostate cancer. We hypothesize that such an under-

standing can help describe changes in physical and psychosocial factors that are important to men beyond traditional urological outcomes, including their association with overall treatment satisfaction.

## Methods

This was a prospective longitudinal assessment of patients from the Department of Urology at Northwestern University's Feinberg School of Medicine in Chicago. Patients were eligible if they met the following inclusion criteria: they had been diagnosed with clinically localized or locally advanced prostate cancer; they had not yet received a primary treatment (eg, surgery, radiation, active surveillance) before their baseline assessment; they were 18 years or older; and they were able to read, write, speak, and understand English. Patients were excluded if they had a physical debilitation that would make participation not feasible or would create undue hardship, or if they had a history of diagnosed severe mental illness or hospitalization for chronic psychiatric reasons, as identified by referring physicians.

Eligible participants were approached before their treatment decision (if any). Patient enrollment occurred in 2 ways. For patients invited to participate during their clinic visit, the research assistant explained the study and obtained written informed consent for interested patients. A unique user identification and password was created for each patient, and they practiced using the touch screen computer while the research assistant observed and provided guidance as needed. When the patients were ready to start their pretreatment online interview, they completed the questionnaires by themselves. For patients who were invited to participate but were not scheduled to return in the foreseeable future, enrollment was carried out differently. In those cases, participating physicians contacted eligible patients who were not scheduled for a visit and informed them of the study opportunity. Interested patients were contacted by the research assistant who provided them with the study website address, which directed them to the online consent form. After a patient had completed the consent form, he was prompted to self-register. He received a unique user identification and password that could be used to complete the baseline assessment and subsequent assessments. However, for interested patients who did not have access to a computer or Internet connection, the research assistant provided them with paper consent forms and paper versions of all study assessments. After participants had completed the baseline assessment, the research assistant provided them with a written schedule of future assessments, which were expected to occur at 1 month posttreatment, 3 months posttreatment, 6 months posttreatment, and 12 months posttreatment.

For all follow-up appointments, participants could complete assessments either at clinic visits or from home using a secure online assessment platform called Assessment Center (https://www.assessmentcenter.net/).[10] The research assistant used a patient log to track participants and their progress in the study, which included study number, patient name (or initials), registration date, date of birth, sex, and timeline of completed or future assessments. The research assistant called or emailed participants (depending on patient preference) about a week before each of their follow-up assessments to facilitate adherence. If the participant did not log into the system by the target day, the research assistant contacted him the following day (target day +1) with a phone or email reminder to log into the system and complete the assessments. If the participant did not log in by midnight 1 day after the target day, the research assistant attempted to contact him one last time (target day +2) with either a reminder to log into the system or to ascertain his status that might be related to his noncompletion. Overall, a participant was called or e-mailed 1 to 3 times to remind him of his assessment. If he was unresponsive after 3 attempts, he was recorded as having withdrawn for an unknown reason.

At baseline and each follow-up time point, study participants completed a battery of patient-reported outcome measures, with most coming from the Patient-Reported Outcomes Measurement Information System (PROMIS)[11] and the Surgical Outcomes Measurement System (SOMS).[12] PROMIS is a National Institutes of Health (NIH) funded measurement system that has helped standardize and improve self-reported assessment of health status, symptoms, side effects, and different aspects of HRQoL, including physical, emotional, cognitive, and social health (www.nihpromis.org). SOMS is a suite of patient-reported outcome measures assessing important aspects of HRQoL after surgery. It was developed with feedback from surgeons, postoperative patients, and surgical nurses. PROMIS items were directly incorporated into numerous SOMS measures to facilitate easier comparisons and score crosswalks across measures and patient populations. In addition to PROMIS and SOMS measures, we also administered several well-known instruments of urological and sexual function, including the International Index of Erectile Function (IIEF) and American Urological Association Symptom Score Index (AUASS).[13,14]

Outcome measures were compared across sociodemographic and clinical variables at each time point using $t$ tests for numerical variables (age) and with chi-square or Fisher exact tests for categorical variables; those variables with significant differences were used as covariates in statistical models. To examine differences in patient-reported scores over time, we used repeated measures analysis of covariance with general linear modeling methods. We used Pearson correlation coefficients to evaluate for correlations between quality-of-life outcomes and treatment satisfaction.

Not all participants completed each of the follow-up

surveys, and reasons for dropout were prospectively documented. Most participants elected surgical resection as their primary treatment compared with the fewer than 10% of patients who chose radiation or chemotherapy as their primary treatment and about 20% of men who chose active surveillance after their initial diagnosis. Therefore, our analysis focused on patients who elected surgical resection. For comparison purposes, we included the HRQoL results from active surveillance patients.

## Results

A total of 105 patients diagnosed with prostate cancer were enrolled in the study. Response rates decreased throughout the study (n = 75 at 1 month; n = 71 at 3 months; n = 64 at 6 months; n = 54 at 12 months). Sociodemographic and clinical characteristics of participants are shown in Table 1. The mean change from pretreatment (baseline) scores for each measure in patients treated with surgery is shown in Table 2, and the mean change from pretreatment scores in patients who elected active surveillance is shown in Table 3 (in both tables, a negative score denotes worsened function, and a positive change denotes improvement).

After surgery, patients reported significantly lower erectile function and sexual satisfaction scores. These included statistically significant decreases for IIEF Erectile Function, IIEF Overall Satisfaction, PROMIS Sexual Satisfaction, PROMIS Sexual Interest, and PROMIS Orgasm. In patients treated with surgery, there were significant improvements in anxiety observed for patients at each follow-up time, whereas significantly worse bladder problems were observed on SOMS Bladder at 1 and 3 months but returned to baseline by 12 months after surgery. AUASS was worse at 1 month but significantly improved at 6 and 12 months. Fatigue scores significantly worsened at 1 month but were no longer significant at 6 and 12 months. Physical Function was worsened at 1 month but not throughout the rest of the study. Bowel Problems (SOMS) were significantly worse at 1 month, but changes became nonsignificant on subsequent assessments. The only 2 domains that did not demonstrate any significant changes over time were Pain Interference and Sleep Disturbance (both SOMS).

In active surveillance patients, sexual function domains were generally unchanged over the course of the study. However, unlike treated patients, there was no significant improvement in anxiety, depression, pain, fatigue, or sleep. In fact, most of these domains demonstrated worsened functioning, although these were not statistically significant. Urinary domains generally remained unchanged.

Pearson correlation coefficients between HRQoL measures and overall treatment satisfaction (assessed by the question, *Are you satisfied with the results of your operation?*) at each follow-up time point in patients treated with surgery are shown in Table 4. Relations between treatment satisfaction and sexual outcomes were generally statistically insignificant (*r*, .08-.56). However, sleep disturbance, depression, pain interference, fatigue, embarrassment, and bladder problems all demonstrated statistically significant positive associations with treatment satisfaction, with coefficients ranging from small to medium in magnitude (*r*, .32-.61). Other outcomes such as anxiety, physical function, and bowel problems demonstrated small to medium statistically significant associations with treatment satisfaction (*r*, .04-.60) but not at every time point. We performed *t* tests to examine treatment satisfaction in patients with detectable initial posttreatment prostate-specific antigen (PSA; >0.01 ng/mL). We found no difference in treatment satisfaction between patients with detectable PSA values and those with undetectable PSA at each time point.

When the patients were asked, *Compared with what you expected, how do you rate the results of your operation?*, most of those treated with surgery reported that the results of their operation were better than they had expected (Figure 1A; p. e137). More than 75% of the patients had results that were as expected or better than expected. When asked, *Compared with what you expected, how do you rate your side effects of the operation?*, almost 70% of patients reported side effects no worse than expected (Figure 1B). When asked, *Are you satisfied with the results of your operation?*, most patients reported that overall, they were satisfied with the results of their operation (Figure 1C). At 12 months, none of the patients reported overall dissatisfaction with their treatment choice. More than 90% of patients were mostly or completely satisfied with the results of their operation.

## Discussion

This prospective study assessed the HRQoL from pretreatment through 12 months posttreatment in men diagnosed with clinically localized prostate cancer that had been treated with surgery. Although the indicators of sexual function significantly decreased over time, they were not meaningfully associated with overall treatment satisfaction. Instead, a host of other factors, including psychosocial (eg, anxiety, depression, body image dissatisfaction, embarrassment), nonurological physical symptoms (pain interference, physical function, sleep disturbance, fatigue), and bladder problems, were significantly related to overall treatment satisfaction. Although this may not be surprising in other clinical oncology paradigms, the sheer surfeit of focus and attention on sexual function has overshadowed aspects of HRQoL that many men report are important to them, despite worsened sexual function outcomes.

Understanding potential treatment-related changes in HRQoL can be challenging for men when choosing providers and different therapeutic options. The increasing complexity of treatment in prostate cancer has created an opportunity to not only understand efficacy on cancer control but also focus on meaningful patient-reported

**TABLE 1** Patient baseline sociodemographic and clinical characteristics (N = 105)

| Variable | n (%) or *mean (SD)* |
|---|---|
| **Educational status** | |
| Some high school | 1 (1.0) |
| High school grad/general equivalency diploma | 8 (7.6) |
| Some college/technical/associate degree | 27 (25.7) |
| College degree (BA/BS) | 26 (24.8) |
| Advanced degree (MA, PhD, MD) | 43 (41.0) |
| **Family household income, US$** | |
| less than 20,000 | 5 (4.8) |
| 20,000-49,999 | 15 (14.4) |
| 50,000-99,999 | 31 (29.8) |
| ≥100,000 | 53 (51.0) |
| **Current relationship status** | |
| Never married | 8 (7.6) |
| Married | 74 (70.5) |
| Committed relationship | 7 (6.7) |
| Separated | 2 (1.9) |
| Divorced | 11 (10.5) |
| Widowed | 3 (2.9) |
| **No. of children** | 1.8 |
| **Height, inches** | 70.1 |
| **Weight, lbs** | 195.8 |
| **Smoking history** | |
| Ever smoked tobacco products | 58 (55.2) |
| Currently smoke tobacco products | 8 (7.6) |
| Average cigarettes smoked a day | 5.4 |
| **Alcohol consumption** | |
| Currently drink alcohol | 85 (81.0) |
| Days a week drink alcohol | 3.2 |
| Alcohol drinks per occasion a day | 2 |
| **Treatment choice** | |
| Radical prostatectomy | 63 (60) |
| Radiation therapy | 9 (8.6) |
| Active surveillance | 21 (20) |
| Chemotherapy | 1 (1) |
| Missing | 11 (10.5) |
| **Clinical stage (n = 104)[a]** | |
| cT1c | 86 (82.6) |
| cT2a | 12 (11.5) |
| cT2b | 3 (2.9) |
| cT2c | 2 (1.9) |
| cT3b | 1 (1.0) |

| Variable | n (%) or *mean (SD)* |
|---|---|
| **Pathological stage (n = 51)[b]** | |
| pT2a | 6 (11.8) |
| pT2c | 30 (58.8) |
| pT3a | 10 (19.6) |
| pT3b | 4 (7.8) |
| pT3c | 1 (2.0) |
| **Prostate-specific antigen (ng/mL)** | 9.7 |
| **Clinical biopsy Gleason score (n = 104)[a]** | |
| 3 + 3 | 52 (50.0) |
| 3 + 4 | 28 (26.9) |
| 4 + 3 | 13 (12.5) |
| 4 + 4 | 6 (5.77) |
| 4 + 5 | 5 (4.8) |
| 5 + 4 | 0 |
| 5 + 5 | 0 |
| **Surgical pathology Gleason score (n = 51)[b]** | |
| 3 + 3 | 21 (35.0) |
| 3 + 4 | 19 (31.7) |
| 4 + 3 | 12 (20.0) |
| 4 + 4 | 3 (5.0) |
| 4 + 5 | 5 (8.3) |
| 5 + 4 | 0 |
| 5 + 5 | 0 |
| **Catheter at time of diagnosis** | 6 (11.1) |
| **Previous cancer diagnosis** | 7 (0.07) |
| **Previous surgery** | |
| Abdominal | 25 (24.0) |
| Superficial soft tissue | 10 (9.6) |
| Orthopedic | 33 (31.7) |
| Other | 23 (22.1) |
| **Comorbid medical conditions** | |
| Coronary artery disease | 9 (8.7) |
| Chronic kidney disease | 1 (1.0) |
| Diabetes mellitus | 12 (11.5) |
| Hyperlipidemia | 39 (37.5) |
| Hypertension | 52 (50.0) |
| Peripheral vascular disease | 1 (1.0) |
| Hypothyroidism | 4 (3.8) |
| Depression | 4 (3.8) |
| Mental health problem (not depression) | 2 (1.9) |
| Other | 44 (42.3) |

[a]One patient completed the baseline survey but was subsequently lost to follow-up. [b]Nine patients completed baseline surveys and underwent treatment but did not complete follow-up questionnaires.

**TABLE 2** Pretreatment baseline and difference from baseline scores of health-related quality-of-life outcomes over 12 months in patients treated with surgery[a]

| Measurement tool/domain | Baseline[b] (n = 63) | Mean score (standard error) | | | |
|---|---|---|---|---|---|
| | | Difference from baseline, months after surgery | | | |
| | | 1 (n = 53) | 3 (n = 50) | 6 (n = 46) | 12 (n = 42) |
| **IIEF** | | | | | |
| Erectile function | 19.80 (1.29) | −15.36* (1.33) | −13.53* (1.31) | −14.37* (1.28) | −12.77* (1.36) |
| Overall satisfaction | 7.03 (0.36) | −2.73* (0.41) | −2.52* 0.36) | −2.64* (0.37) | −2.29* (0.44) |
| **PROMIS** | | | | | |
| Sexual satisfaction | 58.34 (1.24) | −12.12* (3.12) | −9.95* (1.45) | −10.81* (1.41) | −10.92* (1.62) |
| Sexual interest | 54.62 (0.95) | −6.25* (0.99) | −4.77* (0.79) | −3.99* (1.00) | −3.44* (1.01) |
| Orgasm | 12.21 (0.22) | −0.98** (0.35) | −0.43 (0.39) | −0.37 (0.32) | −0.58 (0.40) |
| **SOMS** | | | | | |
| Anxiety | 22.57 (0.53) | 1.96* (0.46) | 2.80* (0.48) | 2.73* (0.51) | 2.34* (0.60) |
| Depression | 25.86 (0.47) | 0.91 (0.49) | 1.21* (0.43) | 1.04** (0.45) | 0.60 (0.58) |
| Pain interference | 28.44 (0.35) | −0.40 (0.52) | 0.49 (0.38) | 0.43 (0.50) | −0.07 (0.50) |
| Fatigue | 31.00 (0.47) | −2.26* (0.59) | −0.63 (0.53) | −0.63 (0.54) | −0.31 (0.66) |
| Sleep disturbance | 16.11 (0.39) | −0.60 (0.42) | −0.21 (0.39) | 0.10 (0.41) | −0.24 (0.45) |
| Physical function limitation | 34.97 (0.30) | −1.60* (0.42) | −0.24 (0.22) | −0.25 (0.36) | −0.24 (0.31) |
| Bladder | 28.79 (0.57) | −4.79* (0.68) | −2.25* (0.55) | −1.22 (0.64) | −0.47 (0.61) |
| Bowel | 31.02 (0.36) | −1.22** (0.49) | 0.59 (0.34) | 0.21 (0.43) | 0.33 (0.36) |
| **AUA Symptom Score** | 26.39 (1.00) | −2.72** (1.02) | 0.09 (0.84) | 2.34** (0.90) | 2.45* (0.82) |

AUA, American Urological Association; IIEF, International Index of Erectile Function; PROMIS, Patient-Reported Outcomes Measurement Information System; SOMS, Surgical Outcomes Measurement System

[a]Negative numbers denote worse; positive numbers denote improvement. [b]Baseline was pretreatment, following diagnosis.

*$P < .01$. **$P < .05$.

outcomes. Hospitals and medical groups are increasingly aware of the importance of improving the patient care experience. Objective measures of patient satisfaction for health care providers, such as the Press-Ganey (www.press-ganey.com) and Net Promoter score, exist to measure and improve patient experience. In prostate cancer, clinicians and large groups, including governmental agencies such as the US Preventive Services Task Force, have often focused on declines in urinary and erectile function[15] without considering the full impact of prostate cancer treatment on global HRQoL. Our study was a prospective, longitudinal, self-reported examination of the impact, positive and negative, of prostate cancer treatment over a 12-month period.

Numerous studies have documented the treatment-related side effects of erectile, urinary, and bowel dysfunction in patients treated for prostate cancer, which may occur after definitive local therapies.[5,16-18] The present study shows a similar impact on urinary, bowel, and erectile domains after treatment. Although erectile function scores remained lower through the course of the 12-month study, bowel and

**TABLE 3** Pretreatment baseline and difference from baseline scores of health-related quality-of-life outcomes over 12 months in patients on active surveillance[a]

| Measurement tool Domain | Baseline[b] (n = 63) | Mean score (standard error) | | | |
|---|---|---|---|---|---|
| | | Difference from baseline, months after surgery | | | |
| | | 1 (n = 53) | 3 (n = 50) | 6 (n = 46) | 12 (n = 42) |
| **IIEF** | | | | | |
| Erectile function | 17.71 (2.37) | −0.29 (1.90) | 1.36 (2.28) | −0.76 (2.83) | 0.16 (2.79) |
| Overall satisfaction | 6.95 (0.51) | 0.03 (0.53) | −0.70 (0.49) | −0.51 (0.61) | −1.30 (0.73) |
| **PROMIS** | | | | | |
| Sexual satisfaction[c] | 54.29 (2.62) | 3.50* (1.14) | 2.15 (1.55) | 4.05 (2.18) | −0.81 (2.17) |
| Sexual interest | 55.24 (1.92) | −0.95 (2.12) | −1.34 (2.32) | −1.92 (2.12) | −3.97 (1.92) |
| Orgasm[c] | 12.43 (0.46) | −0.48 (0.39) | 0.01 (0.46) | 0.13 (0.57) | −0.62 (0.67) |
| **SOMS** | | | | | |
| Anxiety | 22.48 (1.04) | 0.49 (0.84) | 0.38 (0.66) | 1.93 (0.94) | 0.41 (1.34) |
| Depression | 26.95 (0.70) | −1.19 (0.68) | −1.71 (1.18) | −1.28 (1.13) | −2.02 (1.23) |
| Pain interference | 28.43 (0.64) | −0.63 (0.52) | −2.13 (1.24) | −1.67 (1.31) | −1.91** (0.87) |
| Fatigue | 30.33 (1.14) | −1.16 (1.02) | −2.73 (1.44) | −1.26 (1.78) | −2.05 (1.22) |
| Sleep disturbance | 17.48 (0.34) | −0.89 (0.53) | −1.34** (0.63) | −1.16 (1.07) | −1.19 (0.82) |
| Physical function limitation | 34.43 (0.73) | −0.54** (0.25) | −1.63 (1.01) | −1.61 (1.45) | −2.42** (0.83) |
| Bladder | 28.83 (0.91) | −0.40 (0.59) | −0.22 (0.89) | −1.24 (1.04) | −1.47 (0.87) |
| Bowel | 31.19 (0.55) | −0.43 (0.89) | −0.69 (0.74) | −0.69 (0.83) | −2.27 (1.18) |
| **AUA Symptom Score** | 27.57 (1.20) | −0.73 (1.42) | −0.34 (1.62) | −2.58 (1.67) | −2.73 (1.79) |

AUA, American Urological Association; IIEF, International Index of Erectile Function; PROMIS, Patient-Reported Outcomes Measurement Information System; SOMS, Surgical Outcomes Measurement System.

[a]Negative numbers denote worse; positive numbers denote improvement. [b]Baseline was pretreatment, following diagnosis. [c]Fitted with heterogeneous first-order autoregressive covariance structure.

*P < .01. **P < .05.

bladder domains returned to baseline by month 12. Unlike other studies, we also examined psychosocial and nonurological aspects of prostate cancer treatment. We found that there was a measurable and significant positive impact on other HRQoL measurements such as decreased anxiety. Despite a variety of declines across HRQoL domains, most patients reported that their results were largely as they had expected, and their side effects were the same or better than they had expected. No patient in the cohort reported being dissatisfied with his overall treatment, and more than 90% of patients were mostly or completely satisfied with their treatment choice. This highlights the point that while sexual and other urological domains of HRQoL are important, impairments in these areas do not necessarily reflect how many patients perceive success or satisfaction with their treatment choice. We also showed cor-

**TABLE 4** Correlation between treatment satisfaction and patient-reported outcomes following prostate cancer surgical treatment (relations are reported as associations of improved function with improved satisfaction)[a]

| Measurement tool/domain | Treatment satisfaction[b] | | | |
|---|---|---|---|---|
| | 1 month (n = 53) | 3 months (n = 50) | 6 months (n = 46) | 12 months (n = 42) |
| **IIEF** | | | | |
| Erectile function | –0.10 | –0.12 | –0.12 | 0.11 |
| Overall satisfaction | 0.15 | 0.24 | 0.12 | 0.31 |
| **PROMIS** | | | | |
| Sexual satisfaction[c] | 0.56* | -0.08 | 0.39 | 0.55* |
| Sexual interest | 0.19 | 0.06 | 0.20 | 0.06 |
| Orgasm[c] | 0.25 | 0.48* | 0.17 | 0.37 |
| **SOMS** | | | | |
| Anxiety | 0.60** | 0.43** | 0.28 | 0.44** |
| Depression | 0.47** | 0.48** | 0.32* | 0.37* |
| Pain interference | 0.33* | 0.49** | 0.61** | 0.32* |
| Fatigue | 0.56** | 0.40** | 0.51** | 0.46** |
| Sleep disturbance | 0.59** | 0.51** | 0.55** | 0.51** |
| Physical function limitation | 0.28* | 0.24 | 0.43** | 0.20 |
| Bladder | 0.41** | 0.63** | 0.58** | 0.53** |
| Bowel | 0.51** | 0.40** | 0.35* | 0.04 |
| **AUA Symptom Score** | 0.56** | 0.63** | 0.50** | 0.34* |

AUA, American Urological Association; IIEF, International Index of Erectile Function; PROMIS, Patient-Reported Outcomes Measurement Information System; SOMS, Surgical Outcomes Measurement System

[a]Pearson correlation coefficients (*r*). Data were not available for all enrolled participants. Numbers of patients vary for each correlation coefficient from n = 14 to 20 for PROMIS Sexual Satisfaction to the number of patients observed at each time shown at the top of each respective column. [b]Treatment satisfaction ascertained by the question, *Are you satisfied with the results of your operation?* *$P < .05$. **$P < .01$.

which allowed evaluation of HRQoL outcomes at multiple time points throughout the first year after treatment. In addition, we used existing patient-reported outcome tools validated by the NIH to assess changes in HRQoL. PROMIS is an NIH-supported tool that can be leveraged in the pre- and posttreatment periods to identify patients who have impairments with HRQoL. It can provide clinicians with a unique opportunity to detect and intervene in setbacks and side effects to improve patient satisfaction and HRQoL.

Limitations of the current study include that most patients selected surgery for their treatment choice and that not all patients completed all longitudinal questionnaires, although this is expected in longitudinal studies of this nature. Although all the patients were approached and encouraged to participate, many did not participate and were not captured. In addition, not all patients completed end-of-study surveys. These factors may have biased our results because of unmeasurable factors related to nonparticipation or dropout. Our study encompassed the preoperative period up to 12 months postoperatively, which may fail to identify improvements or declines in HRQoL that may occur more than 12 months postoperatively, particularly related to continence and erectile function. The participants were enrolled by 6 surgeons, and we were not able to standardize the preoperative counseling either preoperatively or postoperatively, which may have biased our results. Finally, our study population consisted of predominantly white, married men of higher socioeconomic status; therefore, our results may not be generalizable to newly diagnosed prostate cancer patients overall.

relations between treatment satisfaction and improvement in sleep, anxiety, depression, and fatigue. It is worth noting that although there were decreases in the erectile and sexual function domains after treatment, those factors were not correlated with overall treatment satisfaction. Those factors may not routinely be assessed before, during, and after treatment for prostate cancer in most clinical encounters. However, because they were strongly associated with satisfaction with treatment outcomes in this study, identification in impairments may lead to opportunities to intervene and improve the patient experience. Therefore, important "teachable moments" may be missed (for both patients and providers) during treatment decision-making encounters if other factors beyond sexual and urological outcomes are not adequately considered and addressed. Furthermore, the results of our study may help clinicians counsel patients on their expectations for their recovery after surgery and identify particular issues related to HRQoL to pay close attention to in follow-up visits.

Strengths of our study include its prospective nature,

## Conclusions
By using validated self-administered questionnaires, we found that despite decreased sexual and urinary function, patients treated for prostate cancer were satisfied with their treatment choice. Correlates to higher patient satisfaction included decreased anxiety, depression, fatigue, and sleep disturbances.

**FIGURE** Patient-reported satisfaction with A, results compared with expectations following surgery, B, side effects compared with expectations following surgery, and C, overall satisfaction following surgery.
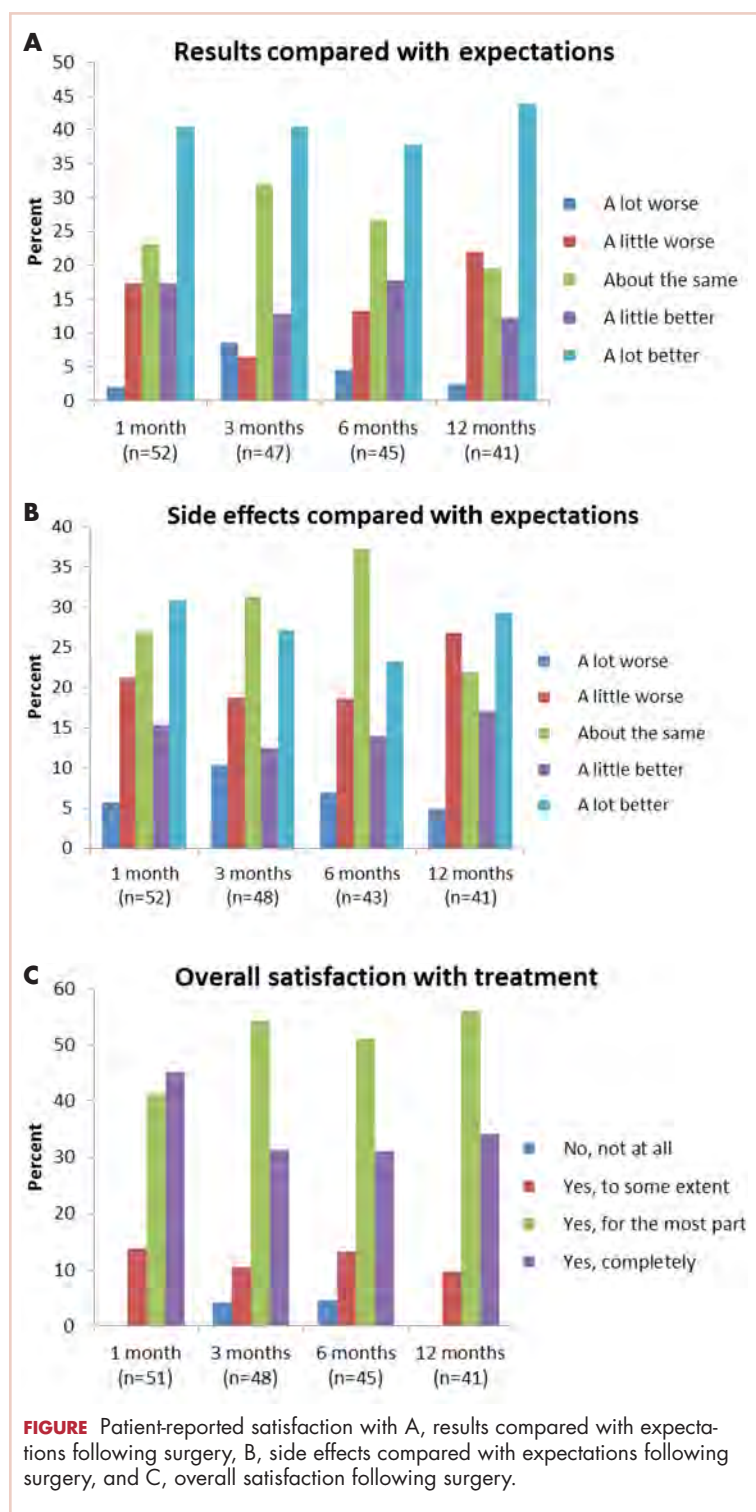
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# The impact of inpatient rehabilitation on outcomes for patients with cancer

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**Background** Patients with cancer have challenges around mobility, activities of daily living, and self-care.

**Objective** To report outcomes of patients who received radiation therapy while on an inpatient rehabilitation facility (IRF).

**Methods** 61 patients admitted to an IRF with either a primary malignant brain tumor, tumor metastatic to the brain, tumor metastatic to the spine with spinal cord injury, or tumor metastatic to bone. Each patient required radiation therapy. The study notes the outcomes of 69 patients admitted with stroke and 23 patients admitted with a traumatic spinal cord injury. Each patient was offered therapy in accordance with the Center for Medicare and Medicaid Services guidelines. Level of function was assessed using Functional Independence Measure. Outcome measures were improvement in function, functional level at discharge, length of stay, and percent discharged to home.

**Results** The patients in the cancer group had significant improvement in function. More than 75% of the patients with cancer returned to their homes. The functional level achieved by patients with primary malignancies of the brain or tumors metastatic to the brain was not significantly different than that of patients with stroke. The functional level achieved by patients with cancer metastatic to the spine was not significantly different than that of patients with a traumatic spinal cord injury. The percent of patients with cancer discharged to home was not significantly different than that of patients without cancer.

**Limitations** The study reports outcomes from only 1 IRF.

**Conclusions** Comprehensive care that includes radiation and rehabilitation at the IRF level benefits appropriately selected patients with cancer.

The American Cancer Society reports that 1.6 million people are diagnosed with cancer each year, of whom 78% are aged 55 years or older. The 5-year survival rate for cancer is 68%.[1] Almost 15.5 million living Americans have been diagnosed with cancer.[2] Many patients with cancer have difficulty walking and with activities of daily living. Patients with primary brain tumors or tumors metastatic to the brain may present with focal weakness or cognitive deficits similar to patients with stroke. Patients with tumors metastatic to the spine may have the same deficits as a patient with a traumatic spinal cord injury. Patients with metastasis to bone may have pathologic fractures of the hip or long bones. Patients may develop peripheral neuropathy associated with a paraneoplastic syndrome, chemotherapy, or critical illness neuropathy. Lehmann and colleagues evaluated 805 patients admitted to hospitals affiliated with the University of Washington Medical School with a diagnosis of cancer and found that 15% had difficulty walking and 20% had difficulty with activities of daily living.[3]

Many patients with cancer can benefit from inpatient rehabilitation.[4,5] Study findings have shown that patients with impairments in function related to cancer are often not referred for rehabilitation. Among the reasons mentioned for that are that oncologists are more focused on treating the patients' cancer than on their functional deficits and that specialists in rehabilitation medicine do not want to be involved with patients with complex medical problems. Rehabilitation facilities may not want to incur the costs associated with caring for patients with cancer.[6]

The present paper looks at the outcomes of 61 consecutive patients with cancer who were admitted to an inpatient rehabilitation facility (IRF) and received radiation therapy concurrent with rehabilitation. It compares the outcomes of the cancer patients with the outcomes of patients without cancer who were admitted with stroke or spinal cord injury, conditions more commonly treated at an IRF.

## Methods

We reviewed electronic medical records of all patients with cancer admitted to the IRF from 2008 through 2013 who received radiation ther-

**TABLE 1** Demographics and analysis of admission Functional Independence Measure, discharge FIM, change in FIM, and length of stay for each subgroup

| | n | Male: Female, % | Average age, y | ADM FIM[ab] | D/C FIM[ab] | Change in FIM[ab] | LoS, d | FIM efficiency | Disposition |
|---|---|---|---|---|---|---|---|---|---|
| *Cancer population* | | | | | | | | | |
| Overall | 61 | 61.3 38.7 | 61.05 | 68.69 | 83.08 | 14.39 | 18.98 | 0.991 | 75.4%, home 18%, acute hospital 4.9%, subacute rehab 1.6%, death |
| Metastasis to bone | 7 | 42.9 57.1 | 66.14 | 76.70 | 87.70 | 12.40 | 11.60 | 1.25 | 71.4%, home 28.6%, acute hospital |
| Primary brain cancer | 23 | 60.9 39.1 | 55.04 | 63.40 | 83.30 | 19.40 | 20.78 | 1.19 | 82.6%, home 13%, acute hospital 4.3%, subacute rehab |
| Metastasis to brain | 16 | 50 50 | 68.19 | 75.60 | 83.30 | 7.60 | 15.81 | 0.80 | 81.3%, home 12.5%, acute hospital 6.3%, subacute rehab |
| Metastasis causing SCI | 15 | 80 20 | 60.27 | 66.50 | 80.40 | 13.90 | 22.93 | 0.78 | 60%, home 26.7%, acute hospital 6.7%, subacute rehab 6.7%, death |
| *Stroke population* | | | | | | | | | |
| Overall | 69 | 40.6 59.4 | 69.13 | 63.12 | 87.52 | 24.40 | 16.80 | 2.00 | 85.5%, home 7.2%, acute hospital 7.2%, subacute rehab |
| *Spinal cord injury population* | | | | | | | | | |
| Overall | 23 | 82.6 17.4 | 42.70 | 58.03 | 89.13 | 31.10 | 39.87 | 1.46 | 87%, home 13%, subacute rehab |

ADM FIM, admission FIM; D/C FIM, discharge FIM; LoS, length of stay; SCI, spinal cord injury; FIM, Functional Independence Measure

[a]All FIM scores are averages. [b]A total FIM score of 78 best separates patients who are likely to be able to go home and those who are likely to need long-term care.[11]

apy while at the facility. We also reviewed the data of all patients without cancer admitted with a diagnosis of stroke in 2013 and all patients admitted with a diagnosis of traumatic spinal cord injury in 2012 and 2013. No patients were excluded from stroke and traumatic spinal cord injury groups.

We recorded the sex, age, diagnostic group, Functional Independence Measure (FIM) admission score, FIM discharge score, length of stay (LoS) in the IRF, place of discharge of each patient (eg, home, acute care, or subacute care), and calculated the FIM efficiency score (change in FIM/LoS) for each patient. The FIM is an instrument that has 18 items measuring mobility, participation in activities of daily living, ability to communicate, and cognitive function.[7] Each item is scored from 1 to 7, with 1 denoting that the patient cannot perform the task and 7 that the activity can be performed independently. The minimum score is 18 (complete dependence), and the maximum score is 126 (independent function). Thirteen items compose the motor FIM score: eating, grooming, bathing, dressing upper body,

dressing lower body, toileting, bladder management, management of bowel, transfer to bed or wheelchair, transfer to toilet, tub transfer, walking (or wheelchair use), and climbing stairs. Five items – comprehension, expression, social interaction, problem solving, and memory – compose the cognitive FIM score.

We used a 1-way analysis of variance to evaluate differences between age and cancer type, age and diagnostic group, admission FIM score and cancer type, discharge FIM score and cancer type, change in FIM and cancer type, LoS and cancer type, and LoS and diagnostic group. The Pearson chi-square test was used to test the goodness of fit between the place of disposition and diagnostic group. The paired *t* test was used to evaluate the improvement in FIM of the patients who were in the cancer groups. The Tukey Simultaneous Tests for Differences of Means was used to compare the FIM efficiency scores of the groups. A 2-sample *t* test was used to evaluate the factors associated with the need for transfer from the IRF to the acute medical service.

**TABLE 2** Comparing primary brain cancer with metastatic brain cancer functional outcomes in change of Functional Independence Measure

| | n | Mean change in FIM | SD | SE mean | Diff of mean | 95% CI | P value |
|---|---|---|---|---|---|---|---|
| Metastasis to brain | 16 | 7.6 | 20.1 | 5.0 | −11.81 | (−22.23 to −0.39) | .043 |
| Primary brain cancer | 23 | 19.4 | 10.3 | 2.2 | | | |

95% CI, 95% confidence interval; Diff of Mean, difference of the means; FIM, Functional Independence Measure; SD, standard deviation; SE mean, standard error of mean

**TABLE 3** Comparing stroke with combined primary and metastatic brain cancer in functional outcomes by change in Functional Independence Measure

| | n | Mean change in FIM | SD | SE mean | Diff of mean | 95% CI | P value |
|---|---|---|---|---|---|---|---|
| Primary and metastatic brain cancer | 39 | 14.6 | 16.0 | 2.6 | −9.8 | (−15.81 to −3.85) | .002 |
| Stroke | 69 | 24.4 | 12.8 | 1.5 | | | |

95% CI, 95% confidence interval; Diff of mean, difference of the means; FIM, Functional Independence Measure; SD, standard deviation; SE Mean, standard error of mean

## Results

The demographic characteristics of the patients in the study and the admission and discharge FIM scores are reported in Table 1. There were initially 62 cancer patients in the radiation group, which was further divided into 4 subgroups based on the site of the primary tumor or metastasis. In all, 23 had a primary malignant brain tumor and received radiation and temozolomide. Sixteen patients had malignancies metastatic to the brain, 15 patients had tumors metastatic to the spine, and 7 had tumors metastatic to the long bones. One patient had laryngeal cancer and was excluded from the study because we did not think that we could do an analysis of a group with only 1 patient. The final number of patients in the cancer group was therefore 61. There were 69 patients in the stroke group and 23 in the spinal cord injury group.

We report improvement in total FIM, motor FIM, and cognitive FIM scores and were able to identify all 18 of the items of the FIM score on 60 of the 61 patients in the cancer group. Improvement in total FIM of the 61 patients in the cancer groups was significant at $P < .001$, as was improvement in motor FIM at $P < .001$. Improvement in cognitive FIM was borderline significant at $P = .05$. Just over 75% of the patients in the cancer group had sufficient enough improvement in their level of function that they were able to return to their homes (Table 1). The average FIM score at the time of discharge was 83.08. This was not significantly different than the level of function of patients discharged after stroke (87.52) or traumatic spinal cord injury (89.13).

The patients with primary brain tumors were younger than the patients with cancer metastatic to the brain ($P =$ .013). The patients with a primary brain tumor had lower admission FIM scores than patients with tumors metastatic to the brain ($P = .027$). The patients with a primary brain tumor had a greater increase in FIM score than patients with metastasis to the brain ($P = .043$; Table 2). There was not a significant difference between these 2 groups in FIM score at discharge or in the likelihood of discharge to home (Table 1). The FIM efficiency score was 1.12 for the patients in the primary brain tumor group and .80 in those with metastasis to the brain. This difference was not significant $P = .96$.

There were 69 patients in the stroke group. We compared the 39 patients with primary or metastatic brain lesion to the stroke group. The patients with primary or metastatic cancer of the brain were younger than the patients with stroke, 60.4 years old versus 69.1 years old ($P = .004$). The patients in the combined cancer group had a higher admission FIM score compared with the stroke patients (68.4 vs 63.12; $P = .05$). The discharge FIM scores were 83.3 in the combined cancer group and 87.5 in the stroke group (Table 1). This difference was not significant, but the improvement in the combined cancer group (14.6) was less than the improvement in the stroke group (24.40; $P = .002$) (Table 3).

The average LoS in the IRF was 18.7 days in the combined cancer group and 16.8 days in the stroke group. This difference was not significant. An average of 82% of the patients in the primary tumor or brain metastasis group and 85.5% of the patients in the stroke group were discharged to home. This difference was not significant. The FIM efficiency score of the patients in the stroke group was 2.0. This was significantly greater than the score for

**TABLE 4** Comparing metastasis to spinal cord with spinal cord injury in functional outcomes by change in Functional Independence Measure

| | n | Mean change in FIM | SD | SE mean | Diff of mean | 95% CI | P value |
|---|---|---|---|---|---|---|---|
| Metastasis to spinal cord | 15 | 13.9 | 12.2 | 3.2 | −17.2 | (−25.93 to −8.47) | <.001 |
| SCI | 23 | 31.1 | 13.9 | 2.9 | | | |

95% CI, 95% confidence interval; Diff of mean, difference of the means; FIM, Functional Independence Measure; SCI, spinal cord injury; SD, standard deviation; SE mean, standard error of mean

the patients in the metastasis to the brain group (0.80; $P$ = .044) but not significantly greater than the primary brain cancer group (1.19; $P$ = .22).

There were 23 patients in the traumatic spinal cord injury group. A comparison of the patients with tumors metastatic to the spine and patients with traumatic spinal cord injury showed that the patients in the cancer group were older (60.27 and 42.70 years, respectively; $P$ = .001). In all, 80% of patients with tumors metastatic to the spine were men. This was not significantly different from the percentage of men in the traumatic spinal cord injury group (82.6%; Table 1). The admission FIM score of the patients with cancer was 66.5 (standard deviation [SD], 13.3) and 58.03 (SD, 15.1) in the patients with a traumatic spinal cord injury (Table 1). The FIM score at discharge was 80.4 (SD, 19.1) in the patients with cancer and 89.1 (SD, 20.3) in the patients with a traumatic spinal cord injury (Table 1). Neither of these were statistically significant. The improvement in patients with cancer was 13.9 (SD, 12.2) and 31.1 (SD, 13.9) in the traumatic spinal cord injured patients. This difference was significant ($P$ < .001; Table 4). The median LoS was 18.98 days in the cancer metastasis to spine group (interquartile range [IQR] is the 25th-75th percentile, 12-30 days). In the traumatic group the median LoS was 23 days (IQR, 16-50 days). This difference was not significant ($P$ = .14 Mann-Whitney test). The mean FIM efficiency score was 1.46 in the traumatic spinal cord injury group and .78 in the group with cancer metastatic to the spine. This difference was not significant ($P$ = .72). Sixty percent of the patients in the cancer group were discharged to home, and 87% of patients in the traumatic spinal cord group were discharged to home. This difference was not significant ($P$ = .12; Fisher exact test).

As far as we can ascertain, this is the first paper that has looked at the outcomes of patients receiving rehabilitation concurrent with radiation of the long bones. The average improvement in FIM was 12.4 (Table 1). The LoS was 11.6 days, and the FIM efficiency was 1.25. In all, 71.4% made enough progress to go home.

Of the total number of cancer patients, 18% were transferred to the acute medical service of the hospital (Table 1). Neither age, sex, type of cancer, nor admission FIM score were associated with the need for transfer to acute

hospital care. Change in FIM score was inversely associated with transfer to acute hospital care ($P$ = .027). Patients whose function did not improve with rehabilitation were most likely to be transferred back to acute hospital care.

## Discussion

Radiation therapy is considered a service that is provided to people who come for treatment as an outpatient. Caregivers may have difficulty transporting patients to radiation if the patient has deficits in mobility. This may be particularly true if the patient is heavy, the caregivers are frail, or perhaps if they live in rural settings where there is no wheelchair-accessible public transportation. There are many factors that help determine whether a patient with functional deficits can be discharged to his or her home. These include sex, age, marital status, family and/or community support, income, and insurance.[8] The FIM is an instrument that indicates how much help a patient needs with mobility and self-care skills. It also correlates with the amount of time that caregivers must spend helping a patient.[9] Study findings have shown that the FIM score is an important determinant of whether a patient can be discharged to home. The total FIM score is as useful as an analysis of the components of the FIM score in predicting whether a patient can return to the community.[10,11] Reistetter and colleagues found a total FIM score of 78 to be the score that best separates patients who are likely to be able to go home and patients who are likely to need long-term care.[11] Bottemiller and colleagues[10] reported that 37% of patients with total discharge FIM scores of less than 40 were discharged to home. They reported that 62% of patients with FIM scores between 40 and 79 were discharged to home, and 88% of patients with scores of 80 or above were discharged to home.[10] The goal in bringing patients to the IRF was to accept and treat patients with reasonable community support and potential to achieve a functional level compatible with discharge to the community. Most patients in each of the cancer groups were able to reach an FIM score of 78 to 80 and to be discharged to home.

Most of the patients in the cancer groups had underlying problems that are not considered curable. The primary goal

was to enable the patients to have some time at home with their families before requiring readmission to a hospital or hospice care. Reasonable LoS and rate of progress are now expected or required by third-party payors and hospital administrators. Physicians at the Mayo Clinic have indicated that a rehabilitation service should aim for an FIM efficiency score of at least .6 points per day.[10] The FIM efficiency of patients in each of the 4 cancer subgroups in this study was higher than this level.

J. Herbert Dietz, Jr was an early advocate of the need to provide comprehensive rehabilitation services for patients with cancer. He first described his work in 1969.[12] Since that time, there have been many papers that have documented the benefits of IRF for patients with cancer. O'Toole and Golden have shown outcomes of a large series of patients from an IRF. They reported that at the time of admission, 14% of patients could ambulate, but at discharge, 80% could ambulate without hands-on assistance. They reported significant improvements in continence, FIM score, and score on the Karnofsky Performance Scale.[13] Marciniak,[14] Hunter,[15] Shin,[16] and Cole,[17] and their respective colleagues have all shown that patients with many different types of cancer benefit from rehabilitation at the IRF level. Gallegos-Kearin and colleagues[4] reported on the care of 115,570 patients admitted to IRF with cancer from 2002 to 2014. Patients had significant improvement in function, with more than 70% of patients discharged to home.[4] Ng and colleagues studied a group of 200 patients who received IRF care and found there was significant improvement in function. Ninety-four percent of patients rated their stay as either extremely good or very good.[5]

Metastasis to the spine is a common problem. It is found in 30% of cancer patients at autopsy. The most common sources of metastasis to the spine are breast, lung, prostate, kidney, and thyroid.[18] Multiple myeloma and lymphoma may also involve the spine. Several authors have shown that these patients benefit from inpatient rehabilitation. Mckinley and colleagues[19] have noted that patients with metastasis to the spine make significant improvement with care at an IRF. Compared with patients with a traumatic spinal cord injury, the cancer patients had shorter LoS, smaller improvement in FIM, equal FIM efficiency (FIM gain/LoS), and equal success in making enough progress to be discharged to home.[19] Eriks and colleagues showed that patients at an IRF in Amsterdam made significant improvement in function as measured by the Barthel's Index.[20] Tang .,[21] and Parsch[22] and their respective colleagues, Murray,[23] and New[24] and colleagues have published findings confirming that patients with spinal cord injury caused by metastasis to the spine make significant progress with inpatient rehabilitation programs. The present study adds to the literature by showing that patients with metastasis to the spine who are receiving radiation can

make progress and be discharged to the community.

There are 24,000 new cases of primary malignant brain tumors in the United States each year.[25] The incidence of metastatic cancer to the brain has been estimated to be 100,000 cases per year in the United States. The most common cancer sources are lung, breast, melanoma, kidney, and colon.[26,27] The first study of patients admitted to an IRF for treatment of brain tumors was published in 1998 by Huang and colleagues[28] who compared the outcomes of 63 patients with brain tumors with the outcomes of 63 patients with stroke. They reported that the patients with the brain tumors made significant improvement in function. There was not a significant difference between the 2 groups of patients in improvement in function, FIM efficiency, or success in discharging the patients to home.[28] Greenberg[29] and Bartolo[30] and their respective colleagues compared the outcomes of patients admitted with brain tumors and patients with stroke and found that improvement in function and discharge to home was similar in the 2 groups. In 2000, Huang and his same colleagues[31] compared a group of patients with brain tumors to a group of patients with traumatic brain injury. They found significant improvement in the function of the patients with brain tumors. Patients in the traumatic brain injury group made more progress but had longer LoS. FIM efficiency was not significantly different between the groups.[31]

Three papers have reported outcomes of patients who received radiation concurrent with inpatient rehabilitation. Tang and colleagues[32] reported 63 patients, of whom 48% percent received radiation concurrent with rehabilitation. The patients who received radiation made significant gains in function, and more than 70% were discharged to home. There was no difference in the outcomes of the patients in the radiation and nonradiation groups.[32] Marciniak[33] and O'Dell[34] and their colleagues also reported that patients with brain tumors that required radiation therapy can benefit from inpatient rehabilitation. The present paper is the fourth (with the largest patient group) to show that patients with primary and metastatic tumors to the brain can benefit from a program that provides radiation concurrent with inpatient rehabilitation. We have shown that patients can achieve functional levels and rates of discharge to home that are not significantly different from those of the most commonly admitted group of patients to IRF – patients with stroke.

In the present study, 18% of all of the cancer patients were transferred to medical services and/or acute hospital care (Table 1). This is consistent with a paper by Asher and colleagues[35] who reported that 17.4% of patients at an IRF with a diagnosis of cancer required transfer back to medical service, and that low admission motor FIM score correlated with the likelihood of transfer back to medical service. In the present paper, the total admission FIM score was not related to the likelihood of return to medical ser-

vice, although a lack of improvement in the FIM score did correlate with transfer to medical service.

All of the papers we reviewed found that appropriately selected patients with cancer make significant improvement in function with treatment at an IRF. Tang and colleagues have also shown that for patients with malignant brain tumors and metastasis to the spine, improvement in function correlates with increased survival.[32] Our paper confirms that patients with primary malignant brain tumors, malignant tumors metastatic to the brain or spine, and tumors metastatic to long bones may benefit from rehabilitation concurrent with radiation. Rehabilitation units are traditionally associated with treating patients with stroke and spinal cord injury. The patients in our study had cancer and were receiving radiation therapy. They had significant improvement in function and FIM efficiency scores that are not below the threshold set as expected for care at an IRF. Most patients in our study achieved a functional level consistent with what is needed to go home.

There is a prospective payment or reimbursement system for rehabilitation units.[36] The payments are based on the admitting diagnosis, the admission FIM score, the age of the patient, and comorbidities. There are 4 tiers for comorbidities with no additional payments for patients in tier 0 but with additional payments for patients with conditions that qualify for tiers 1 through 3. The highest payments are for patients in tier 1. Examples of conditions that can increase payment include morbid obesity, congestive heart failure, vocal cord paralysis, and the need for hemodialysis. There is no increased payment for provision of radiation therapy. There are no reports on the feasibility, in terms of finances, of providing radiation on an IRF. We asked the finance office of the Albany Medical Center to comment on the cost to the hospital of providing radiation therapy to patients on the rehabilitation unit. The hospital's finance department reviewed available data and reported that the variable cost of providing radiation therapy is about 6.5%

of the revenue collected from third-party payors for caring for patients who receive that service (personal communication from the finance office of Albany Medical Center to George Forrest, 2015). Our findings suggest that the Centers for Medicare & Medicaid Services should make an adjustment to the payment system to support the cost of providing radiation to patients at an IRF. Even under the current payment system, for a hospital that has the equipment and personnel to provide radiation treatments, the variable cost of 6.5% of revenue should not be an absolute barrier to providing this service.

## Limitations

This study reports on the experience of only 1 facility. The number of patients in the radiation group is greater than the number of patients in any previous report of people receiving radiation at an IRF, but the statistician does not think it is large enough to allow statistical analysis of covariates such as age, sex, and comorbid conditions. In addition, we did not investigate all of the factors that influence the type of care patients are offered and their LoS, such as hospital policy, insurance coverage, income, and family structure.

## Conclusions

Acute care medical units are now challenged to both reduce LoS and reduce the number of patients who are readmitted to the hospital. Rehabilitation units are challenged to maintain census, as government and private payors are shifting patients from acute rehabilitation units to subacute rehabilitation units. We found that patients with cancer who need radiation are a population of patients who are seen by payors as needing to be in a facility with excellent nursing, therapy, and comprehensive physician services. A comprehensive cancer care program within a rehabilitation unit can be a great benefit to the acute care services, the IRF, and, most importantly, patients and their families.

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# The long-term effects of posttreatment exercise on pain in young women with breast cancer

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**Background** Persistent pain after treatment has been identified in breast cancer populations, with prevalence rates ranging from 25%-60%. Age, surgical procedure, axillary node dissection, and radiation therapy have shown correlation with chronic pain development.

**Objective** To conduct a pilot randomized controlled trial targeting young breast cancer patients to determine the effectiveness of a 12-week exercise program on long-term levels of upper-limb pain, as measured by the Brief Pain Inventory-Short Form (BPI-SF), and pain measured by physical examination of specific shoulder movements.

**Methods** Young adults (18-45 years of age) recently diagnosed with breast cancer consenting to participate in this study were randomly allocated to intervention or control groups. The exercise intervention group participated in a 12-week exercise program starting 3-4 weeks after the cessation of radiation therapy, and the control group received standard care consisting of encouragement for an active lifestyle and pamphlets on the benefits of exercise. The location and severity of pain and its interference with daily life were recorded at the following 6 time points: postsurgery and preradiation (T1, baseline), postradiation and preintervention (T2), and 4 points during an 18-month period postradiation (T3-T6 at 3, 6, 12, and 18 months). In addition, clinical physical assessment of range of motion and pain on active shoulder movements were recorded at each time point.

**Results** 59 young breast cancer patients participated in the study (exercise group: n = 29; control group: n = 30). Over the course of the trial, there were no significant differences between study groups in the BPI-SF measures of pain interference and severity scores. Improvements in pain on shoulder movements were noted in the intervention group at 3 and 6 months postintervention (T3 and T4) but were not sustained over time (by T6, 18 months postradiation). Shoulder girdle–chest wall pain improved at 12 and 18 months postradiation in both groups but persisted despite exercise intervention. Recordings of shoulder pain on physical examination of range showed a distinct pattern of temporal improvement (T3-T5), followed by low levels of pain recurrence at 18 months postradiation (T6) in both groups.

**Limitations** Stringent exclusion criteria, including the absence of any shoulder pathology or pre-existent medical comorbidities impacting upper limb function, long-term follow-up, and the relatively small population of breast cancer patients in this age demographic, limited and prolonged recruitment for this study. In addition, the general activity levels of the young breast cancer survivors who agreed to participate in this exercise intervention study may have had an impact on the significance of results.

**Conclusion** Transient improvements in shoulder pain can be attributed to a 12-week exercise program, but they did not translate to long-term benefits. Moreover, the BPI-SF did not capture shoulder pain and limitations related to upper-limb disability in this study, in contrast with the findings on physical examination.

Breast cancer is one of the most prevalent cancers in women worldwide, with more than 1 million new cases diagnosed annually.[1] Prognosis for the disease has improved significantly, but 25% to 60% of women living with breast cancer experience some level of pain ranging from mild to severe, the nature of which can evolve from acute to chronic.[2] Pre-, intra-, and post-treatment risk factors have been found to correlate with the development of acute and chronic pain and include young age, type of breast surgery (lumpectomy or total mastectomy), axillary node dissection, radiation therapy, and hormonal therapy.[3-5] Chemotherapy, particularly anthracycline- and taxane-based regimens, has also been shown to induce pain, arthralgia, myalgia, and peripheral neuropathy during treatment.[6] In particular, postradiation pain may result

from subcutaneous fibrosis with fixation to underlying musculature and the development of fibrous flaps in the internal axilla.[7] These tissue changes are commonly subclinical, occurring 4 to 12 months postradiation,[8] and can progress undetected until pain and upper-limb disability develop.

The presence of persistent pain has a considerable impact on the quality of life in survivors of breast cancer: psychological distress is prevalent (anxiety, depression, worry, fear), the performance of daily activities is diminished (eg, bathing, dressing, preparing meals, shopping), and economic independence is compromised by the inability to work or reduced employment and income. These factors directly and indirectly contribute to an increase in the use of health care services.[9,10]

The management of pain is often characterized by pharmacologic-related treatment, such as the use of opioids and nonsteroidal anti-inflammatory medications, and nonpharmacologic-related treatment, such as exercise. Empirical evidence has shown that rehabilitative exercise programs, which commonly include a combination of resistance training and aerobic exercises, can effectively reduce pain in breast cancer survivors.[10-12] Women living with breast cancer who are directed to rehabilitative exercise programs experience an improvement not only in pain levels but also in their ability to engage in activities of daily living, in their psychological health, and in their overall quality of life.[13-15] However, despite evidence to support exercise programs to reduce pain related to breast cancer treatment, residual pain and upper-limb discomfort are common complaints in breast cancer survivors, and there is little focus on the duration of effectiveness of such programs for reducing pain after treatment for breast cancer. The objective of this study was to determine if an exercise program initiated postradiation would improve long-term pain levels in a carefully selected population of young women who were living with breast cancer and had no history of shoulder pathology or significant treatment complications.

## Methods

### Design

We used a pilot randomized control trial to compare the long-term effectiveness of a 12-week postradiation exercise program versus standard care on residual pain levels in young women (aged 18-45 years) living with breast cancer. The program was initiated 3 to 4 weeks postradiation to allow for acute inflammatory reactions to subside. Pain severity and interference were assessed using the Brief Pain Inventory-Short Form (BPI-SF), a tool for assessing cancer pain.[16,17] Pain levels for isolated shoulder movements were also recorded on examination by a physical therapist. All measures were collected at 6 time points (T1-T6): postsurgery and preradiation (T1, baseline), postradiation and preintervention (T2), and 4 points during an 18-month period postradiation (T3-T6 at 3, 6, 12, and 18 months postradiation).

### Sample

Young women living with breast cancer who met our eligibility criteria were identified from 2 clinics at the Jewish General Hospital – the Segal Cancer Center and the Department of Radiation Oncology in Montréal, Québec, Canada. Inclusion criteria included women with a diagnosis of stage I to stage III breast cancer, who were 18 to 45 years old, were scheduled for postoperative adjuvant radiation therapy, had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (normal ambulatory function, minimal symptoms), and who consented to participate in the study. Exclusion criteria included women with a metastatic (stage IV) diagnosis; significant musculoskeletal, cardiac, pulmonary, or metabolic comorbidities that would not allow for participation in physical activity; a previous breast cancer diagnosis with treatment to the ipsilateral or contralateral sides; postsurgical lymphedema; postsurgical capsulitis, tendonitis, or other shoulder inflammatory complications; and any contraindication to exercise. The recruitment goal was outlined as 50 patients per group; however, a protracted accrual time because of the stringent study criteria yielded a sample of 29 and 30 patients for the intervention and control groups, respectively, which was sufficient for significant testing of differences between the 2 study groups.[18]

### Variables and measures

**Clinical characteristics.** We used standardized questions and chart review to document the participants' clinical characteristics and to capture information on the following: the stage and subtype of breast cancer, hormonal and human epidermal growth factor receptors (HER2) (estrogen receptor, progesterone receptor, and HER2 status), extent of surgery (lumpectomy or total mastectomy), and other modalities of treatment (eg, chemotherapy, radiation therapy).

**Pain assessment.** The BPI-SF was used to assess participants' cancer-related pain. Pain severity ranged from 0 (no pain), 1 to 4 (mild pain), 5 to 6 (moderate pain), to 7 to 10 (severe pain).[18,19] The questionnaire also identifies the pain interference in daily activities using a Likert scale ranging from 0 (*Does not interfere*) to 10 (*Completely interferes)* in the following 7 domains or subscales: General Activity, Walking, Mood, Sleep, Work, Relations with Others, and Enjoyment

of Life.[16] For the purpose of this study, mean scores were tabulated using both pain intensity and interference scales.

Another important component of the BPI-SF instructs participants to localize pain by means of a body diagram. For purpose of analysis, 3 pain regions were established: shoulder girdle/chest wall on the affected side; neck and other upper extremity, including hand(s), forearm(s), wrist(s), and finger(s); and other regions, including abdominal discomfort, leg(s), hip(s), knee(s), ankle(s), lower back, and feet. In addition, pain levels on movement (Yes/No) were recorded for isolated shoulder flexion, abduction, and horizontal abduction (sitting and standing). The measurements were completed by a single physical therapist throughout the course of the study to minimize variance.

### Procedure

The study protocol was approved by the Research Ethics Board at the Jewish General Hospital. Recruitment occurred from 2011 through 2015. The research was in accordance with the ethical standards of the responsible committee on human experimentation. Eligible women were recruited by the research coordinator who described the purpose, risks, and benefits of the study; advised on confidentiality, data collection, and intervention allocation procedures; and highlighted voluntary participation. The research coordinator addressed any concerns on the part of the participants before obtaining their written informed consent. Random allocation to the intervention and control groups was established using a web-based randomization plan generator (www.randomization.com). A single individual was responsible for the randomization process, and treatment assignments were revealed after each participant's name had been entered. A physical therapist performed 6 sequential evaluations (T1-T6) at the time of participants' medical follow-up appointments.

### Intervention

The 12-week exercise intervention started 3 weeks postradiation and was composed of an initial 6-week program of low-level cardiovascular and resistance exercises that progressed to a set of more advanced exercises for the remaining 6 weeks. Participants were instructed to warm up for at least 10 minutes with a cardiovascular exercise of their choice (eg, a recumbent cross trainer, walking, or stairs) before doing a combined strength, endurance, and stretching exercise program for the upper body.[20] The final portion of the exercise intervention included a period of light cooldown. Weight training resistance levels were based on a maximum 8 to 10 repetitions for strength and a maximum of 20 repetitions for endurance training exercises, which progressed gradually over the course of the 12-week exercise program to ensure participant safety.[21,22] Participants in the intervention group were supervised at least once a week by an exercise physiologist at a center for oncology patients (Hope & Cope Wellness Centre), and patients were encouraged to perform the program at home 2 to 3 times a week. Those who were not able to exercise consistently at the center were provided with equipment and instructed on how to do the program safely at home.

By comparison, the control group received standard care, which included advice on the benefits of an active lifestyle, including exercise, but without a specific intervention. Participants were not restricted in their physical activity and/or sport participation levels, and their weekly activity levels were calculated using the Metabolic Equivalent of Task and recorded at each of the 6 time points.

### Statistical analysis

Descriptive statistics were used to examine participant characteristics. The quantitative data collected through the BPI-SF measures were analyzed with JMP software (version 11.2; SAS Institute, Cary, NC). Continuous variables were tested for statistical significance ($P \leq .05$) through the chi-square (categorical), analysis of variance, and nonparametric Wilcoxon tests. The analyses did not include missing data.

### Results

A total of 59 young women were randomized into the intervention (n = 29) and control (n = 30) groups. Of those, 2 participants dropped out of the study because of family and time constraints, and 3 participants died, 2 from the control and 1 from the intervention group, after subsequently developing metastatic disease. Baseline data including comparative tumor characteristics, surgical interventions, and treatment interventions have been published in relation to other elements of this study.[23,24] The participants had a mean age of 39.2 years (standard deviation [SD], 5.0). More than half of them had an invasive ductal carcinoma (69.5%) and were estrogen positive (78.0%), progesterone positive (74.6%), or HER2 positive (20.3%), whereas 10.2% were triple negative. Most of the participants had undergone breast-sparing procedures (86.4% lumpectomy), and 18.6% had a total mastectomy. By random chance, the intervention group had higher rates of total mastectomy (24.4% and 13.3%, respectively) and surgical reconstruction (12.2% and 6.7%, respectively) compared with the control group. Most of the women (71.2%) received chemotherapy, and all received radiation therapy. In the intervention group, 37.2% received radiation therapy localized to the axilla, and 88% received a boost of radiation to the surgical bed. Self-reported exercise diaries were returned by 15 of the 29 intervention participants, and training frequencies among them varied significantly (1-6 times a week).

The findings showed that there was little variance between the intervention and control groups in BPI-SF severity scores from T1 to T6, so the means and SDs of the BPI-SF scores were grouped at 6 time points (Table 1). There was no statis-

**TABLE 1** Brief Pain Inventory-Short Form mean scores and standard deviation with group category percentages at 6 time points (N = 59)

| | Time point[a] | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | T1 | T2 | T3 | T4 | T5 | T6 |
| **Severity of pain** | | | | | | |
| Mean score (SD)[b] | 1.68 (1.71) | 1.71 (1.38) | 1.84 (1.53) | 1.51 (1.42) | 1.29 (1.51) | 1.46 (1.37) |
| No pain, % | 31.5 | 22.2 | 15.2 | 28.6 | 40.0 | 24.4 |
| Mild, % | 55.6 | 68.5 | 75.8 | 65.7 | 50.0 | 70.7 |
| Moderate, % | 11.1 | 9.3 | 9.1 | 5.7 | 10.0 | 4.9 |
| Severe, % | 1.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Pain interference in daily life** | | | | | | |
| Mean score (SD)[c] | 1.40 (2.01) | 1.32 (1.65) | 1.03 (1.42) | 0.96 (1.73) | 0.54 (0.81) | 0.87 (1.83) |
| No interference, % | 46.3 | 37.0 | 48.5 | 42.9 | 50.0 | 51.2 |
| Mild, % | 42.6 | 50.0 | 45.5 | 51.4 | 50.0 | 43.9 |
| Moderate, % | 9.3 | 13.0 | 6.1 | 2.9 | 0.0 | 4.9 |
| Severe, % | 1.9 | 0.0 | 0.0 | 2.9 | 0.0 | 0.0 |

[a]T1, after surgery and before radiation, baseline; T2, after radiation and before the exercise intervention; T3, 3 months postintervention; T4, 6 months postintervention; T5, 12 months postintervention; T6, 18 months postintervention. [b]Pain severity ranged from 0 (no pain), 1-4 (mild pain), 5-6 (moderate pain), to 7-10 (severe pain). [c]Pain interference scores ranged from 0 (no interference) to 10 (severe interference).

**TABLE 2** Brief Pain Inventory-Short Form domain mean scores and standard deviations at time points 1 and 6 by exercise/intervention or control group

| | Time point[a] | | | | Difference (T6 minus T1) | | P value |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | T1 | | T6 | | | | |
| **Domain[b]** | Intervention | Control | Intervention | Control | Intervention | Control | |
| General activity | 1.22 (2.10) | 1.53 (2.41) | 1.36 (2.41) | 1.23 (2.07) | 0.35 (2.48) | 0.09 (2.65) | 0.7387 |
| Mood | 1.26 (2.10) | 1.67 (2.88) | 1.24 (2.14) | 0.86 (1.21) | 0.26 (2.22) | −0.23 (2.37) | 0.4794 |
| Walking ability | 1.37 (2.62) | 1.13 (2.45) | 1.20 (2.60) | 0.36 (0.79) | 0.09 (3.53) | 0.41 (2.28) | 0.7192 |
| Normal work | 1.19 (2.56) | 1.90 (3.12) | 1.28 (2.46) | 0.91 (1.60) | 0.30 (3.18) | −0.68 (2.95) | 0.2876 |
| Relations with others | 0.74 (1.29) | 1.03 (2.19) | 0.60 (1.87) | 0.14 (0.35) | 0.09 (2.11) | −0.41 (1.18) | 0.5332 |
| Sleep | 1.81 (2.82) | 1.83 (2.90) | 1.36 (2.63) | 1.27 (2.21) | −0.17 (3.52) | −0.27 (3.49) | 0.9252 |
| Enjoyment of life | 0.89 (1.78) | 1.24 (2.31) | 1.36 (2.41) | 1.23 (2.07) | 0.57 (2.48) | −1.09 (2.29) | 0.0249 |

[a]T1, after surgery and before radiation, baseline; T6, 18 months postintervention. [b]Pain interference with domains of daily activity on a visual analogue scale (VAS) of 1-10 were recorded.

tically significant difference between baseline measures at T1 (1.68; SD, 1.17) and measures at 18 months postintervention (T6: 1.46; SD, 1.37). At baseline, 87.7% of the women reported no pain (31.5%) or mild levels of pain (55.6%), and 13% reported moderate or severe pain. Over the duration of the study from T1 to T6, these primarily low levels of pain (BPI-SF, 0-4) remained consistent with a favorable shift toward having no pain (T1: 31.5%; T6: 24.4%). By 18 months postintervention, 95.7% of women reported no or mild pain, with 4.9% reporting moderate pain.

Similarly, there was little variance over time (T1-T6) and no statistically significant differences between the 2 groups in BPI-SF–measured levels of pain interference in daily activities (Table 2). Moreover, a domain analysis showed that there were no statistically significant differences in pain interference scores when comparing the type and extent of surgery (total mastectomy: 0.59 [1.17]; lumpectomy: 0.94 [1.96]). By chance – and not related directly to the objectives of this study – there was a statistically significant difference between the intervention and control groups in the interference of pain on the Enjoyment of Life domain in favor of the control group.

The sites of pain captured by the BPI-SF shed light on the preceding findings (Figure 1). At baseline (T1, postsurgery and preradiation), 37.0% of participants reported pain in the shoulder girdle–chest wall region, whereas 20.4%
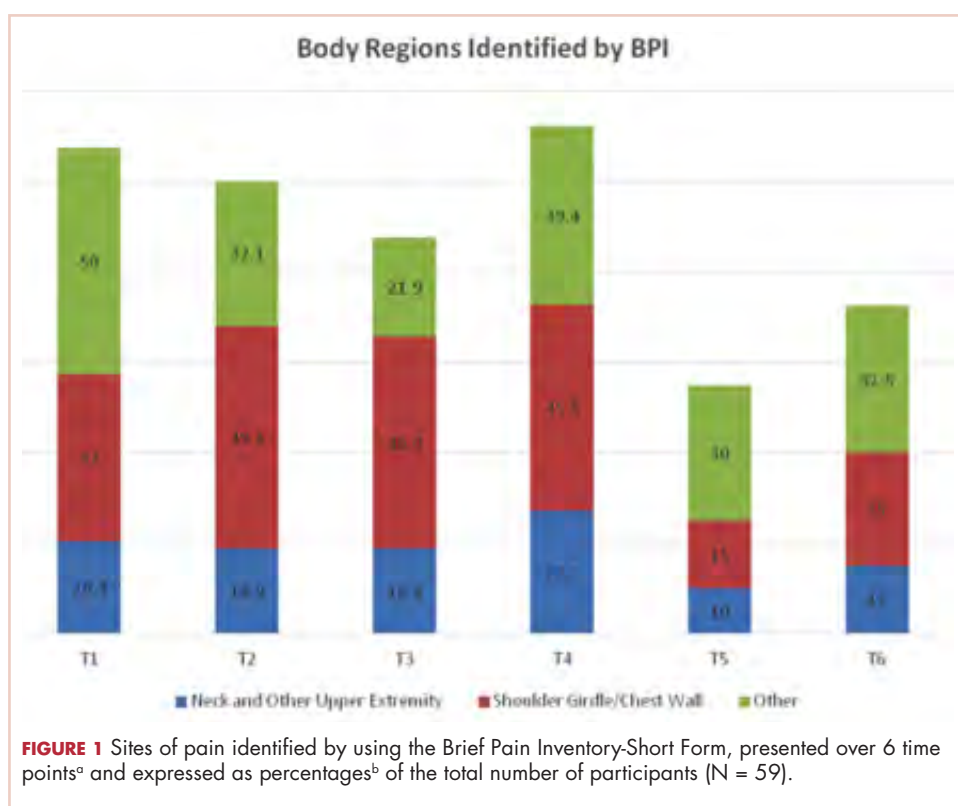
reported pain in the general neck–upper extremity region and 50% in other regions. Postradiation, shoulder girdle–chest wall pain was identified as the highest reported site of pain (49.1%; T2, postradiation and pre-intervention) and remained elevated at 3 months (T3) and 6 months (T4) postradiation (46.9% and 45.5%, respectively). At 12 and 18 months postradiation (T5 and T6), the principal focus of pain shifted once again to "other" regions at 30% and 32.5%, respectively, and the neck–upper extremity region at 10% and 15%, respectively. Shoulder girdle–chest wall pain concomitantly improved at those time points (15% and 25% respectively) but was not eliminated.

Pain levels recorded on physical examination for isolated shoulder range of movements were recently published,[24] and they have been abbreviated and reproduced in this paper (Figure 2) to allow for a comparison of findings between the exercise intervention group and the control group to help determine the sensitivity of these tools for use in breast cancer patients. At baseline, pain levels with active movement were noted to be slightly greater in the intervention group for flexion and abduction. Following the intervention, at 3 and 6 months postradiation (T3 and T4), the intervention group showed a steady decrease in pain levels in flexion and abduction, whereas the control group showed a 5-fold increase in pain with horizontal abduction. Furthermore, participants in the intervention group reported having no pain on movement 12 months postradiation (T5); however, recurrence of pain was apparent with all shoulder movements by 18 months post-radiation (T6) in both the intervention and control groups.

## Discussion

Previous studies have hypothesized that younger age (18-39 years), adjuvant radiotherapy, and axillary node dissection are risk factors for chronic pain in breast cancer survivors.[22,25] Persistent pain is prevalent in 12% to 51% of breast cancer survivors, with up to one-third experiencing some pain more than 5 years after treatment,[26,27] and our study outcomes concur with those findings. In our study, pain, as measured by the BPI-SF, was found to persist for most participants (75.6%) after the 18-month follow-up. The results of our trial showed that a 12-week exercise intervention administered postsurgery and postradiation had no statistically significant effect on long-term (18 months) pain severity and its interference in daily life. It is worth noting that body



**FIGURE 1** Sites of pain identified by using the Brief Pain Inventory-Short Form, presented over 6 time points[a] and expressed as percentages[b] of the total number of participants (N = 59).

regions that had not been directly related to either surgical or radiation treatment for breast cancer were commonly identified as areas of pain but were not specifically targeted by our intervention. However, focusing on pain severity (BPI-SF), our findings suggest that the benefits of targeted upper-extremity exercise on pain in the intermediate time course of follow-up (T3, T4, and T5) was notable compared with the control group, which received standard care. The apparent recurrence of pain at 18 months in both groups was not anticipated and needs to be further investigated.

More specific objective assessments of pain on active shoulder movement identified distinct patterns of pain that could not be isolated using the BPI-SF alone. The incidence and localization of pain on movement differed between the population of women who received a specific exercise intervention and those who received standard care (Figure 2). Patterns of pain over time fluctuated in the control group, whereas the intervention group reported a linear decrease in pain. Residual pain on shoulder movement remained apparent in both groups at 18-months postradiation, but that finding was not reflected in the BPI-SF results. The literature supports our findings on persistent pain among breast cancer survivors,[3,7,8,28-30] and in our study of young women carefully screened and excluded for pre-existent shoulder conditions or comorbid medical conditions, recurrent articular pain was nonetheless prevalent. It seems that unidentified or multiple factors may be part of the etiology of pain in this young adult cohort.

**FIGURE 2** Range of motion and pain level, presented over 6 time points [a] for 4 shoulder movements. Although not statistically significant, at 3 and 6 months postradiation (T3 and T4), the intervention group showed a steady decrease in pain levels on shoulder flexion and abduction movements measured in sitting, in contrast to an increase in pain level with these movements in the control group. The intervention group reported no pain for all 4 movements at 12 months postradiation (T5), but recurrence of pain was apparent with all shoulder movements by 18 months postradiation (T6) in both groups.

[a]T1, postsurgery and preradiation; T2, postradiation and pre-exercise intervention; T3-T6: 3, 6, 12, and 18 months postradiation, respectively. [b]The sites of pain were not mutually exclusive, and decreasing percentages at T5 and T6 are indicative of greater numbers of patients without pain after long term follow-up.

Although the BPI-SF is a generic measurement tool commonly used to assess and measure cancer patients' pain levels, the lack of variance in our BPI-SF severity and interference outcomes over time (T1-T6) (Table 1, Table 2), the variety of "other" unrelated regions (Figure 1) identified by the BPI-SF, and the contrast in our findings on specific physical examination emphasize the potential limitations of this clinical tool. Moreover, the BPI-SF has not been validated specifically for breast cancer. Harrington and colleagues have recommended using the BPI-SF to assess pain in women with breast cancer,[31] but the use of a more multidimensional measurement tool that evaluates axillary, chest, trunk, and upper-limb pain may prove to be more valuable in this population.

**Limitations**
Recruitment of young adult women was difficult because of our stringent inclusion criteria, the long-term follow-up, and the relatively small population of breast cancer patients in this age demographic. Therefore, the duration of the recruitment phase, despite our having access to a specialized young adult and adolescent clinic in our institute, greatly surpassed the expectations we had when we designed the study. In addition, there remains an inherent bias in participants who accept participation in a study that includes exercise interventions. Potential participants who exercise regularly or have a positive inclination toward doing exercise are more likely to participate. Despite the prescription of a targeted 12-week upper-limb intervention in this study, the general activity levels of both groups may have had an impact on the significance of this study. In addition, the low adherence to the use of self-reported logs failed to capture the true compliance rates of our participants because their lack of tracking does not indicate failure to comply with the program. The use of weekly or biweekly telephone calls to monitor compliance rates of activity more vigilantly may be used in future studies.

## Conclusions

Advances in clinical management of breast cancer have improved survival outcomes, and morbidity over recent years, yet symptoms such as pain remain prevalent in this population. The results of this study showed that a targeted, 12-week upper-limb exercise intervention postradiation transiently improved levels of shoulder pain without a concomitant impact on chronic pain or any positive influence on activities of daily living 18 months posttreatment. Furthermore, future studies should use a variety of measurement tools to evaluate trunk and upper-limb pain in women with breast cancer and investigate the optimal timing of postradiation exercise interventions.

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# Carcinoma of the colon in a child

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Colon cancer is not common in childhood even though cases have been reported in children and adolescents.[1,2] Although it is sporadic, it can arise in the setting of predisposing illnesses such as familial polyposis syndrome or inflammatory bowel disease.[2-5] Only 1 or 2 cases per million children are reported globally each year, but the incidence has been noted to be on the rise.[2] The nonspecific gastrointestinal symptoms and anemia as features of the disease could also be seen in other common childhood ailments, such as helminthiasis in our region in West Africa. As a result, unless there is a high index of suspicion at the outset, there is a risk that colon cancer will be diagnosed at a late stage, especially in children with no apparent predisposing factor.

In this case, an 11-year-old girl presented to our institution with abdominal pain, melena, abdominal swelling, and iron deficiency anemia. A positive family history of colon cancer in the mother and a brain tumor in an elder sibling prompted a search for and subsequent diagnosis of colon cancer. Her case highlights the importance of a high index of suspicion in making an early diagnosis to achieve the best possible outcomes. This case is being reported in line with the SCARE guidelines.[6]

## Case summary and presentation

An 11-year-old girl presented to our facilty with recurrent abdominal pain of 8 months duration, a 4-month history of progressive paleness of the palms, and a month-long fever. There was an associated change in bowel habit to about 2-3 times per day, weight loss despite a preserved appetite, and black, tarry stools. A month before she presented, she developed low-grade pyrexia, dysuria, and pica.

She was treated for iron deficiency anemia at a peripheral hospital where she first sought for care with oral iron, folic acid, and vitamin C, but with no improvement in symptoms.

She was the youngest of 8 children born to parents who were first cousins. Her father had died in a car accident when she was a year old, and her mother had died 6 years later after being diagnosed with and treated for colon cancer. An elder sibling died of a brain tumor at the age of 9 years.

On admission to our institution, the girl looked acutely ill. She was severely pale, but afebrile and anicteric. She had no petechial or purpuric skin rashes, but had glossitis with areas of papules on the anterior two-thirds of the dorsum of the tongue. She had no gingival hypertrophy, but had significant peripheral lymphadenopathy and weighed 67% of the weight for her age. In addition, she had generalized abdominal pain and a soft, well-circumscribed tender mass located at the right iliac fossa was palpated and estimated to be 8 cm x 6 cm.

A full blood count showed severe hypochromic microcytic anemia, with a red blood cell count of 2.53 x $10^{12}$/L, packed cell volume of 9%, white blood cell count 9.4 x$10^9$/L, platelet cell count of 453 x $10^9$/L, mean corpuscular volume of 48.6 fl, and a red cell distribution width of 23.7%. Iron studies could not be done because we lacked the facilities, but a bone marrow aspiration biopsy showed reduced bone marrow iron stores. A fecal occult blood test was positive for blood, but negative for culture, ova, or cysts. An abdominopelvic ultrasound showed the well-circumscribed mass at the right iliac fossa, and that was confirmed by a computed-tomographic scan (Figure 1). An upper endoscopy revealed fundal and prepyloric erosions and reflux eosophagitis.

Although findings from a sigmoidoscopy were normal, a histology of biopsied tissues showed features of chronic inflammation.

There was a delay in arriving at the final diagnosis because the patient's family faced financial difficulties and some of the imaging procedures were not available at our institution. Other diagnoses that were entertained and managed in this case were iron deficiency anemia from peptic ulcer disease. Six weeks after her initial presentation to our institution, the patient had an exploratory laparotomy. The findings intra-operatively were those of a huge tumor involving the ascending colon measuring 16 x14 cm and extending to involve the cecum and mesenteric lymph nodes (Figure 2).

Kidneys, liver and spleen were macroscopically normal. An assessment of Duke's stage 3C colon cancer was made and she had an extended radical hemicolectomy with anastomosis.
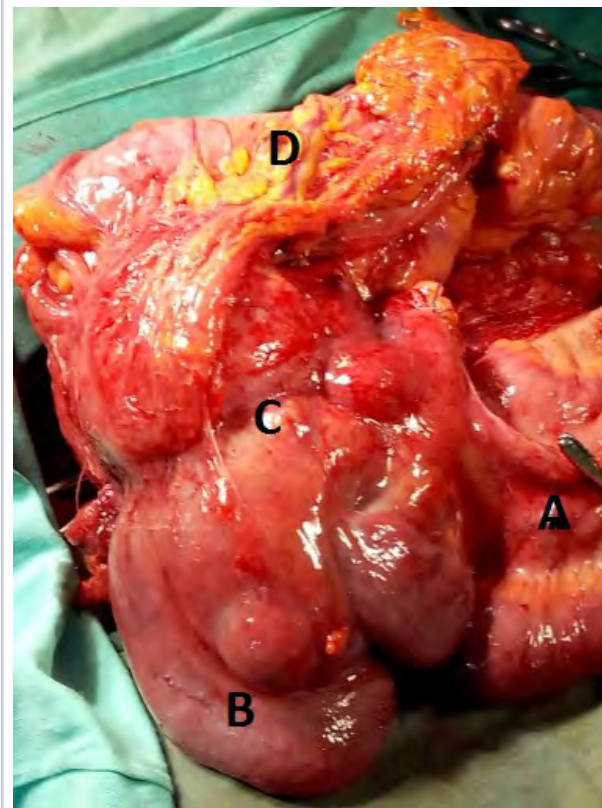
A 44.5-cm long right hemicolectomy segment comprising a 17-cm ileal segment, a 6-cm cecum, 21.5-cm ascending colon, and an 8-cm appendix was removed. The tumor was located in the ascending colon at 7.5 cm from the distal resection margin and extending 1 cm into the cecum. It had a circumference of 27 cm with fibrinous exudates on its peritoneal surface. Dissection revealed uneven circumferential thickening of the bowel wall, luminal dilatation, marked mucosal ulcerations, and liquid content made up of fecal material and necrotic debris. The tumor cut surface was solid white. We also removed 4 lymph nodes. Other uninvolved areas showed focal mucosal hyperemia, but no polyps were observed. Histology showed moderately differentiated adenocarcinoma (pT4) with ¼ nodal involvement (Figure 3).

The patient's postoperative course was uneventful, and she had adjuvant chemotherapy with oral capecitabine and intravenous oxaliplatin. She completed the 8-cycle protocol with excellent clinical response and minimal adverse events were recorded. A repeat abdominal CT scan showed no residual tumor (Figure 4), and her full blood count showed normal hematological profile with no evidence of iron deficiency. She is presently on follow up 2 years after confirmation of the diagnosis. (Her histo-
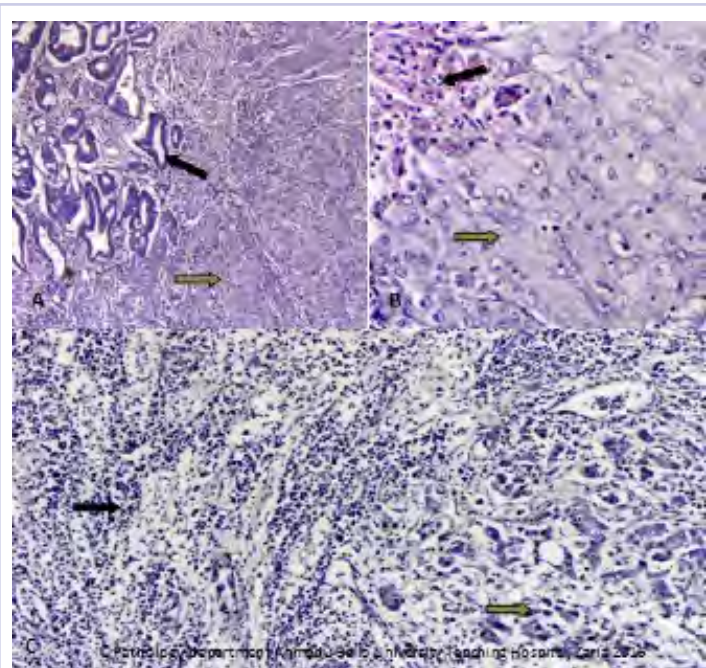
**FIGURE 3** Moderately differentiated adenocarcinoma (H&E). **A,** the tumor at low magnification (x40) showing irregular malignant glands (MG) and sheets and nodules of undifferentiated carcinoma component (U). **B,** higher magnification (x630 high dry) showing the tumor cells with vesicular nuclei prominent nucleoli and variable amount of cytoplasm (U); necrosis is noted (TN). **C,** the single involved lymph node (x100); the tumor nests (MG) are seen amidst the medullary sinuses and cords (MS&C) of the lymph node.



**FIGURE 4** A repeat abdominal computed-tomographic scan after surgery and 8 cycles of adjuvant chemotherapy showed no residual tumor.

logical diagnosis was made June 2016, and her last clinic follow-up was March 2018.

## Discussion

Our patient presented with symptoms of abdominal pain, dysuria, melena, and pallor as in other case reports.[7-10] A diagnosis of iron deficiency anemia was initially entertained in view of the hematologic profile, and for which management was instituted. The findings of gastric and duodenal erosions on endoscopy further supported the assumption for and treatment of peptic ulcer disease. Iron deficiency in this patient was owing to chronic blood loss from a tumour located at the upper parts of the. Vague and nonspecific symptoms are associated with delayed diagnosis and poor prognosis.[1-5,11] Nonspecificity of symptoms is typical feature of colon cancer as reported in other studies.[1,11-13] However, the strong family history of colon cancer heightened suspicion in this case, otherwise the diagnosis of an ascending colon tumor could have been delayed until much later and with graver consequences.

The diagnosis of colon cancer in this child was made about a year after her initial symptoms, and 3 months after her presentation to us. Ascending and transverse colon cancers are usually diagnosed late because the symptoms

of intestinal obstruction – frank bleeding – will not present until the illness is substantially advanced. Ameh and Nmadu reported a case series of 8 patients from our facility with rectosigmoid tumor, of whom 6 had mucinous adenocarcinaoma and 5 of those 6 had stage 3C disease. Although the patient in the present case had an advanced disease at diagnosis, she had a moderately differentiated histology in contrast to the 6 previously reported cases, who had mucinous histology.[14]

Previous studies have shown that colorectal carcinoma is a rare disease worldwide, with an annual age-adjusted incidence of 0.38 people/million.[1,2] When it occurs in the young, familial or hereditary predisposition should be highly suspected.[1-3] To date, there is scant literature on children younger than 16 years in Nigeria.[15] Various studies have found a relationship between patients with early-stage colon cancer and inherited genetic predisposition to the disease.[2,5] Familial adenomatous polyposis syndrome is an autosomal dominant disorder characterized by the development of polyps during the first decade of life, extensive polyposis in the second decade, and transformation into frank carcinoma in early adulthood.[1-5]

Although our patient's mother was diagnosed with and died of colon cancer, the type of which could not be ascertained because her records could not be traced. However,

the operative and histological findings in this patient did not suggest the presence of polyposis. The clinical phenotype for the autosomal recessive mismatch repair deficiency includes susceptibity to glioma, leukemia, lymphoma, and colorectal carcinoma in children and young adults.[1,5] Screening for genetic markers in the child in the present case might have identified the genetic abnormalities involved and would have been invaluable in the evaluation of her 6 surviving siblings and further management of this family. In conclusion. A high index of suspicion should prompt inclusion of colon cancer in the differential diagnosis of nonspecific gastrointestinal symptoms associated with colon cancer in children.

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# Effective management of severe radiation dermatitis after head and neck radiotherapy

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Head and neck cancer is among the most prevalent cancers in developing countries.[1] Most of the patients in developing countries present in locally advanced stages, and radical radiation therapy with concurrent chemotherapy is the standard treatment.[1] Radiation therapy is associated with radiation dermatitis, which causes severe symptoms in the patient and can lead to disruption of treatment, diminished rates of disease control rates, and impaired patient quality of life.[2] The management of advanced radiation dermatitis is difficult and can cause consequential late morbidity to patients.[2] We report here the rare case of a patient with locally advanced tonsil carcinoma who developed grade 3 radiation dermatitis while receiving radical chemoradiation. The patient's radiation dermatitis was effectively managed with the use of a silver-containing antimicrobial dressing that yielded remarkable results, so the patient was able to resume and complete radiation therapy.

## Case presentation and summary

A 48-year-old man was diagnosed with squamous cell carcinoma of the right tonsil, with bilateral neck nodes (Stage T4a N2c M0; The American Joint Committee on Cancer staging manual, 7th edition). In view of the locally advanced status of his disease, the patient was scheduled for radical radiation therapy at 70 Gy in 35 fractions over 7 weeks along with weekly chemotherapy (cisplatin 40 mg/m²). During the course of radiation therapy, the patient was monitored twice a week, and symptomatic care was done for radiation-therapy–induced toxicities.

The patient presented with grade 3 radiation dermatitis after receiving 58 Gy in 29 fractions over 5 weeks (grade 0, no change; grades 3 and 4, severe change). The radiation dermatitis involved the anterior and bilateral neck with moist desquamation of the skin (Figure 1). It was associated with severe pain, difficulty in swallowing, and oral mucositis. The patient was subsequently admitted to the hospital; radiation therapy was stopped, and treatment was initiated to ease the effects of the radiation dermatitis. Analgesics were administered for the pain, and adequate hydration and nutritional support was administered through a nasogastric tube. The patient's score on the Bates-Jensen Wound Assessment Tool (BWAT) for monitoring wound status was 44, which falls in extreme severity status.

In view of the extreme severity status of the radiation dermatitis, after cleaning the wound with sterile water, we covered it with an antimicrobial dressing that contained silver salt (Mepilex AG; Mölnlycke Health Care, Norcross, GA). The dressing was changed regularly every 4 days. There was a gradual improvement in the radiation dermatitis (Figure 2). By day 10, the wound had healed significantly, and by day 16, it was almost completely healed. The Bates-Jensen wound score and the pain score (visual analog scale) are shown in Table 1. Radiation therapy was withheld for 5 days and was resumed after the improvement of radiation dermatitis on day 5 (Figure 2), after which the patient completed his scheduled radiation therapy doses of 70 Gy in 35 fractions over 7 weeks with a gap of 5 days.

## Discussion

Head and neck cancer is one of the most common cancers in developing countries.[1] Most patients present with locally advanced disease, so chemoradiation is the standard treatment in these patents. Radiation therapy is associated with acute and chronic toxicities. The common radiation therapy toxicities are directed at skin and mucosa, which leads to radiation dermatitis and radiation mucositis, respectively.[2] These toxicities are graded as per

**FIGURE 1** Acute grade 3 radiation dermatitis after 5 weeks of initiating radiation therapy.



**FIGURE 2** The healing phases of the radiation dermatitis at days 5, 10, and 16.

the Radiation Therapy Oncology Group (RTOG) criteria (Table 2).[3]

Acute radiation dermatitis is radiation therapy dose-dependent and manifests within a few days to weeks after starting external beam radiation therapy. Its presentation varies in severity and gradually manifests as erythema, dry or moist desquamation, and ulceration when severe. These can cause severe symptoms in the patient, leading to frequent breaks in treatment, decreased rates of disease control, and impaired patient quality of life.[2] Apart from RTOG grading, radiation dermatitis can also be scored using the BWAT. This tool has been validated across many studies to score initial wound status and monitor the sub-

sequent status numerically.[4] The radiation dermatitis of the index case was scored and monitored with both RTOG and BWAT scores.

The management of advanced radiation dermatitis is difficult, and it causes consequential late morbidity in patients. A range of topical agents and dressings are used to treat radiation dermatitis, but there is minimal evidence to support their use.[5] The Multinational Association for Supportive Care in Cancer treatment guidelines for prevention and treatment of radiation dermatitis have also concluded that there is a lack of sufficient evidence in the literature to support the superiority for any specific intervention.[6] Management of radiation dermatitis varies

**TABLE 1** Wound and pain scores, days 1 to 16

| Day | Wound score[a] | Pain score[b] |
|-----|----------------|---------------|
| 1 | 44 | 7 |
| 5 | 29 | 5 |
| 10 | 20 | 4 |
| 16 | 13 | 3 |

[a]Based on the Bates-Jensen Wound Assessment Tool (score range: 5-65, with 13 as wound regeneration and 60 as wound degeneration). [b]Visual analog scale (score range: 0-10, with 0 as no pain and 10 as worst pain).

**TABLE 2** Radiation Therapy Oncology Group acute skin toxicity score

| Score | Effects |
|-------|---------|
| 0 | No change over baseline |
| 1 | Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating |
| 2 | Tender or bright erythema, patchy moist desquamation/moderate edema |
| 3 | Confluent, moist desquamation other than skin folds, pitting edema |
| 4 | Ulceration, hemorrhage, necrosis |

among practitioners because of the inconclusive evidence for available treatment options.

The use of silver-based antimicrobial dressings has been reported in the literature in the prevention and treatment of radiation dermatitis, but with mixed results.[7] Such dressings absorb exudate, maintain a moist environment that promotes wound healing, fight infection, and minimize the risk for maceration, according to the product informa-

tion sheet.[8] Clinical study findings have shown silver to be effective in fighting many different types of pathogens, including Methicillin-resistant *Staphylococcus aureus* and other drug-resistant bacteria.

Aquino-Parsons and colleagues studied 196 patients with breast cancer who were undergoing whole-breast radiation therapy.[9] They showed that there was no benefit of silver-containing foam dressings for the prevention of acute grade 3 radiation dermatitis compared with patients who received standard skin care (with moisturizing cream, topical steroids, saline compress, and silver sulfadiazine cream). However, the incidence of itching in the last week of radiation and 1 week after treatment completion was lower among the patients who used the dressings.

Diggelmann and colleagues studied 24 patients with breast cancer who were undergoing radiation therapy.[10] Each of the erythematous areas (n = 34) was randomly divided into 2 groups; 1 group was treated with Mepilex Lite dressing and the other with standard aqueous cream. There was a significant reduction in the severity of acute radiation dermatitis in the areas on which Mepilex Lite dressings were used compared with the areas on which standard aqueous cream was used.

The patient in the present case had severe grade 3 acute radiation dermatitis with a BWAT score indicative of extreme severity. After cleaning the wound with sterile water, instead of using the standard aqueous cream on the wounds, we used Mepilex AG, an antimicrobial dressing that contains silver salt. The results were remarkable (Figure 2 and Table 2). The patient was able to restart radiation therapy, and he completed his scheduled doses.

This case highlights the effectiveness of a silver-based antimicrobial dressing in the management of advanced and severe radiation dermatitis. Further large and randomized studies are needed to test the routine use of the dressing in the management of radiation dermatitis.

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# Striking rash in a patient with lung cancer on a checkpoint inhibitor

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Lung cancer remains the most common cause of cancer death in the United States and worldwide.[1] Despite advances in the treatment of the disease and development of targeted therapy, the 5-year overall survival in stage IV non–small-cell lung cancer remains poor, ranging from 6% to 10%.[2] More recently, checkpoint inhibitors have had a major impact on the treatment of lung cancer. Nivolumab was the first program cell death protein-1 (PD-1) inhibitor approved for malignant melanoma.[3] In July 2015, it was approved as a second-line treatment of squamous cell carcinoma of the lung.[4] Since then, the use of nivolumab has extended to other malignancies such as head and neck cancer, renal cell carcinoma, and the list continues to expand. In lung cancer, it demonstrated superior overall survival of 9 months, compared with 6 months with docetaxel.[4] Other checkpoint inhibitors such as pembrolizumab[5] and atezolizumab[6] were subsequently developed, and are also used in the treatment of lung cancer.

Serious potential autoimmune complications arise in up to 30% of patients treated with PD-1 inhibitors. Dermatologic toxicity is the most common immune-related adverse event in these patients. In addition to vitiligo, most common is a reticular maculopapular rash on the trunk and extremities. Other adverse events, such as photosensitivity, alopecia, xerosis, and hair color changes, are reported less frequently.[7] We report here a case of rash at an unusual location (auricular and periauricular) with skin exfoliation mimicking other common skin conditions such as eczema and psoriasis.

## Case presentation and summary

A 57-year-old woman with a history of cerebrovascular accident with residual left lower-leg paresis presented for acute onset expressive aphasia in the absence of other constitutional or neurological findings. Magnetic resonance imaging of the brain showed a posterior, left parietal lobe lesion of 1.6 cm with intralesional hemorrhage and surrounding edema suggestive of brain metastasis. The patient had a 35 pack-year history of smoking. A staging work-up with computed-tomographic (CT) scans showed a spiculated enhancing nodule in the superior segment of the right lower lobe plus mediastinal adenopathy.

The patient underwent a CT-guided core biopsy of the spiculated nodule, which was found to be consistent with adenocarcinoma of the lung. It was negative for *EGFR* mutation or *ALK* rearrangement. She received stereotactic radiosurgery to the left posterior parietal lesion, and after completion of radiation, was started on systemic chemotherapy with cisplatin plus pemetrexed for adenocarcinoma of the lung. She received 4 cycles of chemotherapy. Repeat imaging with a PET-CT showed interval increase of the mediastinal hypermetabolic lymphadenopathy with new hypermetabolic pretracheal lymph nodes and interval development of multiple liver metastases in the right and left lobes of the liver (Figure 1). She was started on second-line therapy with nivolumab at a dose of 240 mg every 2 weeks. The treatment was complicated initially by new onset grade 2 papular pruritic rash after cycle 2 of therapy. The rash involved the upper and lower extremities, sparing the palms, soles, trunk, abdomen, and the back. It resolved with treatment delay and topical steroids.

The patient resumed treatment with nivolumab after complete resolution of the rash. However, she developed grade 2 nephritis after cycle 5 with a creatinine level of 1.98 mg/dL (reference range, 0.6-1.2 mg/ dL). This was resolved after treatment with oral prednisone, at a starting dose of 1 mg/kg and tapered over 4 weeks. PET CT scans obtained after cycles 5 and 11 showed no metabolic activity in the mediastinum or the liver and markedly decreased uptake in the right lower lobe nodule, down to an
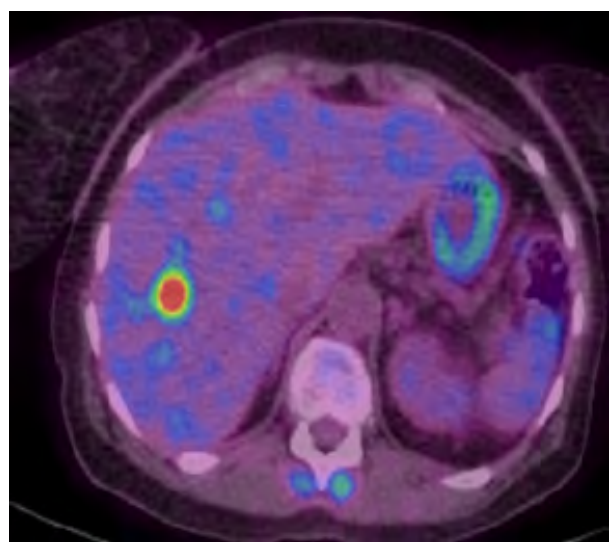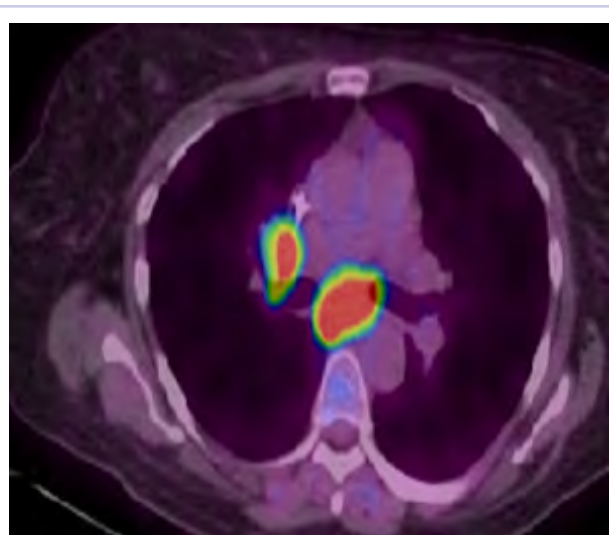
FIGURE 1 PET-CT of **A,** chest, right hilar soft tissue mass, SUV 9.2, plus subcarinal node (SUV 12.8), and **B,** abdomen, with hypermetabolic focus in liver.
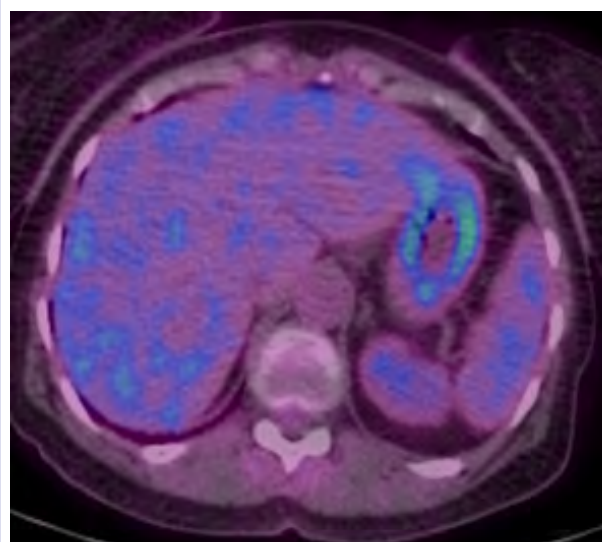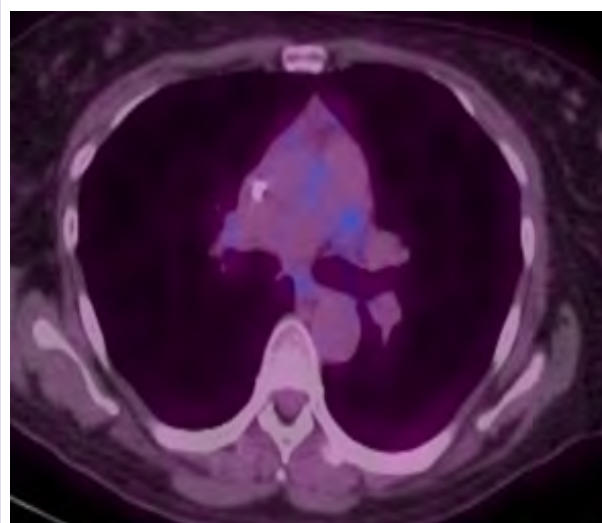


FIGURE 2 PET-CT of **A,** chest showing resolution of hypermetabolic lesions, and **B,** resolution of hypermetabolic lesions, physiologic uptake of FDG in liver.

SUV of 1.7 with no new nodules. An MRI of the brain was stable (Figure 2).

After cycle 16 of nivolumab, the patient developed a severe eczematous rash with excoriations at the base of both ears involving the periauricular and auricular areas bilaterally (Figure 3). She had a normal otoscopy exam, however, she also developed a maculopapular rash over the anterior abdomen (not shown). After failure of topical steroids and 1 week of oral antibiotics, she was started on prednisone 1 mg/kg daily. She was seen after 1 week and had a significant response to the treatment, with resolution of the periauricular and auricular eczematous lesions as well as the abdominal rash (Figure 4). She completed 4 weeks of steroid therapy on a tapering schedule. Treatment with nivolumab was resumed afterward with no adverse

autoimmune complications. At her last visit (25 months after initiating a PD-1 inhibitor), there was no clinical or radiologic evidence of lung cancer nor any of autoimmune adverse effects.

## Discussion

Among multiple autoimmune complications, dermatologic toxicity is the most common immune-related adverse event, occurring in about 30% to 40% of patients[7,8] and with an average onset of 3-4 weeks after initiating treatment with checkpoint inhibitors.[9] In addition to vitiligo, the most common type of rash described is a reticular maculopapular rash on the trunk and extremities.[10] Other findings, such as photosensitivity, alopecia, xerosis, and hair color changes, have been reported in smaller numbers. Skin exfoliation, as seen

**FIGURE 4** Resolution of the rash after 1 week of treatment with steroids.



**FIGURE 3** Severe eczematous rash with skin excoriations and irritation at the base involving periauricular areas bilaterally (before treatment)

Ear, nose, and throat surgeons are more likely to encounter such a complication with the expanded use of PD-1 and PD-ligand 1 inhibitors in advanced head and neck cancers. The differential diagnosis includes localized eczema, psoriatic rash, skin infection, or an autoimmune phenomenon.

The location of the rash was also of concern because there have been reports of autoimmune inner-ear disease related to immunotherapy.[11] After the failure of treatment with empiric antibiotics and topical steroids, in addition to the development of a new rash on her abdomen, we concluded that this case might represent an unusual autoimmune skin complication. The resolution of the skin lesions in both locations (the ears and the abdomen) with the oral steroid therapy, supported our suspected diagnosis of autoimmune dermatitis.

It is essential that these complications are detected early and misdiagnosis is avoided because timely treatment with steroids will prevent progression to more severe problems such as Steven-Johnson syndrome, toxic epidermal necrolysis,[12] or extension into the inner ear.[11]

This case is part of a growing spectrum of other unusual cases seen with immunotherapy treatment, such as erythema nodosum-like reactions,[13] bullous dermatitis,[14] and psoriasiform eruptions.[15] It highlights the need for an awareness of expanding dermatologic complications from immunotherapy beyond the reported common manifestations. Established guidelines and algorithms for the management of immune-related dermatologic toxicity are available to assist the physician in treatment (Table 1).[16] Skin biopsy should be considered if the diagnosis remains uncertain, although starting

in the present case, has been reported in fewer than 1% of the cases.[4] Perivascular lymphocytic infiltrates extending deep into the dermis are most likely to be seen if the lesions are biopsied. Both the location of the rash in our patient and its relapsing nature are rare and make it more interesting as it presents a diagnostic dilemma for treating physicians.

empiric treatment with steroids is a widely acceptable approach. Reassessing the skin rash in 48 hours to 1 week after treatment initiation is crucial because steroid-refractory cases will need additional immunosuppression. Early termination of steroids is associated with higher recurrence rate, therefore tapering steroids over 4 weeks is highly recommended before resuming treatment with checkpoint inhibitors.

In summary, increased awareness among health care professionals of the common and unusual complications of immunotherapy agents is important and essential in patient care. In addition to oncologists, head and neck surgeons, pulmonologists, urologists, dermatologists, and general internists will encounter patients with immunotherapy-related complications. Patient education should be emphasized to ensure prompt investigation and treatment of complications. Finally, it is not yet clear whether the development of autoimmune reactions predicts disease response to treatment. In a series of 134 patients with lung cancer, the occurrence of autoimmune adverse events correlated with improved survival.[17] More research is needed to identify prognostic and predictive biomarkers for response to immunotherapy.

## Conclusion

This pattern of autoimmune dermatitis localizing to the ears is rare (<1% of cases of dermatitis). Nevertheless, it raises the awareness for dermatologic complications of immunotherapy beyond the classical reported manifestations. Prompt diagnosis and treatment is essential to avoid serious complications such as Steven-Johnson syndrome, toxic epidermal necrolysis, and potentially damage to the inner ear.

**TABLE 1** Management of skin toxicity of checkpoint inhibitors[a]

| Grade, manifestation | Management |
|---|---|
| *Grade 1* Skin rash, with or without pruritus, <10% of BSA | ■ Avoid irritants and sun, topical emollients recommended<br>■ Topical steroids of low-moderate potency, ±topical or oral antihistamines for itching<br>■ Continue CPI |
| *Grade 2* Skin rash, 10%-30% of BSA | ■ Continue supportive management as above<br>■ Topical steroids or lotion of moderate potency, ±topical or oral antihistamines for itching<br>■ Continue CPI |
| *Grade 3* Skin rash >30% of BSA, OR grade 2 with significant symptoms | ■ Hold CPI<br>■ Initiate steroids at 0.5-1 mg/kg prednisone equivalent, for 3-7 days, then taper over 1-2 weeks, in severe cases IV, then transition to oral, taper over 2-4 weeks<br>■ Restart CPI if rash returns to grade 1 or mild grade 2, discuss with patient |
| *Grade 4* Skin sloughing >30%, with associated symptoms (erythema, purpura, epidermal detachment) | ■ Start IV methylprednisolone 1-2 mg/kg, get urgent consultation with dermatologist<br>■ Discontinue CPI |

BSA, body surface area; CPI, checkpoint inhibitors

[a]Modified from Haanen et al[16]

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# Recurrence of a small gastric gastrointestinal stromal tumor with high mitotic index

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Gastrointestinal stromal tumor (GIST) is the most common soft tissue sarcoma of the gastrointestinal tract, usually arising from the interstitial cells of Cajal or similar cells in the outer wall of the gastrointestinal tract.[1,2] Most GISTs have an activating mutation in KIT or platelet-derived growth factor receptor alpha (PDGFRA). Tumor size, mitotic rate, and anatomic site are the most common pathological features used to risk stratify GIST tumors.[3-10] It is important to note when using such risk calculators that preoperative imatinib before determining tumor characteristics (such as mitoses per 50 high-power fields [hpf]) often changes the relevant parameters so that the same risk calculations may not apply. Tumors with a mitotic rate ≤5 mitoses per 50 hpf and a size ≤5 cm in greatest dimension have a lower recurrence rate after resection than tumors with a mitotic rate >5 mitoses per 50 hpf and a size >10 cm, and larger tumors can have a recurrence rate of up to 86%.[11,12] Findings from a large observational study have suggested that the prognosis of gastric GIST in Korea and Japan may be more favorable compared with that in Western countries.[13]

The primary treatment of a localized primary GIST is surgical excision, but a cure is limited by recurrence.[14,15] Imatinib is useful in the treatment of metastatic or recurrent GIST, and adjuvant treatment with imatinib after surgery has been shown to improve progression-free and overall survival in some cases.[3,16-18] Responses to adjuvant imatinib depend on tumor sensitivity to the drug and the risk of recurrence. Drug sensitivity is largely dependent on the presence of mutations in KIT or PDGFRA.[3,18] Recurrence risk is highly dependent on tumor size, tumor site, tumor rupture, and mitotic index.[1,3,5,6,8,9,18,19] Findings on the use of gene expression patterns to predict recurrence risk have also been reported.[20-27] However, recurrence risk is poorly understood for categories in which there are few cases with known outcomes, such as very small gastric GIST with a high mitotic index. For example, few cases of gastric GIST have been reported with a tumor size ≤2 cm, a mitotic rate >5 mitoses per 50 hpf, and adequate clinical follow-up. In such cases, it is difficult to assess the risk of recurrence.[6] We report here the long-term outcome of a patient with a 1.8 cm gastric GIST with a mitotic index of 36 mitoses per 50 hpf and a KIT exon 11 mutation.

## Case presentation and summary

A 69-year-old man presented with periumbilical and epigastric pain of 6-month duration. His medical history was notable for hyperlipidemia, hypertension, coronary angioplasty, and spinal surgery. He had a 40 pack-year smoking history and consumed 2 to 4 alcoholic drinks per day. The results of a physical examination were unremarkable. A computed-tomographic (CT) scan showed no abnormalities. An esophagoduodenoscopy (EGD) revealed gastric ulcers. He was treated successfully with omeprazole 20 mg by mouth daily.

A month later, a follow-up EGD revealed a 1.8 × 1.5 cm submucosal mass 3 cm from the gastroesophageal junction. The patient underwent a fundus wedge resection, and a submucosal mass 1.8 cm in greatest dimension was removed. Pathologic examination revealed a GIST, spindle cell type, with a mitotic rate of 36 mitoses per 50 hpf with negative margins. Immunohistochemistry was positive for CD117. An exon 11 deletion (KVV558-560NV) was present in KIT. The patient's risk of recurrence
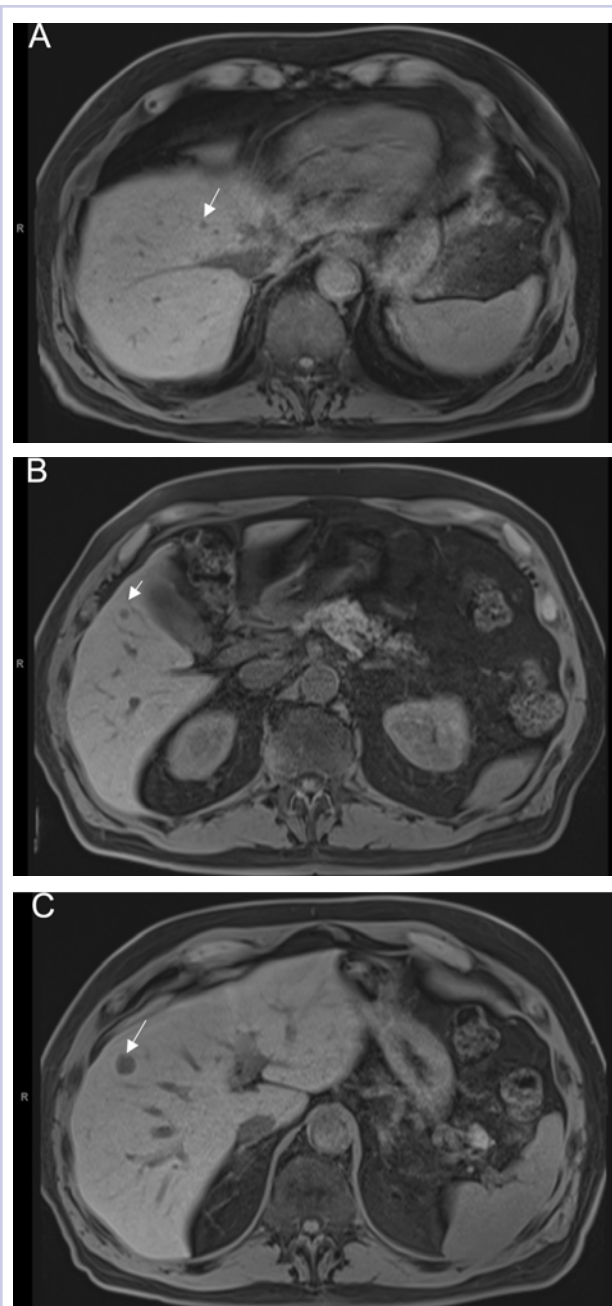
FIGURE 1 Magnetic resonance imaging of the liver demonstrating metastatic disease (arrows, A and B), with a 1.2 × 1.3-cm mass in the hepatic segment 4a/8 (C).



FIGURE 2 Computed-tomographic scan images of the abdomen and pelvis with contrast, before initiation of imatinib (A) and 16 months after initiation of imatinib (B).

was unclear, and his follow-up included CT scans of the abdomen and pelvis every 3 to 4 months for the first 2 years, then every 6 months for the next 2.5 years.

A CT scan about 3.5 years after primary resection revealed small nonspecific liver hypodensities that became more prominent during the next year. About 5 years after primary resection, magnetic resonance imaging (MRI) revealed several liver lesions, the largest of which mea-

sured at 1.3 cm in greatest dimension. The patient's liver metastases were readily identified by MRI (Figure 1) and CT imaging (Figure 2A). Most GISTs are fluorodeoxy-glucose (FDG) avid on positron-emission tomography (PET) imaging. In contrast, this patient's liver metastases had no detectable FDG uptake (not shown). A liver biopsy revealed recurrent GIST (Figure 3). Imatinib mesylate was begun at 400 mg per day orally. After 2 months, the liver lesions were reduced in size, with the largest lesion shrinking to 0.5 cm in greatest dimension. The liver lesions continued to decrease in size and number (Figure 2B). At 16 months after starting imatinib, there was no sign of tumor progression.

## Discussion

Small gastric GISTs are sometimes found by endoscopy performed for unrelated reasons. Recent data suggest that the incidence of gastric GIST may be higher than previously thought. In a Japanese study of patients with gastric cancer in which 100 stomachs were systematically exam-
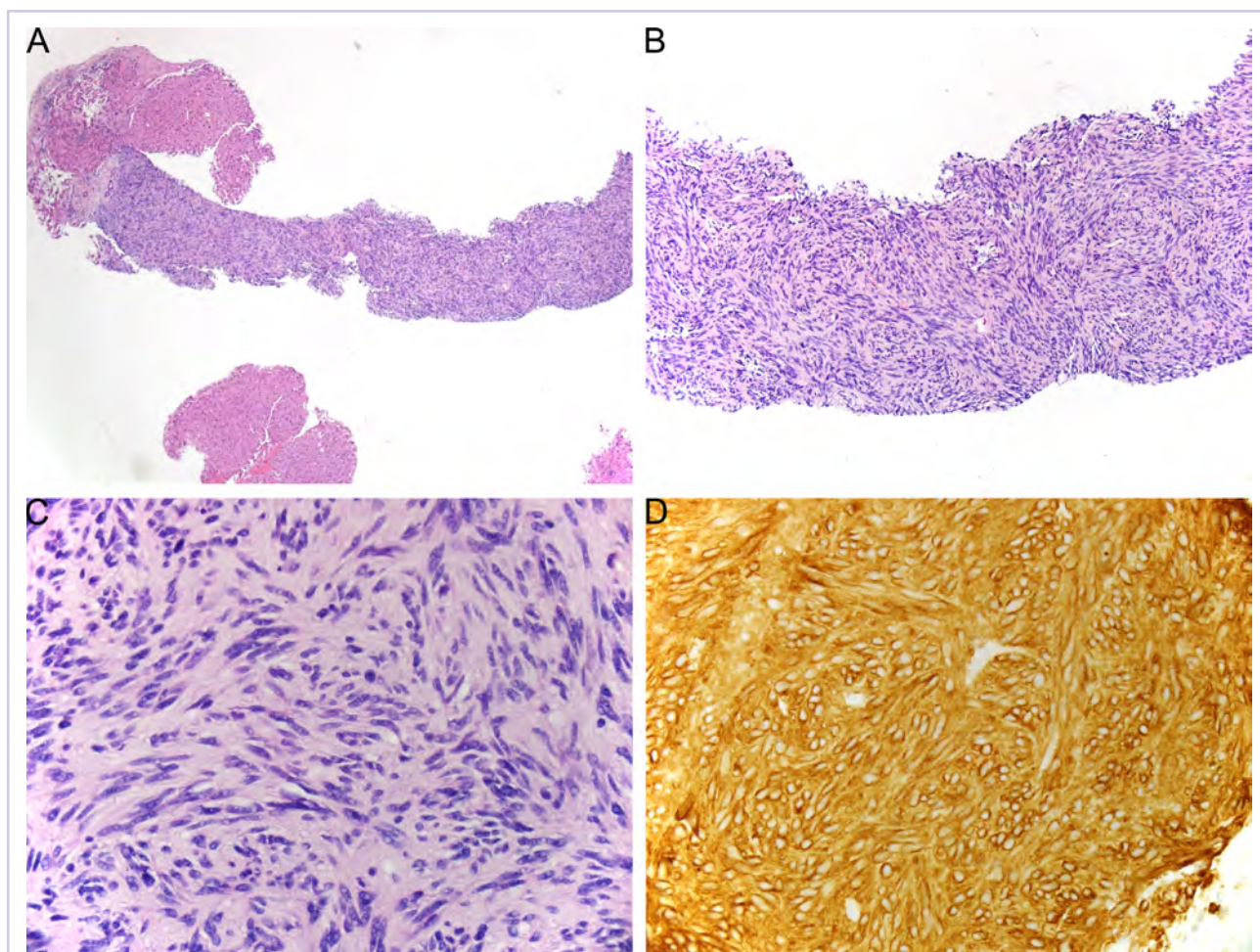
**FIGURE 3** Histopathology of liver metastases showing (A) GIST (H&E, x10); (B) spindle cell tumor arranged in intersecting tight fascicles (H&E, x20); (C) metastatic GIST (H&E stain, x40); and (D) strong CD117 immunoreactivity in liver metastasis (x40).

ined pathologically, 50 microscopic GISTs were found in 35 patients.[28] Most small gastric GISTs have a low mitotic index. Few cases have been described with a high mitotic index. In a study of 1765 cases of GIST of the stomach, 8 patients had a tumor size less than 2 cm and a mitotic index greater than 5. Of those, only 6 patients had long-term follow-up, and 3 were alive without disease at 2, 17, and 20 years of follow-up.[7] These limited data make it impossible to predict outcomes in patients with small gastric GIST with a high mitotic index.

For patients who are at high risk of recurrence after surgery, 3 years of adjuvant imatinib treatment compared with 1 year has been shown to improve overall survival and is the current standard of care.[10,17] A study comparing 5 and 3 years of imatinib is ongoing to establish whether a longer period of adjuvant treatment is warranted. In patients with metastatic GIST, lifelong imatinib until lack of benefit is considered optimal treatment.[10] All patients should undergo KIT mutation analysis. Those with the PDGFRA D842V mutation, SDH (succinate dehydrogenase) deficiency, or neurofibromatosis-related GIST should not receive adjuvant imatinib.

This case has several unusual features. The small tumor size with a very high mitotic rate is rare. Such cases have not been reported in large numbers and have therefore not been reliably incorporated into risk prediction algorithms. In addition, despite a high mitotic index, the tumor was not FDG avid on PET imaging. The diagnosis of GIST is strongly supported by the KIT mutation and response to imatinib. This particular KIT mutation in larger GISTs is associated with aggressive disease. The present case adds to the data on the biology of small gastric GISTs with a high mitotic index and suggests the mitotic index in these tumors may be a more important predictor than size.

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# Tumor heterogeneity: a central foe in the war on cancer

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A major challenge to effective cancer treatment is the astounding level of heterogeneity that tumors display on many different fronts. Here, we discuss how a deeper appreciation of this heterogeneity and its impact is driving research efforts to better understand and tackle it and a radical rethink of treatment paradigms.

## A complex and dynamic disease

The nonuniformity of cancer has long been appreciated, reflected most visibly in the variation of response to the same treatment across patients with the same type of tumor (*inter*-tumor heterogeneity). The extent of tumor heterogeneity is being fully realized only now, with the advent of next-generation sequencing technologies. Even within the same tumor, there can be significant heterogeneity from cell to cell (*intra*-tumor heterogeneity), yielding substantial complexity in cancer.

Heterogeneity reveals itself on many different levels. Histologically speaking, tumors are composed of a nonhomogenous mass of cells that vary in type and number. In terms of their molecular make-up, there is substantial variation in the types of molecular alterations observed, all the way down to the single cell level. In even more abstract terms, beyond the cancer itself, the microenvironment in which it resides can be highly heterogeneous, composed of a plethora of different supportive and tumor-infiltrating normal cells.

Heterogeneity can manifest spatially, reflecting differences in the composition of the primary tumor and tumors at secondary sites or across regions of the same tumor mass and temporally, at different time points across a tumor's natural history. Evocative of the second law of thermodynamics, cancers generally become more diverse and complex over time.[1-3]

## A tale of 2 models

It is widely accepted that the transformation of a normal cell into a malignant one occurs with the acquisition of certain "hallmark" abilities, but there are myriad ways in which these can be attained. Two key models can be used to explain how tumors develop – the clonal evolution model and the cancer stem cell (CSC) model (Figure 1).

### The clonal evolution model

As cells divide, they randomly acquire mutations as a result of DNA damage. The clonal evolution model posits that cancer develops as the result of a multi-step accumulation of a series of "driver" mutations that confer a promalignant advantage to the cell and ultimately fuel a cancerous hallmark.

This evolution can occur in a linear fashion, whereby the emergence of a new driver mutation conveys such a potent evolutionary advantage that it outcompetes all previous clones. There is limited evidence for linear evolution in most advanced human cancers; instead, they are thought to evolve predominantly through a process of branching evolution, in which multiple clones can diverge in parallel from a common ancestor through the acquisition of different driver mutations. This results in common clonal mutations that form the trunk of the cancer's evolutionary tree and are shared by all cells and subclonal mutations, which make up the branches and differ from cell to cell.

More recently, several other mechanisms of clonal evolution have been proposed, including neutral evolution, a type of branching evolution in which there are no selective pressures and evolution occurs by random mutations occurring over time that lead to genetic drift, and punctuated evolution, in which there are short evolutionary bursts of hypermutation.[4,5]

### The CSC model

This model posits that the ability to form and sustain a cancer is restricted to a single cell type – the cancer stem cells – which have the unique capacity for self-renewal and differentiation. Although the forces of evolution are still involved in this model, they act on a hierarchy of cells, with stem cells sitting at the top. A tumor is derived from a single stem cell that has acquired a mutation, and the heterogeneity observed results both from the differentiation and the accumulation of mutations in CSCs.
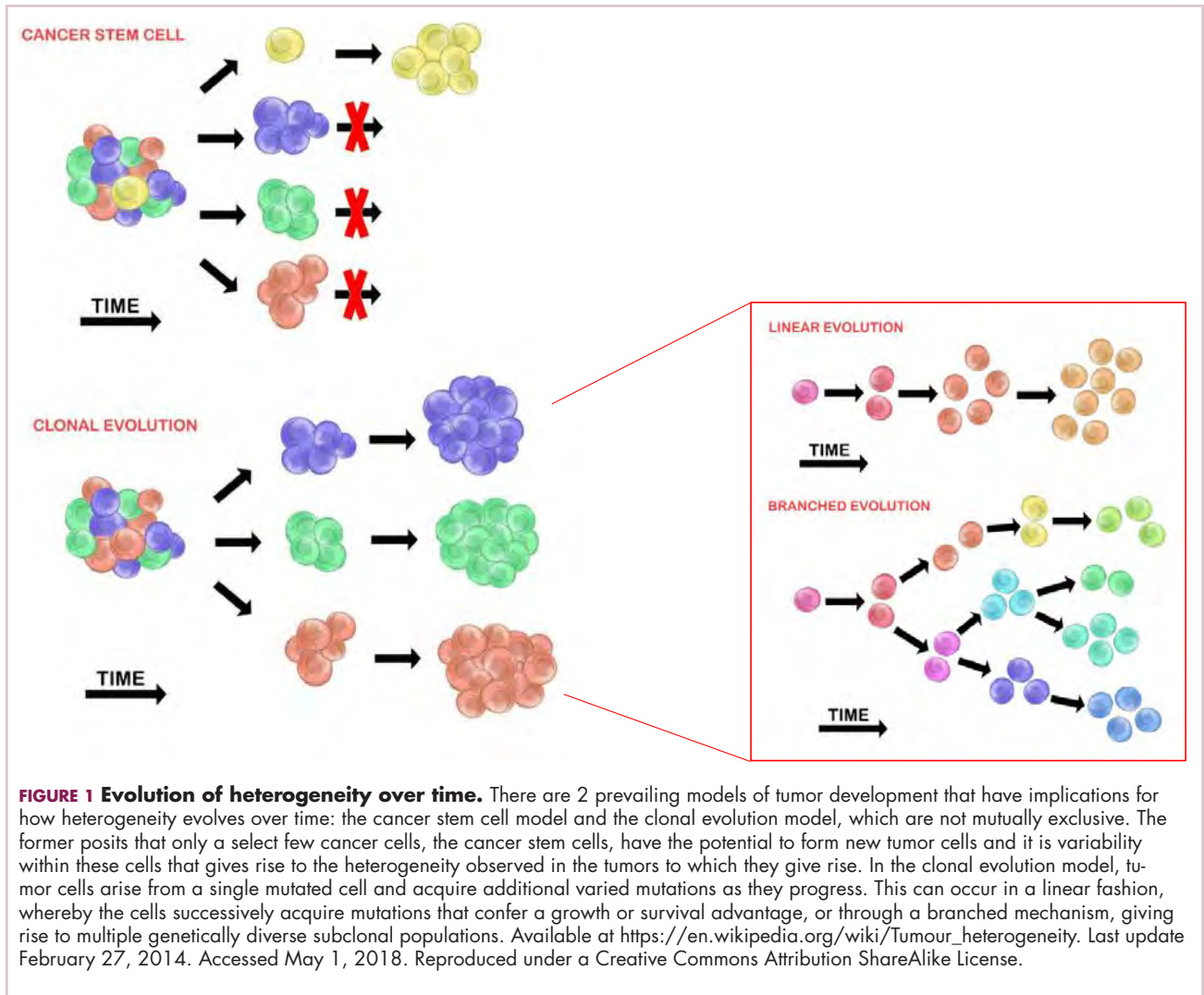
**FIGURE 1 Evolution of heterogeneity over time.** There are 2 prevailing models of tumor development that have implications for how heterogeneity evolves over time: the cancer stem cell model and the clonal evolution model, which are not mutually exclusive. The former posits that only a select few cancer cells, the cancer stem cells, have the potential to form new tumor cells and it is variability within these cells that gives rise to the heterogeneity observed in the tumors to which they give rise. In the clonal evolution model, tumor cells arise from a single mutated cell and acquire additional varied mutations as they progress. This can occur in a linear fashion, whereby the cells successively acquire mutations that confer a growth or survival advantage, or through a branched mechanism, giving rise to multiple genetically diverse subclonal populations. Available at https://en.wikipedia.org/wiki/Tumour_heterogeneity. Last update February 27, 2014. Accessed May 1, 2018. Reproduced under a Creative Commons Attribution ShareAlike License.

Accumulated experimental evidence suggests that these models are not mutually exclusive and that they can all contribute to heterogeneity in varied amounts across different tumor types. What is clear is that heterogeneity and evolution are intricately intertwined in cancer development.[1,2,6]

### An unstable genome

Heterogeneity and evolution are fueled by genomic alterations and the genome instability that they foster. This genome instability can range from single base pair substitutions to a doubling of the entire genome and results from both exposure to exogenous mutagens (eg, chemicals and ultraviolet radiation) and genomic alterations that have an impact on important cellular processes (eg, DNA repair or replication).

Among the most common causes of genome instability are mutations in the DNA mismatch repair pathway proteins or in the proofreading polymerase enzymes. Genome instability is often associated with unique mutational signatures – characteristic combinations of mutations that arose as the result of the specific biological processes underlying them.[7]

Genome-wide analyses have begun to reveal these mutational signatures across the spectrum of human cancers. The Wellcome Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) database has generated a set of 30 mutational signatures based on analysis of almost 11,000 exomes and more than 1,000 whole genomes spanning 40 different cancer types, some of which have been linked with specific mutagenic processes, such as tobacco, UV radiation, and DNA repair deficiency (Table 1).[8]

One potential downside to genome instability for cancer cells is that it can lead to massive deleterious effects that overwhelm the genome and lead to cell death. A potential way to overcome this is for the changes to be restricted to a small portion of the genome and there is evidence for this in the discovery of patterns of localized hypermutation (kataegis) described in breast cancer genomes and in several

**TABLE 1** COSMIC mutational signatures in cancer[a]

| Process | Associated signatures | Cancer types | Description |
|---|---|---|---|
| Age-related mutagenesis | Signature 1 | All cancer types, most samples | ■ Associated with small numbers of small insertions and deletions, resulting from spontaneous deamination of 5-methylcytosine |
| | Signature 5 | All cancer types, most samples | ■ Associated with a predominance of T>C substitutions in the ApTpN trinucleotide context with transcriptional strand bias, thought to result from loss of the *FHIT* gene |
| Homologous recombination deficiency | Signature 3 | Breast, ovarian, and pancreatic cancers | Associated with an increased number of large insertions and deletions with microhomology at the breakpoints. Related to a failure of DNA double-strand break repair by homologous recombination (eg, *BRCA1/2* mutations) |
| APOBEC enzymes | Signature 2 | 22 cancer types, most common in cervical and bladder cancers, in at least 10% of samples | ■ Enriched for C>T and C>G substitutions, commonly associated with the phenomenon of local hypermutation known as kataegis, thought to arise from cytidine deaminase activity of the AID/APOBEC enzyme family. |
| | Signature 13 | Same as Signature 2 | ■ As above, but associated with mainly C>G mutations |
| DNA mismatch repair deficiency | Signature 6 | ■ 17 cancer types, most common in colorectal and uterine cancers | Associated with high numbers of small insertions and deletions at mono/polynucleotide repeats and microsatellite instability, related to defective DNA mismatch repair |
| | Signature 15 | ■ Stomach cancers and a single small cell lung carcinoma | |
| | Signature 20 | ■ Stomach and breast cancers | |
| | Signature 26 | ■ Breast, cervical, stomach, and uterine cancers | |
| DNA proofreading | Signature 10 | 6 cancer types, most common in uterine and colorectal cancers | Associated with huge numbers of mutations, thought to result from altered activity of the error-prone polymerase POLE |
| Base excision repair | Signature 18 | Colorectal cancer[b] | Associated with enrichment of transversion mutations (G:C>T:A), related to defective *MUTYH* gene and base excision repair deficiency |
| UV radiation | Signature 7 | Skin, head and neck, and oral squamous cancers | Associated with large numbers of CC>TT dinucleotide mutations at dipyrimidines, related to UV light exposure |
| Alkylating cytotoxic drugs | Signature 11 | Melanoma and glioblastoma | Associated with a strong transcriptional strand bias for C>T substitutions, related to treatment with alkylating agents |
| Tobacco | Signature 4 | Head and neck, liver, and esophageal cancers; lung adenocarcinoma; lung squamous cell carcinoma; small cell lung carcinoma | ■ Associated with transcriptional strand bias for C>A mutations, related to exposure to tobacco carcinogens |
| | Signature 29 | Gingivo-buccal oral squamous cell carcinoma | ■ Associated with transcriptional strand bias for C>A mutations and CC>AA dinucleotide substitutions, related to exposure to chewing tobacco |
| Immunoglobulin gene hypermutation | Signature 9 | Chronic lymphocytic leukemia and malignant B-cell lymphoma | Associated with enrichment of T>G transversions, related to the error-prone polymerase . Observed predominantly in cancers with immunoglobulin gene hypermutation |

[a]References: Wellcome Sanger Institute. Signatures of mutational processes in human cancer. https://cancer.sanger.ac.uk/cosmic/signatures. Update/publication date not available. Accessed May 1, 2018. Volinia S, et al. The ubiquitous 'cancer mutational signature' 5 occurs specifically in cancers with deleted *FHIT* alleles. Oncotarget. 2017;8(60):102199-102211. Pilati C, et al. Mutational signature analysis identifies MUTYH deficiency in colorectal cancers and adrenocortical carcinomas. J Pathol. 2017;242:10-15. [b]Signature 18 has been observed in other cancer types, but it has not yet been linked to base excision repair in those cases.

**TABLE 2** Targeting DNA repair pathways

| Drug | Manufacturer | Mechanism of action | Most advanced clinical setting (clinicaltrials.gov identifier) |
|---|---|---|---|
| Olaparib (Lynparza) | AstraZeneca | PARP inhibitor | *FDA approved* <br> *BRCA*-mutated ovarian cancer (2014) <br> Maintenance therapy ovarian cancer (2017) <br> *BRCA*-mutated metastatic breast cancer (2018) <br> *Phase 3* <br> *BRCA*-mutated pancreatic cancer (POLO; NCT02184195) |
| Niraparib (Zejula) | Tesaro | PARP inhibitor | *FDA approved* <br> Maintenance therapy ovarian cancer <br> *Phase 3* <br> Maintenance therapy SCLC (NCT03516084) <br> Maintenance therapy ovarian cancer (NCT02655016) |
| Rucaparib (Rubraca) | Pfizer | PARP inhibitor | *FDA approved* <br> *BRCA*-mutated ovarian cancer (2016) <br> Maintenance therapy ovarian cancer (2018) <br> *Phase 3* <br> *BRCA*-mutated ovarian cancer (ARIEL-4; NCT02855944) <br> HRD-positive mCRPC (TRITON3; NCT02975934) |
| Veliparib | Abbott | PARP inhibitor | *Phase 3* <br> In combination with temozolomide in GBM (NCT02152982) |
| Talazoparib | BioMarin | PARP inhibitor | *Phase 2* <br> *BRCA*/PTEN/HRD-positive cancers (NCT02286687) <br> *BRCA*-wildtype TNBC/solid tumors (NCT02401347) <br> HRD-positive squamous cell lung cancer (NCT03377556) <br> mCRPC (NCT03148795) |
| MSC2490484A | EMD-Serono | DNA-PK inhibitor | *Phase 1* <br> In combination with RT in advanced cancers (NCT02516813) |
| CC-115 | Celgene | DNA-PK inhibitor | *Phase 1* <br> In combination with enzalutamide in mCRPC (NCT02833883) |
| AZD0156 | AstraZeneca | ATM inhibitor | *Phase 1* <br> In advanced cancer (AToM; NCT02588105) |
| VX-970 | Vertex | ATR inhibitor | *Phase 2* <br> Urothelial cancer (NCT02567409) <br> Ovarian cancer (NCT02627443) |
| AZD6738 | AstraZeneca | ATR inhibitor | *Phase 2* <br> In combination with olaparib in SCLC (SUKSES-N2; NCT03428607) <br> In combination with acalabrutinib in CLL (NCT03328273) |
| Prexasertib (LY2606368) | Eli Lilly | CHK1/2 inhibitor | *Phase 2* <br> SCLC (NCT02735980) <br> *BRCA*-mutated breast or ovarian cancer or CRPC (NCT02203513) <br> Solid tumors with replicative stress or HRD (NCT02873975) <br> Ovarian cancer (NCT03414047) |
| AZD1775 | AstraZeneca | Wee1 kinase inhibitor | *Phase 2* <br> SCLC (NCT02688907) <br> In combination with cisplatin in breast cancer (NCT03012477) <br> +/- cytarabine in AML or MDS (NCT02666950) |
| Nivolumab (Opdivo) | Bristol-Myers Squibb | Immune checkpoint inhibitor | *FDA approved* <br> MSI-H or dMMR CRC (2017) <br> *Phase 2* <br> Prostate cancer with DNA repair defects (ImmunoProst; NCT03040791) <br> Uterine cancer with dMMR/MSI-H (NCT03241745) |
| Pembrolizumab (Keytruda) | Merck | Immune checkpoint inhibitor | *FDA approved* <br> MSI-H or dMMR cancers (2017) <br> *Phase 2* <br> mCRPC with DNA damage repair defects (NCT03248570) |

*Table 2 continued from previous page*

| Drug | Manufacturer | Mechanism of action | Most advanced clinical setting (clinicaltrials.gov identifier) |
|---|---|---|---|
| Atezolizumab (Tecentriq) | Genentech | Immune checkpoint inhibitor | *Phase 3* dMMR CRC in combination with bevacizumab and chemotherapy (NCT02997228) |
| Durvalumab (Imfinzi) | AstraZeneca | Immune checkpoint inhibitor | *Phase 2* MSI-H or POLE-mutated mCRC (NCT03435107) |

AML, acute myeloid leukemia; ATM, ataxia telangiectasia mutated protein; ATR, ataxia telangiectasia and rad3 related protein; BRCA, breast cancer susceptibility gene; CHK1/2, checkpoint kinase 1/2; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; dMMR, defective mismatch repair; GBM, glioblastoma; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; MSI-H, microsatellite instability-high; PARP, poly(ADP)ribose polymerase; POLE, DNA polymerase epsilon; PTEN, phosphatase and tensin homolog; RT, radiation therapy; SCLC, small cell lung cancer

novel classes of chromosomal rearrangements described in other genome sequencing studies (eg, chromothripsis and chromoplexy).[9]

## Fueling resistance

Arguably, heterogeneity presents one of the most significant barriers to effective cancer therapy, and this has become increasingly true in the era of personalized medicine in which targeted therapies take aim at specific molecular abnormalities.

It is vital that drugs target the truncal alterations that are present in all cancer cells to ensure that the entire cancer is eradicated. However, it is not always possible to target these alterations, for example, at the present time tumor suppressor proteins like p53 are not druggable.

Even when truncal alterations have been targeted successfully, such as epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) chromosomal rearrangements in non–small-cell lung cancer (NSCLC) and *BRAF* mutations in melanoma, the long-term efficacy of these drugs is almost invariably limited by the development of resistance.

Tumor heterogeneity and the clonal evolution it fuels are central drivers of resistance. Because tumors are dynamic and continue to evolve, anticancer treatments can act as a strong selective pressure and drive the emergence of drug-resistant subclones that allow the tumor to persist. In fact, study findings have revealed that small populations of resistant cells may be present before treatment. Thus, resistance may also occur as a result of the outgrowth of preexisting treatment-resistant cells that suddenly find that they acquire a survival advantage in the presence of a drug.[1,6]

## Tackling heterogeneity

Despite extensive clinical documentation of the existence of heterogeneity and its underlying mechanisms across a range of tumor types, the development of novel clinical trial designs and therapeutic strategies that account for its effects have only recently begun to be explored.

For the most part, this was because of a lack of effective methods for evaluating intratumor heterogeneity. Multiregion biopsies, in which tissue derived from multiple different regions of a single tumor mass or from distinct cancerous lesions within the same patient, give a snapshot of tumor heterogeneity at a single point in time. The repeated longitudinal sampling required to gain a deeper appreciation of tumor heterogeneity over the course of tumor evolution is often not possible because of the morbidity associated with repeated surgical procedures.

Liquid biopsies, in which DNA sequencing can be performed on tumor components that are found circulating in the blood of cancer patients (including circulating tumor cells and cell-free circulating tumor DNA) have rapidly gained traction in the past several decades and offer an unprecedented opportunity for real-time assessment of evolving tumor heterogeneity.

They have proved to be highly sensitive and specific, with a high degree of concordance with tissue biopsy, they can identify both clonal and subclonal mutations, and they can detect resistance substantially earlier than radiographic imaging, which could permit earlier intervention.[10,11] The first liquid biopsy-based companion diagnostic test was approved by the US Food and Drug Administration in 2016, for the detection of *EGFR* mutations associated with NSCLC.

Yet, even liquid biopsy alone is not able to fully dissect the extent of tumor heterogeneity, especially because it is limited in its ability to assess spatial heterogeneity. Truly effective assessment of tumor heterogeneity is likely to require a combination of liquid biopsy, carefully selected tumor tissue biopsies, imaging diagnostics, and biomarkers.

The ongoing TRACERx (Tracking cancer evolution through therapy [Rx]) trials are evaluating a combination of approaches to follow tumor evolution across the course of treatment. The study in NSCLC began in 2014 with a target enrollment of 842 patients and will follow patients over 6 years. Preliminary data from the first 100 patients were recently published and demonstrated that increased intratumor heterogeneity correlated with increased risk of recurrence or death.[12]

If patients consent, the TRACERx trials also feed into the PEACE (Posthumous evaluation of advanced cancer

environment) trials, which are collecting postmortem biopsies to further evaluate tumor heterogeneity and evolution. TRACERx trials in several other cancer types are now also underway.

## Cutting off the source

The main therapeutic strategies for overcoming tumor heterogeneity are focused on the mechanisms of resistance that it drives. It is becoming increasingly apparent that rationally designed combinations of drugs are likely to be required and might need to be administered early in the course of disease to prevent resistance.

However, according to mathematical modeling studies, combinations of at least 3 drugs may be necessary.[13] In many cases, this is unlikely to be feasible owing to the unavailability of drugs for certain targets and issues of toxicity, as well as the high cost.

An alternative strategy is to use immunotherapy, because a single treatment can target multiple neoantigens simultaneously. Although immunotherapy has proved to be a highly effective treatment paradigm in multiple tumor types, resistance still arises through varied mechanisms with tumor heterogeneity at their core.[14,15]

A promising avenue for drug development is to cut off the source of tumor heterogeneity – genomic instability and the mutagenic processes that foster it (Table 2). This is exemplified by the success of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with breast cancer susceptibility (*BRCA1/2*) gene mutations.
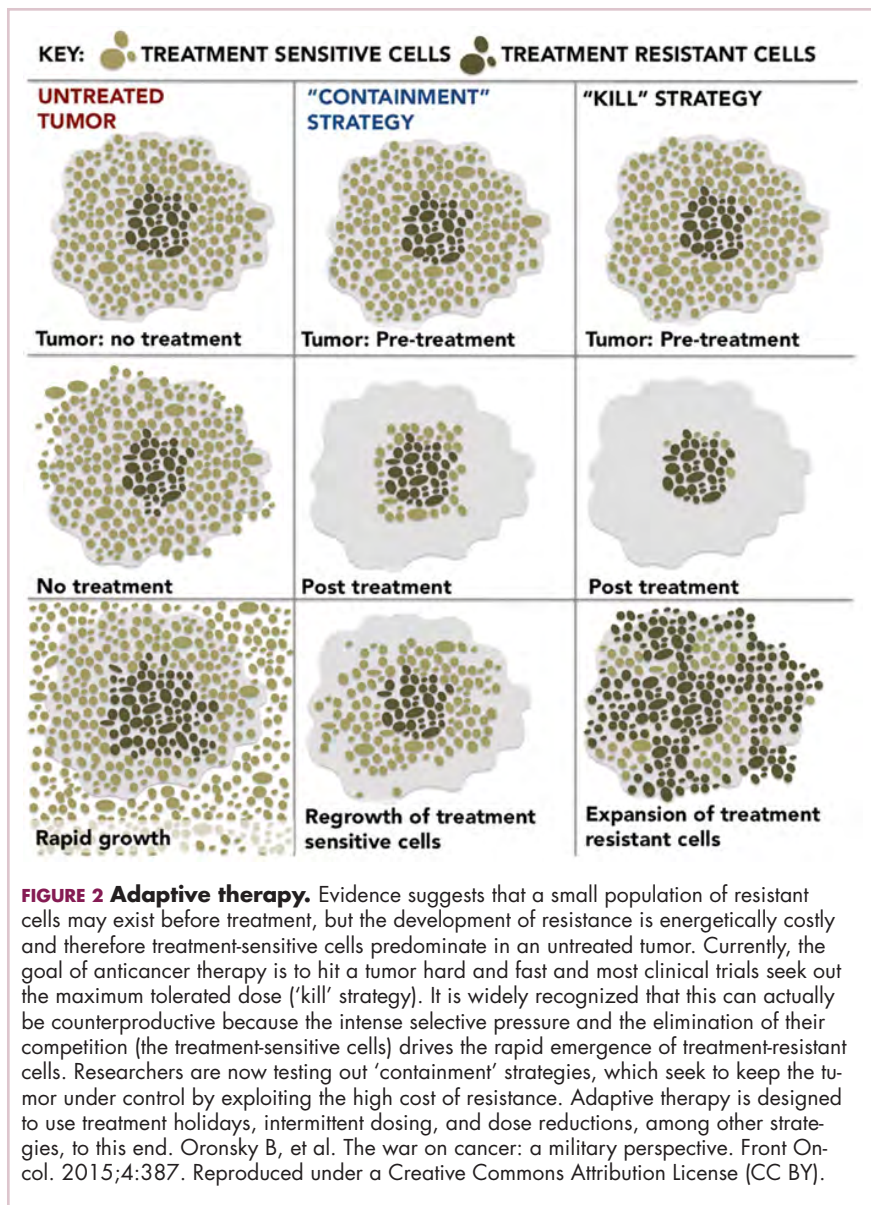
Both germline and somatic mutations in the *BRCA1/2* genes are observed in 10% to 15% of patients with ovarian cancer and a substantial number of patients with other types of cancer, including breast, pancreatic, and prostate cancers.[16,17]

These genes play a central role in the homologous recombination (HR) pathway of DNA repair, which repairs double-strand breaks in DNA. PARP inhibitors target a different DNA repair pathway, base excision repair, which repairs single-strand breaks. The use of PARP inhibitors in patients with *BRCA1/2* mutations is designed to create irreparable damage to the DNA repair processes and drive an unsustainable level of genome instability that leads to cell death, whereas normal cells without HR deficiency can survive.[18]

A growing number of PARP inhibitors are now approved for use in the United States for the treatment of ovarian cancer. In January, olaparib became the first PARP inhibitor approved for patients with *BRCA1/2*-mutant breast cancer, based on data from the OlympiAD trial in which 302 patients were randomized to receive olaparib 300 mg twice daily or physician's choice of chemotherapy. Olaparib improved progression-free survival from 4.2 months to 7.0 months (hazard ratio, 0.58; *P* = .0009), and the most common adverse events included anemia, nausea, fatigue, and vomiting.[19]

Tumors with other defects in HR have also shown susceptibility to PARP inhibition, shifting interest toward identifying and treating these tumors as a group, independent of histology – about a quarter of all tumors display HR deficiency.[20] This novel strategy of targeting mutational processes across a range of tumor types has also been exploited in the development of immunotherapies.



**FIGURE 2 Adaptive therapy.** Evidence suggests that a small population of resistant cells may exist before treatment, but the development of resistance is energetically costly and therefore treatment-sensitive cells predominate in an untreated tumor. Currently, the goal of anticancer therapy is to hit a tumor hard and fast and most clinical trials seek out the maximum tolerated dose ('kill' strategy). It is widely recognized that this can actually be counterproductive because the intense selective pressure and the elimination of their competition (the treatment-sensitive cells) drives the rapid emergence of treatment-resistant cells. Researchers are now testing out 'containment' strategies, which seek to keep the tumor under control by exploiting the high cost of resistance. Adaptive therapy is designed to use treatment holidays, intermittent dosing, and dose reductions, among other strategies, to this end. Oronsky B, et al. The war on cancer: a military perspective. Front Oncol. 2015;4:387. Reproduced under a Creative Commons Attribution License (CC BY).

Patients with defects in the mismatch repair (MMR) pathway and microsatellite instability (MSI) – multiple alterations in the length of microsatellite markers within the DNA – are more sensitive to immunotherapy, likely because they are predisposed to a high level of somatic mutations that can serve as neoantigens to provoke a strong anti-tumor immune response.

In 2017, 2 immune checkpoint inhibitors were approved for use in patients with MSI-high or defective MMR (dMMR) cancers. The indication for pembrolizumab (Keytruda) was independent of tumor histology, the first approval of its kind. It was based on the results of 5 clinical trials in which 149 patients with MSI-H or dMMR cancers were given pembrolizumab 200 mg every 3 weeks or 10 mg/kg every 2 weeks for a maximum of 24 months. The overall response rate was 39.6%, including 11 complete responses and 48 partial responses.[21]

## A new paradigm

Treatment of a tumor is one of the major selective pressures

**TABLE 3** Select ongoing clinical trials incorporating intratumor heterogeneity

| Trial name/ identifier | Phase | Sponsor | Description |
|---|---|---|---|
| NCT02415621 | NA | H Lee Moffitt Cancer Center and Research Institute | Adaptive (on and off scheduling) abiraterone therapy for metastatic CRPC; patients will be enrolled who achieve ≥50% decline in their PSA levels while on abiraterone and treatment will not be reinitiated until there is a ≥50% increase in PSA |
| NCT03511196 | 1 | H Lee Moffitt Cancer Center and Research Institute | Intermittent ADT for stage IV castration-sensitive prostate cancer; PSA and testosterone level will be used to guide treatment |
| NCT03416153 | 2 | University of Michigan Cancer Center | Individualized adaptive de-escalated radiotherapy for HPV-related oropharyngeal cancer; uses pre- and midtreatment imaging to guide de-escalation |
| NCT03122522 | 2 | Memorial Sloan Kettering Cancer Center | Adaptive dosing of ipilimumab and nivolumab combination immunotherapy |
| NCT02771314 | 2 | Hellenic Oncology Research Group | Liquid biopsy used as a tool to evaluate resistance to first and third generation EGFR TKIs in *EGFR*-mutant NSCLC; genetic evolution and biological characteristics of CTCs will be monitored over time after treatment |
| TRACERx NCT01888601 | NA | University College London | Tracking non–small-cell cancer evolution through therapy; after tumors from diagnosis to relapse and tracking genetic evolution |
| TRACERx-TNBC NCT03077776 | NA | UNICANCER | Tracking triple-negative breast cancer evolution through therapy; examining the relationship between intratumor heterogeneity and response to neoadjuvant chemotherapy |
| TRACERx-Renal NCT03226886 | NA | Royal Marsden NHS Foundation Trust | Tracking renal cell carcinoma evolution through therapy |
| NCT02993536 | NA | Abramson Cancer Center of the University of Pennsylvania | After the clonal evolution of B cells in high-risk CLL after idelalisib-rituximab treatment |
| NCT03059641 | NA | GenePlus-Beijing Co Ltd | Therapeutic resistance and clonal evolution assessed with liquid biopsy of NSCLC patients in China |
| CHRONOS NCT03227926 | 2 | Fondazione del Piemonte per l'Oncologia | Evaluating the safety and efficacy of rechallenge with panitumumab driven by Ras resistance dynamics in patients with metastatic CRC; using liquid biopsy to determine extended-Ras alterations |
| NCT0342529 | 1 | John Wayne Cancer Institute | A longitudinal assessment of tumor evolution in patients with brain cancer following treatment with temozolomide + RT, ipilimumab monotherapy or ipilimumab + nivolumab combination therapy |
| DARWIN I NCT02183883 | | | Deciphering afatinib response and resistance with intratumor heterogeneity; patients registered in the TRACERx study will receive afatinib |
| DARWIN II NCT02314481 | 2 | University College London | Deciphering antitumor response and resistance with intratumor heterogeneity; evaluating the impact of intratumor heterogeneity on anti-PD-L1 therapy |

ADT, androgen deprivation therapy; CLL, chronic lymphocytic leukemia; CTC, circulating tumor cells; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; RT, radiation therapy; PD-L1, programmed cell death ligand 1; PSA, prostate specific antigen.

that shapes its evolution and recent evidence has emerged that these selective pressures can be highly dynamic. Study findings have shown that there is a cost associated with evolution of resistant subclones and, if the selective pressure of therapy is removed, that cost may become too high, such that resistant subclones are then outcompeted by drug-sensitive ones. There have been reports of reversal of drug resistance when drug treatment is interrupted.

The current treatment paradigm is to try to eliminate tumors by hitting them hard and fast with the maximum tolerated dose (MTD) of a drug. However, there is increasing appreciation that this may be inadvertently fostering more rapid disease progression because it selects for the emergence of resistant cells and eliminates all their competitors (Figure 2).

This is driving a potential paradigm shift, in which researchers are applying concepts from evolutionary biology and the control of invasive species to the treatment of cancer. Instead of completely eliminating a cancer, a strategy of adaptive therapy could be used to set up competition between different subclones and keep tumor growth in check by exploiting the high cost of resistance.[22]

Adaptive therapy involves the use of treatment holidays, intermittent dosing schedules or reduced drug doses, rather than using the MTD. Adaptive therapy was tested recently in mice with triple-negative and estrogen receptor-positive breast cancer. The standard maximum dose of chemotherapy was compared with adaptive therapy with either reduced doses or skipped doses as the tumor responded. Tumor growth initially decreased with all 3 treatment scenarios, but then regrew when chemotherapy was stopped or doses were skipped. However, adaptive therapy with lower doses resulted in long-term stabilization of the tumor where treatment was eventually able to be withdrawn.[23] Clinical trials of several different types of adaptive therapy strategies are ongoing (Table 3).

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# CAR T-cell approvals: multiple myeloma likely next up

Sharon Worcester

The next major approval in the chimeric antigen receptor (CAR) T-cell therapy arena will target multiple myeloma, according to Carl June, MD, the Richard W Vague Professor in Immunotherapy and a pioneer in CAR T-cell research at the University of Pennsylvania, Philadelphia. That approval is anticipated sometime in 2019, and will "completely transform oncology," Dr June said in a recent interview.

"Myeloma is the most common blood cancer in adults, and there's never been a curative therapy, but now there is a subset of patients who look like they're cured with CAR T cells."

### Researcher-turned-patient

The first treated patient in a trial of a novel anti–B-cell maturation antigen (BCMA)–specific CAR T-cell therapy (CART-BCMA)[1] developed by University of Pennsylvania researchers in collaboration with Novartis is part of that subset. Earlier this year, Woodring Wright, MD, a professor of cell biology and medicine at the University of Texas (UT) Southwestern Medical Center in Dallas, outed himself as that first patient when he announced that CART-BCMA saved his life.[2]

Dr Wright had been diagnosed with multiple myeloma about 12 years ago and had failed 11 previous chemotherapies before he was enrolled in the CART-BCMA trial. He remains cancer free more than 2 years after receiving CART-BCMA and he's now conducting CAR T-cell–related research in his UT Southwestern laboratory to broaden the effectiveness of current CAR T-cell therapies. In particular, he is looking at whether the small percentage of patients in whom CAR T-cell therapy does not work might benefit from telomerase to lengthen telomeres, because most patients who fail CAR T-cell therapy are elderly and might have terminally short telomeres. [2]

Dr Carl June

### Pharma lines up the trials

An ongoing University of Pennsylvania trial led by Adam D Cohen, MD, director of myeloma immunotherapy at the Abramson Cancer Center, has an overall response rate of 64%; initial phase 1 efficacy and safety results were reported at the 2016 annual meeting of the American Society of Hematology (ASH).[3] In addition, multiple companies are pursuing registration trials for CAR T-cell therapies in myeloma, Dr June said.

Among those companies are bluebird bio and Celgene, which together are developing an anti-BCMA CAR T-cell therapy known as bb2121. The product was granted breakthrough therapy designation by the US Food and Drug Administration in November 2017 and will thus receive expedited review by the agency. It has also been fast-tracked in Europe.

The decision to fast-track bb2121 in the United States was based on preliminary results from the CRB-410 trial.[4] Updated findings from that trial were presented at the 2017 ASH annual meeting and showed an overall response rate of 94% in 21 patients, with 17 of 18 patients who received doses above $50 \times 10^6$ CAR+ T cells having an overall response, and 10 of the 18 achieving complete remission. The progression-free survival rates were 81% at 6 months, and 71% at 9 months, with responses deepening over time. The complete response rates were 27% and 56% in May and October of 2017, respectively.

Responses were durable, lasting more than 1 year in several patients, the investigators reported. Phase 2 of the trial – the global pivotal KarMMa trial – is currently enrolling and will dose patients at between 150 and $350 \times 10^6$ CAR+ T cells.[5]

Janssen Biotech Inc and Legend Biotech USA Inc/ Legend Biotech Ireland Ltd have also joined forces to develop an anti-BCMA CAR T-cell

product for multiple myeloma, Dr June said. The companies announced in late 2017 that they had entered into "a worldwide collaboration and license agreement" to develop the CAR T-cell drug candidate, LCAR-B38M.[6] It has been accepted for review by the China Food and Drug Administration and is in the planning phase of clinical studies in the United States for multiple myeloma, according to that announcement.

**Cost, financial toxicity, and a new therapeutic landscape**
The rush for the approval of a CAR T-cell therapy for myeloma will lead to a welcome addition to the treatment armamentarium not just because of the clinical benefits, but because of the possibility of reducing disease-related costs (p. e177). Although myeloma represents only about 2% of all cancers, it is responsible for 7% of cancer costs, Dr June noted, and since many patients live with their disease for a long time, that can mean substantial "financial toxicity" being associated with treatment for the disease. "So CAR T-cell therapy for myeloma will bring a huge change to the practice of oncology," he added.

Dr June explained that tisagenlecleucel, the first CAR T-cell therapy to be approved (in August 2017; p. e126), was for pediatric acute lymphoblastic leukemia that had relapsed at least twice.[7] "That's only about 600 kids a year in the United States, so it's an ultra-orphan market," he said. However, with the subsequent October 2017 approval of axicabtagene ciloleucel for certain cases of large B-cell lymphoma[8] and the anticipated myeloma approval, CAR T-cell therapy will move away from that orphan status.

"There are a lot of difficulties whenever you change to something new," he said, comparing the CAR T-cell therapy evolution to that of bone marrow transplantation in the 1980s, when many voiced concern about the new therapy because it was available at only 2 centers in the United states and required a high level of specialized skill. "But over the years, millions of transplants have been done [and] they're done at many community centers. And it's the same thing with CARs." There are now 30 centers offering CAR T-cell therapy and people have to be trained. "It's a new skill set, and it will take time," he said.

**Access to trials: balancing demand and availability**
That delay can be particularly frustrating because there are many patients who might benefit "in a major way" from CAR T-cell therapy, but who can't get on a clinical trial, Dr June noted.

"There's more demand than availability, and it's going to take a while" for that to change, he said. The solution most likely will involve the complementary use of off-the-shelf CAR T cells in some patients to induce remission and perhaps provide a bridge to another definitive therapy, and ultrapersonalized CAR T-cell therapy in others, as well as combinations that include CAR T cells and targeted agents or checkpoint inhibitors.

CRISPR-Cas9 gene editing is also being considered as a tool for engineering multiple myeloma cellular immunotherapy (and other cancer treatments), as in the Parker Institute-funded NYCE study,[9] Dr June said. "We're actually removing the [programmed death-1] gene and the T-cell receptors ... it shows enormous potential for gene editing. CRISPR is going to be used for a lot of things, but the first use is with T-cell therapies, so we're really excited about that trial."

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# Unravelling the CAR T-cell therapy reimbursement riddle

Alicia Gallegos

Physicians may finally have some clarity on payment for inpatient administration of 2 chimeric antigen receptor (CAR) T-cell therapies if a proposed rule from the Centers of Medicare & Medicaid Services becomes final.

The agency is seeking to assign ICD-10-PCS codes XW033C3 and XW043C3 to the use of axicabtagene ciloleucel (Yescarta; Kite Pharma, acquired by Gilead in October 2017) and tisagenlecleucel (Kymriah; Novartis) in the inpatient setting for fiscal year 2019. It is also considering the creation of a new Medicare Severity-Diagnosis Related Group (MS-DRG) code for procedures involving the use of CAR T-cell therapy drugs.

Stephanie Farnia, director of health policy and strategic relations for the American Society for Blood and Marrow Transplantation, said the proposal demonstrates that CMS is listening to physicians' concerns about CAR T payments and working to provide a more reasonable framework. "The primary point of significance is that CAR-T care episodes should be assigned to a specific MS-DRG in FY2019, which will give physicians a clearer sense of inpatient reimbursement in advance," she said in an interview.

Uncertainty about inpatient payment for administration of the 2 approved CAR T therapies (see p. e126) have been a lingering concern of specialists who use, or are interested in using, the therapies. In April 2018, CMS announced payment rates for outpatient administration of the 2 drugs, settling on $395,380 for axicabtagene ciloleucel and $500,839 for tisagenlecleucel. The two medications have list prices of $373,000 and $475,000, respectively.

However, physicians noted at the time that even if the drugs were first administered in the outpatient setting, inpatient care is likely to occur with CAR T-cell therapies because some patients will need to

Dr Helen Heslop

be admitted for monitoring for serious side effects. In such cases, all payments would then become part of the inpatient stay as per CMS's 3-day payment window rule.

In the most recent payment proposal, CMS stated that its clinical advisers believe that patients receiving treatment with CAR T-cell therapy would have similar clinical characteristics and comorbidities as patients treated with autologous bone marrow transplant therapy, who are currently assigned to MS-DRG 016 *Autologous Bone Marrow Transplant with CC/MCC.* Therefore, CMS officials said they would suggest ICD-10-PCS procedure codes XW033C3 and XW043C3 to pre-MDC MS-DRG 016. In addition, the agency is proposing to revise the title of MS-DRG 016 to *Autologous Bone Marrow Transplant with CC/MCC or T-cell Immunotherapy.*

The agency emphasized that it invites public comment on alternative payment approaches for CAR T-cell therapies in the context of the pending, new technology add-on payment applications by the CAR-T drugmakers Novartis and Kite Pharma/Gilead. If approved, the technology add-on payments would provide an additional and separate payment equivalent to up to 50% of the product cost plus the MS-DRG payment received for the episode of care.

## Shifts and realignments in the face of new developments

The CMS announcement is the latest development in the rapidly growing landscape of CAR T-cell therapies. In 2017, the Food and Drug Administration approved tisagenlecleucel for pediatric acute lymphoblastic leukemia and axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma in adults, and in May 2018, the agency expanded the indication for tisagenlecleucel to include adults with

relapsed/refractory large B-cell lymphoma.

Further advancements are expected for CAR T-cell therapies in 2018, said Cai Xuan, PhD, senior analyst in oncology and hematology for GlobalData, a data analytics and commercial intelligence firm.

For starters, pharmaceutical companies are now working toward next-generation CAR T-cell therapies that can be mass produced, Dr Xuan noted. At a recent American Association for Cancer Research meeting, for example, the biopharmaceutical company Cellectis presented early clinical data in pediatric B-cell acute lymphoblastic leukemia for its off-the-shelf CAR T-cell candidate UCART19. In addition, CRISPR Therapeutics presented preclinical data for one of its off-the-shelf CAR T-cell candidates for multiple myeloma, and the company announced it would apply for approval to start human trials by the end of 2018.

"The trend for 2018 is focused on how to eliminate some of the profitability issues with first-generation CAR Ts because companies realize that manufacturing individualized treatments for each patient is not an ideal business model," Dr Xuan said in an interview.

More market competition is also in the forecast, particularly from smaller companies, Dr Xuan said. "We are likely to see larger companies acquiring smaller ones once their CAR T technology has matured to a certain point. We have seen it with the Gilead-Kite acquisition and Celgene's acquisition of Juno Therapeutics. This trend will continue as long as smaller companies are able to develop proprietary next-generation CAR T technologies."

### Cost, accessibility, and real-world side effects

The key concerns about the therapies are cost and accessibility, especially for the Medicare population. Cost estimates have put the cost of CAR T-cell therapies as high as $1.5 million per patient and that could make them inaccessible for many.

"There remain unanswered questions about value and cost in older adults," said Walid F Gellad, MD, codirector for the Center for Pharmaceutical Policy and Prescribing at the University of Pittsburgh. "There are many life-saving treatments in the medical system that cost much less than this therapy. Presumably, its cost will go down as the indications expand and the experience with creating the CAR T cells improves. At least, one would hope."

The creation of off-the-shelf, third-party products would help improve accessibility for CAR T-cell therapies and lower cost, said Helen Heslop, MD, director of the Center for Cell and Gene Therapy at Baylor College of Medicine, Houston. "In the longer term, there's obviously a lot of people looking at how [the treatments] can be made more accessible. These are the first-generation CAR T [products], and I think there'll be lots of refinements both to make them more effective and safer and also to use a third-party product to bring the cost of goods down."

Other lingering unknowns about CAR T-cell therapies include how many patients in real-world clinical practice will have serious side effects, compared with those in trials, and the long-term recurrence rates after therapy use, Dr Gellad noted. He recently proposed in an article that government payers reimburse only the cost of manufacturing and some predetermined mark-up for such therapies until confirmatory trials demonstrate clinical benefit (N Engl J Med. 2017;376[21]:2001-4).

The current CAR T-cell therapies are only the beginning, said Dr Richard T Maziarz, MD, a bone marrow transplantation and blood cancer specialist at the Oregon Health and Science University Knight Cancer Institute in Portland. "Genetically engineered cell products are going to explode over the course of the next decade. 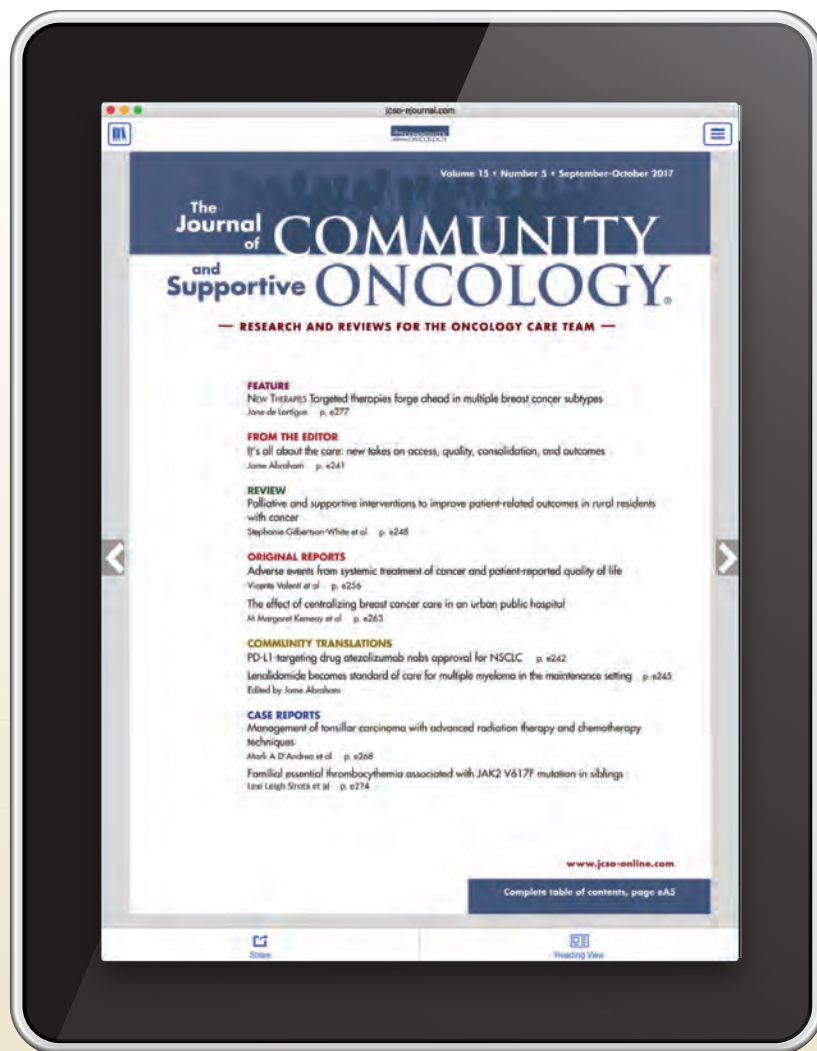This is not the end of the line, this is the starting point."