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KIMBERLY JOHUNG ON
SBRT in RCC
When Surgery Is Not an Option
‘Excellent control, minimal toxicity’
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William C. Wood, MD
Continued Professional Engagement and Personal Fulfillment for Clinicians After Full-Time Practice, Saturday, June 1, 8:30 AM to 8:45 AM, Room E350; Co-author, Impact of Clinical Risk Category on Prognosis and Prediction of Chemotherapy Benefit in Early Breast Cancer by Age and the 21-Gene Recurrence Score in TAILORx (abstract e23159)

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Daniel C. McFarland, DO
Building Programs to Prevent Burnout and Suicide in Oncology Providers, Monday, June 3, 1:55 PM to 2:15 PM, Room S504; Tumor Mutation Burden and Depression in Lung Cancer: Association With Inflammation (abstract e23159)

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Joseph Miccio, MD, and Kimberly Johung, MD, PhD
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• ASCO 2019 Meet and Greet
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When Surgery Is Not an Option in Renal Cell Carcinoma: The Evolving Role of Stereotactic Body Radiation Therapy

Joseph Miccio, MD, and Kimberly Johung, MD, PhD

ABSTRACT: Historically, radiation therapy has played a limited role in the management of renal cell carcinoma because early studies showed that it had no benefit in the neoadjuvant or adjuvant settings. Thus, radiation has typically been employed for only palliation of metastatic sites. As the ability to deliver conformal high-dose-per-fraction radiation became available, studies began to show excellent local control when treating oligometastatic sites of renal cell carcinoma with stereotactic body radiation therapy (SBRT). Recently, SBRT has been studied in the management of the primary tumor in nonsurgical patients with localized renal cell carcinoma. Excellent local control rates and low rates of treatment-related toxicity were reported with single-fraction (26 Gy) and multi-fraction (36 to 45 Gy in 3 fractions or 40 to 50 Gy in 5 fractions) regimens. While the evidence to date is limited by small cohort sizes and variability in treatment approaches, the reported outcomes are promising. Ongoing studies will continue to define how renal SBRT fits into the management of patients who are not eligible for surgery.

Introduction
Curative-intent treatment of localized renal cell carcinoma entails surgical resection with a radical or partial nephrectomy. Early randomized studies failed to show a survival benefit with the addition of neoadjuvant[1,2] or adjuvant[3,4] radiotherapy. Moreover, renal cell carcinoma is considered a radioresistant histology based on in vitro studies.[5] Thus, radiation therapy has historically been limited to the palliative setting for patients with renal cell carcinoma. Stereotactic radiosurgery (SRS) has long been used for effective local control of intracranial metastases from renal cell carcinoma, most often with a single fraction of high-dose radiation therapy.[6-9] With the advent of technology allowing for safe delivery of highly conformal high-dose-per-fraction radiation therapy to extracranial sites, stereotactic body radiation therapy (SBRT) is now widely used to treat oligometastatic disease. Excellent local control rates of higher than 90% at 1 year have been demonstrated for metastatic renal cell carcinoma lesions in the spine[8,10-12] and visceral sites.[9,13-15] The findings of these clinical studies coincided with another study demonstrating the efficacy of ablative high-dose-per-fraction radiation therapy in treating renal cell carcinoma in a mouse model.[16] These results suggest

Perspective
Viraj Master, MD, PhD, FACS, comments on local control in RCC on page 172.
## Published Prospective Studies of SBRT in the Treatment of Localized RCC

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Patients (N)</th>
<th>Inclusion Criteria</th>
<th>Median Follow-Up</th>
<th>Dose/Fractionation</th>
<th>Outcome</th>
<th>Toxicity</th>
</tr>
</thead>
</table>
| Siva 2017[28]   | 33           | • ECOG 0–2  
• Single lesion  
• Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery | 24 months | • 26 Gy in 1 fraction for tumors ≤ 5 cm  
• 42 Gy in 3 fractions for tumors > 5 cm | • 100% 2-year local control  
• 90% freedom from distant progression | • 58% grade 1 (mostly chest wall pain and fatigue)  
• 21% grade 2 (mostly fatigue and nausea)  
• 3% grade 3 (fatigue) |
| Siva 2016[27]   | 21           | • ECOG 0–2  
• Single lesion  
• Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery | 13 months | • 26 Gy in 1 fraction for tumors ≤ 5 cm  
• 42 Gy in 3 fractions for tumors > 5 cm | • NR | • Average GFR decrease of 8.7 mL/min at 1 year after treatment |
| Staehler 2015[21] | 40 (RCC, 75%) | • Unable to spare kidney during surgery  
• Tumors < 4 cm | 28 months | • 25 Gy in 1 fraction | • 98% local control at 9 months | • 3% grade 1 erythroderma  
• 8% grade 1 fatigue  
• 5% grade 1 nausea |
| Ponsky 2015[24] | 19           | • Poor surgical candidates  
• KPS ≥ 60 | 14 months | • 24–48 Gy in 4 fractions  
• 2 Gy per fraction dose escalation | • NR | • 5% grade 2 fatigue  
• 5% grade 4 duodenal ulcers  
• 5% grade 2 urinary incontinence  
• 11% grade 3 renal toxicity |
| Pham 2014[26]   | 20           | • ECOG 0–2  
• Single lesion  
• Medically inoperable/high risk for surgery due to likelihood of dialysis or refused surgery | NR | • 26 Gy in 1 fraction for tumors ≤ 5 cm  
• 42 Gy in 3 fractions for tumors > 5 cm | • NR | • 60% grade 1–2 side effects  
• Fatigue most common, followed by dermatitis, chest wall pain, and nausea |
| McBride 2013[23] | 15           | • Medically inoperable  
• Tumors ≤ 5 cm  
• KPS ≥ 70 | 37 months | • 21–48 Gy in 3 fractions  
• 2 Gy per fraction dose escalation | • 87% local control  
• 1 failure occurred in 21-Gy and 27-Gy arms | • 13% grade 1 nausea  
• 33% grade 1 fatigue  
• 13% late grade 3 renal dysfunction  
• Mean GFR decrease, 18 mg/dL |
| Kaplan 2010[25] | 12           | • Medically inoperable  
• Tumors ≤ 5 cm  
• KPS ≥ 70 | 14 months | • 21–39 Gy in 3 fractions  
• 2 Gy per fraction dose escalation | • 92% local control  
• 1 failure in 21-Gy arm | • Two patients with chronic renal failure had worsening of renal function |
| Svedman 2006[13] | 4 with localized disease; 26 with metastatic disease; 10 received SBRT to the kidney | • Locally recurrent or inoperable RCC 
• Life expectancy > 3 months | 52 months for living patients  
22 months for deceased patients | • 5–15 Gy in 2–5 fractions | • 98% local control | • 57% grade 1–2 cough, fatigue, skin rash, and/or local pain |

ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; KPS = Karnofsky performance status; NR = not reported; RCC = renal cell carcinoma; SBRT = stereotactic body radiation therapy.
that ablative doses of radiation therapy delivered with stereotactic techniques have the potential to impact outcomes in renal cell carcinoma, whereas the role of standard fractionated radiation therapy is limited.

In light of the promising outcomes seen with SBRT for metastatic sites of renal cell carcinoma, renal SBRT is increasingly being evaluated for treatment of the primary tumor in nonsurgical candidates. There are several retrospective[17-20] and prospective[13,21-28] studies evaluating the role of SBRT in the treatment of non-metastatic renal cell carcinoma, which have demonstrated excellent local control rates with minimal toxicity, and additional studies are ongoing. This review summarizes the current evidence supporting the use of SBRT as treatment for inoperable renal cell carcinoma, with a focus on prospective studies. We will provide recommendations for patient selection and review the technical aspects of treatment, as well as the expected toxicities.

### Review of the Evidence for SBRT in Localized Renal Cell Carcinoma

#### Prospective studies

Although only a limited number of prospective studies evaluating SBRT in localized renal cell carcinoma have been published, the results are encouraging (Table 1). Interpretation of these studies is limited by the small number of patients treated, lack of long-term follow-up, and the varying dose fractionation schemes. The trials evaluated cohorts of 10 to 40 medically inoperable patients treated with doses of 25 to 26 Gy in 1 fraction, 24 to 48 Gy in 4 fractions, or 21 to 48 Gy in 3 fractions. With an average follow-up of 13 to 52 months, local control rates ranged from 87% to 100%. In the most recently published prospective series, 33 patients with renal cell carcinoma received SBRT to the primary tumor (26 Gy in 1 fraction or 42 Gy in 3 fractions for larger tumors), and the 2-year local control rate was 100%.[28] A larger study published in 2015 included 40 patients who received 25 Gy in a single fraction to primary renal

## Table 2 Published Retrospective Studies of SBRT in the Treatment of Localized RCC

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Patients (N)</th>
<th>Inclusion Criteria</th>
<th>Dose/Fractionation</th>
<th>Local Control</th>
<th>Toxicity</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaidar 2017[18]</td>
<td>6</td>
<td>• Nonsurgical candidates with tumors &gt; 4 cm</td>
<td>• 39 Gy in 3 fractions</td>
<td>• 100%</td>
<td>• 33% grade 1 nausea, 17% grade 2 colitis</td>
<td>• 5–6 mm of target motion in each direction, on average</td>
</tr>
<tr>
<td>Chang 2016[17]</td>
<td>16</td>
<td>• Any primary tumor treated with SBRT (including patients with metastatic disease)</td>
<td>• 30–40 Gy in 5 fractions</td>
<td>• 100%</td>
<td>• 6% grade 2 nausea, 13% grade 4 renal toxicity (2 patients with CKD required dialysis after treatment)</td>
<td>• Mean GFR decrease of 14.4%</td>
</tr>
<tr>
<td>Sun 2016[20]</td>
<td>40 (RCC, 60%)</td>
<td>• Any primary tumor treated with SBRT</td>
<td>• 21–48 Gy in 3 fractions</td>
<td>• 92.7%</td>
<td>• NR</td>
<td>• Reduced tumor size and growth rate, no change in enhancement pattern</td>
</tr>
<tr>
<td>Yamamoto 2016[36]</td>
<td>14</td>
<td>• Tumors ≤ 5 cm, inoperable or patient refused surgery</td>
<td>• 50–70 Gy in 10 fractions</td>
<td>• NR</td>
<td>• No &lt; grade 2 toxicity</td>
<td>• 20–30 Gy in 10 fractions was correlated with renal atrophy assessed on imaging</td>
</tr>
<tr>
<td>Lo 2014[19]</td>
<td>3</td>
<td>• Inoperable patients treated with SBRT for RCC</td>
<td>• 40 Gy in 5 fractions</td>
<td>• 100%</td>
<td>• NR</td>
<td>• No &lt; grade 2 toxicity</td>
</tr>
<tr>
<td>Wang 2014[30]</td>
<td>9</td>
<td>• History of radical nephrectomy for previous RCC, ECOG ≤ 2</td>
<td>• 60–85 Gy in 5–7 fractions with gamma-SBRT</td>
<td>• 64.8%</td>
<td>• 22% grade 1 leukocytopenia, 22% grade 1 colitis, 22% grade 2 colitis</td>
<td>• No grade 2 toxicity</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; NR = not reported; RCC = renal cell carcinoma; SBRT = stereotactic body radiation therapy.
### TABLE 3 Technical Approaches of Published Prospective Studies of SBRT in Patients With RCC

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Treatment System</th>
<th>Immobilization</th>
<th>Respiratory Management</th>
<th>On-Treatment Imaging</th>
<th>Dosage</th>
<th>Target Volumes</th>
<th>Fiducial Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siva 2017[28]</td>
<td>LINAC-based (Varian TrueBeam™ STx or Trilogy™)</td>
<td>Vacuum immobilization (Elekta BodyFIX® dual vacuum device using both thoracic and pelvic setups)</td>
<td>• Pre-, mid-, and post-treatment cone beam CT</td>
<td>• 26 Gy in 1 fraction • 42 Gy in 3 fractions for tumors &gt; 5 cm • 99% of PTV to full prescription dose</td>
<td>ITV created using maximum inspiration, maximum expiration, and MIP datasets</td>
<td>PTV = ITV + 5 mm</td>
<td>No</td>
</tr>
<tr>
<td>Siva 2016[27]</td>
<td>LINAC-based (Varian TrueBeam™ STx or Trilogy™)</td>
<td>Vacuum immobilization (Elekta BodyFIX® dual vacuum device using both thoracic and pelvic setups)</td>
<td>• Pre-, mid-, and post-treatment cone beam CT</td>
<td>• 26 Gy in 1 fraction • 42 Gy in 3 fractions for tumors &gt; 5 cm • 99% of PTV to full prescription dose</td>
<td>ITV created using maximum inspiration, maximum expiration, and MIP datasets</td>
<td>PTV = ITV + 5 mm</td>
<td>No</td>
</tr>
<tr>
<td>Staehler 2015[21]</td>
<td>CyberKnife</td>
<td>NR</td>
<td>Target tracking</td>
<td>NR</td>
<td>• 25 Gy in 1 fraction • Prescribed to the 70% isodose line</td>
<td>NR</td>
<td>Yes—3 gold fiducials</td>
</tr>
<tr>
<td>Ponsky 2015[24]</td>
<td>CyberKnife</td>
<td>• Synchrony vest • Vacuum cushion</td>
<td>• Expiratory phase CT • Expiratory phase MRI</td>
<td>NR</td>
<td>• 24 Gy in 4 fractions • Increased by 2 Gy per fraction</td>
<td>PTV = GTV + 0–3 mm</td>
<td>Yes—3 or more gold fiducials</td>
</tr>
<tr>
<td>Pham 2014[26]</td>
<td>LINAC-based (Varian TrueBeam™ STx or Trilogy™)</td>
<td>Vacuum immobilization (Elekta BodyFIX® dual vacuum device using both thoracic and pelvic setups)</td>
<td>• Pre-, mid-, and post-treatment cone beam CT</td>
<td>• 26 Gy in 1 fraction (42 Gy in 3 fractions for tumors &gt; 5 cm) • 99% of PTV to full prescription dose</td>
<td>ITV created using maximum inspiration, maximum expiration, and MIP datasets</td>
<td>PTV = ITV + 5 mm</td>
<td>No</td>
</tr>
<tr>
<td>McBride 2013[23]</td>
<td>Robotic radiosurgical device</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>• 21–48 Gy in 3 fractions • 2 Gy per fraction dose escalation</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kaplan 2010[25]</td>
<td>CyberKnife</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>• 21–39 Gy in 3 fractions • 2 Gy per fraction dose escalation</td>
<td>PTV = GTV + 3 mm</td>
<td>Yes—gold fiducials</td>
</tr>
<tr>
<td>Svedman 2006[13]</td>
<td>LINAC-based</td>
<td>Stereotactic frame • Vacuum pillow • Abdominal compression</td>
<td>• CT scan with abdominal compression</td>
<td>NR</td>
<td>• 5–15 Gy in 2–5 fractions • 50% higher dose to center of target compared with periphery</td>
<td>PTV = CTV + 5–10 mm (transverse) or 10 mm (CC)</td>
<td>NR</td>
</tr>
</tbody>
</table>

4D = four-dimensional; CC = craniocaudal; CTV = clinical tumor volume; GTV = gross tumor volume; ITV = internal target volume; LINAC = linear accelerator; MIP = maximum intensity projection; NR = not reported; PTV = planning target volume; RCC = renal cell carcinoma; SBRT = stereotactic body radiation therapy.
tumors (75% of which were renal cell carcinoma), and the 9-month local control rate was 98%, though longer follow-up is lacking.[21] While these prospective studies demonstrate promising rates of local control with SBRT, there are no completed randomized phase III trials to date comparing SBRT with other local therapy modalities.

The prospective dose escalation studies evaluated doses ranging from 21 to 48 Gy in 3 fractions,[23,25] and 24 to 48 Gy in 4 fractions.[24] For the 3-fraction studies, local failure only occurred in 1 patient receiving 21 Gy and 1 patient receiving 27 Gy.[23,25] These results suggest that for 3-fraction regimens, a minimum of 11 Gy per fraction should be considered, which is the minimum dose at which no patient in these studies experienced a local failure. This is consistent with the consensus statement from the International Radiation Oncology Consortium for Kidney, which recommends a total dose of 36 to 45 Gy for 3-fraction regimens.[29] For 5-fraction regimens, a total dose of 40 to 50 Gy is recommended. In the 4-fraction dose-escalation study, the local control rate for the 15 patients with evaluable responses was 100%.[24] The study did not report on toxicity levels for individual doses, but overall, no dose-limiting toxicity was reached (defined as any treatment-related ≥ grade 3 gastrointestinal/genitourinary toxicity or any grade 4 toxicity). For treatment in a single fraction, 25 to 26 Gy has been studied,[21,22,26,28] with no significant difference in toxicities or negative impact on local control rates compared with multi-fraction regimens.[24-28]

Thus, multiple fractionation schemes appear to be effective. While studies are lacking to compare these regimens, total dose and fraction size should be influenced by the size of the primary tumor and its proximity to the adjacent normal tissues.

**Retrospective studies**

Retrospective studies of SBRT in place of surgery for renal cell carcinoma also showed excellent local control outcomes, ranging from 64.8% to 100% (*Table 2*). The largest series of 40 patients with renal tumors (60% of which were renal cell carcinoma) reported a 92.7% local control rate with 21 to 48 Gy in 3 fractions, with a median follow-up of approximately 18 months.[20] In the second largest series of 16 patients treated with 30 to 40 Gy in 5 fractions, the local control rate was 100%, with a median follow-up of 19 months.[17] Only one study demonstrated a suboptimal 1-year local control rate, of 64.8%, for patients treated with 60 to 85 Gy in 5 to 7 fractions, but the study population included patients with more advanced disease who had failed in the contralateral kidney after a prior nephrectomy.[30] The efficacy of renal SBRT is further supported by a meta-analysis of both prospective and retrospective studies, which showed an estimated weighted 2-year local control rate of 92.9%.[31]

**Technical considerations**

Delivery of precise, highly conformal ablative doses of radiation to the kidney requires reproducible patient setup and appropriate respiratory motion management. Technical approaches utilized in published studies are varied (*Table 3*). Respiratory motion management is essential to deliver a highly conformal treatment because the mean displacement of the kidneys with respiration is 0.75 cm, with a range of 0.10 to 2.15 cm for the left kidney and 0.11 to 1.92 for the right kidney.[32] Most displacement occurs in the superior-inferior direction. Furthermore, on-treatment imaging is essential given variability in patient setup.[33] With dual-vacuum immobilization (or Vac-Lok™ Cushions with abdominal compression), the average three-dimensional displacement of the target post-treatment was restricted to 1 mm, with a maximal displacement in any direction of ≤ 3 mm. This suggests that, with adequate immobilization, respiratory excursion and interfraction motion is limited, and respiratory gating methods may not be essential.[34]

The most recent prospective series used LINAC-based SBRT without fiducials and a four-dimensional (4D) CT simulation for respiratory motion management.[22,28] Other series utilizing CyberKnife® treatment platforms employed real-time target tracking of implanted gold fiducials.[21,24] Planning tumor volume (PTV) expansions differ based on treatment platform, with real-time target tracking of gold fiducials and CyberKnife® utilizing a PTV of 0.0 to 3.0 mm,[24] and LINAC-based SBRT based on 4D CT with no fiducials or target tracking utilizing a PTV of 5.0 mm.[22,28] Tables detailing suggested dose constraint values for different dose/fractionation schemes are reported by Pham[26] and Siva.[29]

**Response evaluation**

One of the challenges of SBRT is the interpretation of post-treatment radiographic studies, and defining characteristics that coincide with treatment response or recurrence. Renal cell carcinoma is generally slow-growing, and it has a similarly slow radiographic response to SBRT. The largest study of tumor response included 41 tumors treated with SBRT. The mean pretreatment linear growth rate was 0.68 cm per year; post-treatment, the linear growth rate regressed by an average of 0.37 cm per year. The study found no significant changes in enhancement on CT or MRI when comparing pre- and post-treatment imaging.[20]
The authors of the accompanying article are to be congratulated for a highly detailed and informative review of a fast-evolving concept in the care of kidney cancer patients, namely the role of radiation therapy in localized kidney cancer. The role of radiation therapy for the treatment of symptomatic kidney cancer metastases is well established, and most modern approaches favor higher-fraction, shorter-duration treatments, which is certainly favored by both patients and their caregivers. At our very high-volume kidney cancer center, I routinely refer all of my patients with symptomatic kidney cancer metastases for site-directed treatment utilizing either radiosurgery or percutaneous approaches. The benefit is clear.

However, with regard to localized kidney cancer, the gold-standard curative therapy is currently surgery. The field has moved to active surveillance for many patients who are not candidates for surgical treatment. The data supporting active surveillance are extensive, with long-term studies showing that active surveillance of small renal masses is associated with excellent survival. In this review, the authors correctly observe that the local control, if measured purely by size, is not an appropriate measure. After radiotherapy, is the kidney cancer dead or not? Control of growth itself is not the oncologic outcome of interest per se. It is notable that the most recent publication cited by the authors demonstrates a 100% local control rate, but the development of distant metastases in 11% of patients.[1] If radiotherapy was working to kill the tumor, this number compares unfavorably to active surveillance. For a population of patients who have essentially T1 tumors, this is higher than expected, even among patients who I would counsel regarding active surveillance. The ideal trial would randomize patients to active surveillance or radiotherapy, with both local and distant endpoints, in addition to quality-of-life endpoints.

Renal function after radiation must be considered, as the authors point out. Radiation to the kidneys produces modest declines in kidney function, which is very important information. But, clinically, many patients experience declines in kidney function over time, particularly those with highly compromised kidney function. Patients who have stage 4 or 5 chronic kidney disease may not be able to tolerate the small declines in kidney function associated with radiation therapy.

As it currently stands, radiation therapy for localized kidney cancer should be considered only in the context of clinical trials, particularly prospective trials. In my humble opinion, the ideal study would be prospective in nature, evaluating patients with biopsy-proven, high-grade kidney cancer that is growing, meaning it meets the criteria for treatment. As the field learns more from genetic studies, such as the TRACERx Renal trial,[2] we will be able to distinguish lethal tumors from indolent tumors. Many times, the indolent tumors are found in older, frail patients with comorbidities.

Possibly the most exciting prospect of radiation therapy, for which the authors detail a number of clinical trials in progress, is its immunomodulatory role, with or without systemic therapy agents, in the treatment of patients with kidney cancer. Multimodal therapy for renal cancer, including radiation therapy, may be important. Our field needs to design the appropriate trials to prove it.

FINANCIAL DISCLOSURE: Dr. Master has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/SBRT-in-RCC

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to impact renal function. A study of 21 patients treated with SBRT showed that the glomerular filtration rate (GFR) decreased by 8.7 mL per minute on average at 1 year post-treatment.[22] Similarly, in a pooled analysis of 223 patients treated with renal SBRT, the average GFR decreased by ~5.5 mL per minute after SBRT.[35] For more fractionated regimens, a dose distribution of 20 to 30 Gy in 10 fractions had a strong correlation with renal atrophy as assessed on CT scan.[36] In a case report of a patient treated with 26 Gy in 1 fraction, regional kidney function after SBRT was assessed with 99mTc dimercaptosuccinic acid single photon emission tomography/CT, and renal function was preserved in regions receiving less than 13 Gy in a single fraction.[37] Although most nephrotoxicity experienced with renal SBRT is subclinical, toxicity is increased in patients with underlying chronic kidney disease (CKD), with reported cases of stage 4 to 5 CKD requiring dialysis after SBRT.[17] The low toxicity rates may be due to the parallel function of nephrons, allowing for preserved renal function if a substantial portion of normal kidney is spared. Long-term toxicity after SBRT, however, is unknown.

**Patient selection**

Surgery remains the standard curative-intent therapy for localized renal cell carcinoma. Thus, SBRT for renal cell carcinoma should be considered only in patients who have contraindications to surgery. Some studies also treated renal cell carcinoma patients with SBRT if they refused surgery.[22,26,28] However, patients should be educated that surgery is the standard of care prior to considering SBRT in this population. Recent German guidelines on the role of radiation therapy in renal cell carcinoma state that SBRT is currently considered an experimental option due to the small number of patients reported in the literature, though it will likely have an increased role in the future as results from ongoing studies continue to emerge.[38]

Renal SBRT has also been studied in several other patient populations, including patients with metastatic disease as an alternative to cytoreductive nephrectomy,[39] those with bilateral renal tumors,[30,40] and those with a contralateral recurrence after nephrectomy.[41] The studies of these patient populations are small, and recommendations for SBRT in these settings should be made only after careful consideration of other options with acknowledgement of the sparsity of outcomes data.

**Future Directions**

The role of SBRT in localized renal cell carcinoma is actively being defined, and given its excellent short-term local control rates and minimal toxicity, it will likely play a more prominent role in future management. There are several ongoing studies of SBRT as an alternative to surgery in localized renal cell carcinoma, which should add to the currently limited body of evidence supporting its use. One phase II study is evaluating renal impairment in 30 inoperable renal cell carcinoma patients treated with SBRT at 27.5 to 40 Gy in 5 fractions (ClinicalTrials.gov identifier: NCT03747133). Another study plans to enroll 30 inoperable patients to evaluate quality of life after SBRT (35 to 40 Gy in 5 fractions), as well as cost effectiveness (ClinicalTrials.gov identifier: NCT03108703). The ARREST study will treat a similar cohort of 30 patients with SBRT (35 Gy in 5 fractions) and assess for toxicity as a primary endpoint (ClinicalTrials.gov identifier: NCT02853162). FASTRACK II, the largest ongoing phase II study, plans to treat 70 renal cell carcinoma patients with SBRT—either 26 Gy in 1 fraction (if < 4 cm) or 42 Gy in 3 fractions (if > 4 cm), with a primary outcome of freedom from local progression assessed by Response Evaluation Criteria in Solid Tumors (RECIST; ClinicalTrials.gov identifier: NCT02613819). Another phase II study plans to enroll 16 inoperable patients and treat them with SBRT to 36 Gy in 3 fractions, 40 Gy in 4 fractions, or 40 Gy in 5 fractions, to evaluate local control (ClinicalTrials.gov identifier: NCT02141919).

Current studies are also evaluating the efficacy of renal SBRT in combination with other local or systemic therapies. A phase I dose-escalation study is ongoing to evaluate SBRT doses of 30, 40, and 50 Gy in 5 fractions followed by microwave ablation, with a primary outcome of dose-limiting toxicity (ClinicalTrials.gov identifier: NCT02782715). An area of particular interest is the potential for a synergistic effect with SBRT and concomitant immunotherapy. Recent studies have demonstrated the effectiveness of SBRT and immunotherapy in mouse models of renal cell carcinoma,[42] specifically that SBRT has immunomodulatory effects in patients undergoing cytoreductive nephrectomy after SBRT.[43] In one mouse model of renal cell carcinoma, investigators showed that the combination of ablative radiotherapy and programmed death 1 (PD-1) blockade induced near-complete regression.

Continued on page 177
Non–Small-Cell Lung Cancer After Mantle Radiation: A Case Report and Brief Review

Carlos A. Lopez, MD, MPH, and Emily S. Tonorezos, MD, MPH

ABSTRACT: Survivors of childhood and young adult cancer are at risk for developing subsequent malignant neoplasms, including lung cancer. As survival rates in this group continue to improve and patients enter later decades in life, determining the optimal surveillance and counseling strategies with regards to subsequent cancers remains a challenge. In this case report, we present a non-Hodgkin lymphoma survivor who was incidentally found to have non–small-cell lung cancer 30 years after undergoing treatment that included mantle radiation. We discuss the treatment-related risk factors for lung cancer in this population and potential implications for long-term follow-up.

Introduction
As a result of improving treatment and supportive care, the population of childhood and young adult cancer survivors is expected to continue to rise over the coming years.[1] Childhood and young adult cancer survivors are at increased risk for a multitude of adverse late effects, including subsequent malignant neoplasms.[2-5] The historical mainstay for treatment of non-Hodgkin lymphoma has been chemotherapy with or without radiation therapy (RT); both alkylating chemotherapy and RT have been associated with the development of subsequent malignant neoplasms, including malignancies of the skin, breast, thyroid, gastrointestinal tract, and lung.[2, 6-12] In the general population, results from the National Lung Screening Trial (NLST) indicate that surveillance for lung cancer among smokers who are at high risk confers a mortality benefit. [13] What remains unclear is what the optimal lung cancer surveillance strategy is for childhood and young adult survivors who received RT to the lung fields. In the absence of a large definitive randomized controlled trial directly investigating this question, clinicians taking care of these survivors must rely on retrospective epidemiological studies, registry data, and statistical modeling where available. The aim of this paper is to describe a case of non–small-cell lung cancer (NSCLC) following mantle RT for non-Hodgkin lymphoma and to briefly review the epidemiology of lung cancer in childhood and young adult cancer survivors, with the goal of assisting the clinician in thinking about lung cancer risk in this population.

Case Report
A 61-year-old woman who was a survivor of non-Hodgkin lymphoma was referred for abdominal CT by her outside gynecologist for a chief complaint of left flank pain. An 8-mm left pulmonary nodule was incidentally noted in the left lower lobe. A repeat scan showed no growth in the nodule 2 months later. However, a subsequent scan 8 months after the first demonstrated interval growth of the nodule to a size of 14 × 11 mm. At that point, she was referred to thoracic surgery for biopsy and definitive treatment.

Her previous medical history was significant for non-Hodgkin lymphoma diagnosed at age 30, for which she received cyclophosphamide, vincristine, prednisone, methotrexate, doxorubicin, mercaptopurine, carbustine, and L-asparaginase. She also underwent mantle and pericardial irradiation (total dose, 35 Gy). At her annual survivorship
appointment, her other medical problems were noted to be hypothyroidism and hyperlipidemia. She had no history of tobacco, alcohol, or drug use, and she denied environmental exposures, including to asbestos.

To evaluate her pulmonary nodule, she underwent a PET scan, which showed increased 18F-fluorodeoxyglucose (FDG) uptake, raising suspicion for lung neoplasm. A fine needle aspiration biopsy of the left lung nodule revealed lung adenocarcinoma. She underwent a left lower lobe anterior segmentectomy and mediastinal lymph node dissection. After an uneventful recovery from surgery, she was followed with periodic re-imaging. Pathology of the nodule confirmed a diagnosis of stage IA NSCLC (T1aN0m0). She has remained disease-free for longer than 3 years after surgery.

**Review**

We performed a brief review of the English language literature using PubMed from inception to March 12 of this year, with combinations of the search terms “childhood cancer,” “lymphoma,” “survivor,” “lung cancer,” and “subsequent neoplasm,” as well as their derivatives. Bibliographies of literature identified by our search strategy were also hand searched for additional relevant articles and reviews of this population. Case reports, case series, institutional experiences, registry studies, and reviews discussing the incidence and clinical characteristics of lung cancers diagnosed in childhood and young adult survivors were all included. Studies not commenting on lung cancer specifically were excluded.

**Discussion**

In our report, we describe the case of a female non-Hodgkin lymphoma survivor who at age 61 had an incidental finding on imaging that was later revealed to be NSCLC. Given the absence of any identifiable environmental exposures, our case raises the concern that her earlier treatment with mantle RT contributed to her lung cancer risk. In addition, her disease-free survival 3 years after surgical resection illustrates the potential benefit of an early diagnosis and raises the question of whether other survivors with a history of RT to fields including the lungs would benefit from a CT-based lung cancer detection program.

In the cancer survivor population, the development of malignancies after RT is well-recognized, but heterogeneity in risk factors (including primary tumor biology, age at treatment, duration of follow-up, environmental exposures, and hereditary predisposition) has made attempts to estimate attributable risk difficult.[14] In a 2009 study on the Childhood Cancer Survivor Study (CCSS) cohort, the 20-year overall cumulative incidence of subsequent malignant neoplasms in 14,358 5-year childhood cancer survivors was estimated to be approximately 3% to 4%.[15] This group included patients treated for leukemia, lymphoma, neuroblastoma, soft-tissue sarcoma, bone cancer, central nervous system cancer, or Wilms tumor. Of these patients, 67% received RT, which was identified as a significant risk factor. Using Surveillance, Epidemiology, and End Results (SEER) Program cancer registries, Inskip et al reported a similar pattern of epidemiology in subsequent malignant neoplasms, including 7 cases of lung cancer among a cohort of 25,965 2-month survivors of childhood cancer.[16] Though the absolute number of cases was small, the expected number of lung cancers in this age group was even smaller, resulting in an observed-to-expected ratio (O/E) of 7.4 (P < .05). Importantly, survivors with a history of RT had an O/E ratio for cancers of the lung and bronchus of 17.0 (P < .05), while those without a history of RT had an O/E ratio of 5.4 (not significant).[16]

A 2011 meta-analysis of 23 studies by Pirani et al sought to investigate the overall risk for secondary malignancies in non-Hodgkin lymphoma survivors; pooling the results of 12 studies, the lifetime risk of developing lung cancer after non-Hodgkin lymphoma was 1.53 (233,293 total patients; 95% CI, 1.36–1.73) compared with controls without a history of the disease.[17] A 2013 meta-analysis of 21 studies by Ibrahim et al estimated that the cumulative incidence of lung cancer at 20-year follow-up after treatment for Hodgkin lymphoma ranged from 0.1% to 6.2%.[18] With a mean latency of 11.5 years between primary treatment and development of lung cancer.[19] A pooled analysis of German cancer registry data estimated that the standardized incidence ratio for lung cancer in non-Hodgkin lymphoma survivors was 2.08 (95% CI, 1.84–2.33); in Hodgkin lymphoma survivors, it was 3.64 (95% CI, 2.93–4.47).[20]

Higher treatment doses with radiation appear to impart a higher risk for lung cancer, as illustrated in an institutional retrospective study by Almargro-Casado et al in 2016.[19] Exposure to RT was associated with solid neoplasm development in these survivors, with an increased risk for lung cancer (hazard ratio, 4.0; 95% CI, 1.1–11.6) in patients receiving RT doses greater than 42 Gy compared with patients receiving less than 42 Gy. The median overall survival (OS) after lung cancer diagnosis was 12.6 months. However, patients diagnosed incidentally prior to the onset of symptoms had more favorable staging and better prognoses compared with patients who had been diagnosed after the onset of symp-
toms (median OS, 4.91 months vs 5.9 months).

It remains unclear to what extent underlying biological or genetic factors in the non-Hodgkin lymphoma survivor population could contribute to the risk of subsequent lung cancer. Friedman et al noted a statistically significant increase overall in the risk of malignancy (standardized incidence ratio [SIR], 1.8; 95% CI, 1.3–2.5) in siblings of patients with non-Hodgkin lymphoma compared with the general population, suggesting a genetic or environmental component[21]; notably, however, no increased risk for lung cancer was noted in siblings (SIR, 1.3; 95% CI, 0.6–2.9). Similarly, in a study by Landgren et al, non-Hodgkin lymphoma survivors with a positive family history of cancer did not have a statistically significant increased risk of developing lung cancer compared with similar survivors without a family history of cancer (risk ratio, 1.99; 95% CI, 0.73–5.39).[22]

A 2018 paper by Holmqvist et al sought to investigate the risk of subsequent malignant neoplasms after treatment for childhood Hodgkin lymphoma; they examined a cohort of 1,136 patients with Hodgkin lymphoma who were treated before age 17 between 1955 and 1986.[23] The cumulative incidence of lung cancer was 2.3% by age 50 years, though the highest at risk were men treated with chest RT at age <10 years, with a cumulative incidence of 4.2% by age 50 years; indeed, 10 of the 11 lung cancer cases they identified were in men, and were diagnosed a median of 28 years after Hodgkin lymphoma.

When compared with the general population, male survivors had an SIR of 26.7, whereas the SIR for women was 3.3 (95% CI, 0.2–14.6). Notably, all 11 lung cancer cases developed in patients who had received chest RT. A limitation voiced by most investigators in these retrospective studies is that patient smoking status is commonly unavailable, but is suspected to contribute significantly to lung cancer risk in lymphoma survivors.[17-20] The male predominance (76%) of lung cancer cases has been speculated to be due to historical differences in tobacco use between men and women.[18,24] A synergistic mechanism between radiation exposure and smoking is suggested,[19,23] and highlights the need to address smoking status with cancer survivors.

Currently, the existing evidence does not support a CT-based lung cancer detection program for survivors who have never smoked, and survivorship guidelines do not recommend lung cancer surveillance based on RT or chemotherapy history.

Another ongoing area of investigation is on how the risk of lung cancer changes over time as survivors age.[14] Early reports from the CCSS cohort reported few cases of lung cancer: in fact, none were reported in their 2001 paper (median age, 23 years; range, 8–47 years)[25]; 4 cases were reported in the 2006 paper, of which 3 were Hodgkin lymphoma survivors.[26] Though few in number, these cases represented an elevated risk compared with the general population (overall SIR, 3.1; 95% CI, 1.2–8.2).[26] A CCSS report in 2015 by Turcotte et al that investigated subsequent malignant neoplasm incidence during the fifth and sixth decades of life showed that most of the lung cancers they identified occurred after age 40 (5 cases after age 40, 1 case before; all cases had received radiation).[27] Of note, no excess risk for lung cancer was identified compared with the general population; this finding was speculated to be due to the risk of lung cancer also increasing in the general population in later decades of life, which would mitigate the difference in risk between the two groups.

The NLST demonstrated a mortality benefit from screening high-risk patients (age, 55–74 years, with at least a 30 pack-year tobacco history) with low-dose CT compared with chest radiography.[13] Patients screened with low-dose CT had earlier staging and fewer deaths compared with those screened with chest radiography. The results of this trial impacted guidelines, with multiple expert groups recommending the incorporation of lung cancer screening with low-dose CT in patients at high risk.[28-30] The current Children’s Oncology Group guidelines recommend that survivors exposed to chest or axillary radiation during treatment be counseled on the potential benefits and harms of spiral CT scanning for patients at highest risk.[31] Risks of spiral CT scanning in this setting include the possibility of a false-positive finding, which could result in patient distress, biopsy-associated morbidity, and unnecessary surgery. In the NLST, the rate of false-positive findings was very high in both screening groups (96.1% for CT, 93.9% for chest x-ray).[13] Other important questions that remain are: What is the radiation dose threshold that should be used to identify patients at highest risk? Should there be an optional screening interval? And, how do we incorporate the possible interaction between RT and tobacco use into screening decisions?

Conclusion
In any patient, the news of a cancer diagnosis can be devastating; however, as our case demonstrates, diagnosis at an early stage can result in a favorable outcome. Current survivorship guide-
lines do not recommend lung cancer surveillance based on a history of RT or chemotherapy. Yet, these exposures are likely relevant to risk.

At this time, the existing evidence does not appear to support a role for a CT-based lung cancer detection program among survivors who never smoked. Whether the demonstrated benefit of a CT-based lung cancer detection program can be applied to childhood and young adult cancer survivors without a history of smoking or to other survivors who have received radiation to the lungs is unknown. Future studies that include modeling of surveillance strategies may be helpful. Regardless of their baseline risk or exposure to radiation, all patients should be counseled on smoking cessation.

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When Surgery Is Not an Option in Renal Cell Carcinoma

Continued from page 173

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SBRT is a reasonable treatment for nonsurgical patients with localized RCC, and future studies will help define its place in multimodality therapy.

Finanical Disclosure: The authors have no significant financial interest in or other relationship with the manufacturer of any service or provider of any product mentioned in this article.

For references visit cancernetwork.com/NSCLC-in-NHL-survivors

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In this installment of Ask the PI, ONCOLOGY spoke with the lead investigator of the ATOMIC trial (ClinicalTrials.gov identifier: NCT02912559), Frank A. Sinicrope, MD, about utilizing immunotherapy in the adjuvant setting for colon cancer based on its impressive results in a subset of metastatic colorectal cancers.

Q: First, what immunotherapy agents are currently used in patients with colorectal cancer?

DR. SINICROPE: Currently, the use of immunotherapy in the treatment of colorectal cancer is restricted to a subset of metastatic tumors (~5%) that show deficiency in DNA mismatch repair.[1-3] These tumors have a defect in the ability to repair nucleotide mismatches in DNA, which results in microsatellite instability (MSI). MSI tumors are genetically unstable and carry numerous mutations that trigger the expression of neoantigens, which serve to attract abundant lymphocytes into the tumor. These “inflamed” tumors have been shown to respond favorably and, in some cases, dramatically to immune checkpoint inhibitors. The US Food and Drug Administration (FDA) has approved the use of immune checkpoint inhibitors for only those with metastatic colorectal cancers with MSI. Currently approved treatments include the anti–programmed death 1 (PD-1) antibodies pembrolizumab and nivolumab given as monotherapy, as well as the combination of nivolumab plus low-dose ipilimumab, an anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) antibody.[1-3] Importantly, pembrolizumab was approved for the treatment of patients with any type of solid tumor with MSI, so it’s not restricted to colorectal cancer. The combination of nivolumab and ipilimumab was shown to produce a higher response rate and better outcomes[3] when indirectly compared with nivolumab monotherapy from another study, and was associated with increased but manageable toxicities. Despite impressive results with these immunotherapy agents, it is important to note that only half of patients with metastatic disease demonstrate durable responses; therefore, studies to identify and circumvent resistant mechanisms are ongoing.

There are completed and multiple ongoing clinical trials to determine if the much larger group of non-MSI, or microsatellite stable, metastatic colorectal cancers might also benefit from immunotherapy, but thus far most of these studies have been negative. However, various strategies are being tested to see if we can increase the extent of inflammation within the tumor to better sensitize them to immunotherapy drugs.

Q: Can you tell us about the design of this new phase III trial that you are leading, including which patients are eligible?

Dr. Sinicrope reviews the phase III ATOMIC trial, which is testing standard chemotherapy alone or in combination with the anti–PD-L1 antibody atezolizumab as adjuvant therapy in a subset of colon cancer patients.

Evaluating Immunotherapy in Nonmetastatic Colorectal Cancer

Dr. Sinicrope is a Professor of Medicine and Oncology and Co-Director of the GI Cancer Program at the Mayo Clinic Comprehensive Cancer Center, Rochester, Minnesota.
Dr. Sinicrope: The ATOMIC trial is looking to see if immunotherapy that has been effective in metastatic colon cancers with MSI due to DNA mismatch repair deficiency can be applied to earlier-stage disease, specifically nonmetastatic stage III colon cancer. Currently, the standard of care after surgical resection for stage III colon cancers is chemotherapy for 3 or 6 months, depending on risk grouping determined by T and N stage data. Adjuvant therapy, including immunotherapy for patients following surgical removal of their tumor, is directed towards eradicating micrometastases. This strategy using immunotherapy has been successful in patients with stage III melanoma, in which an immune checkpoint inhibitor was effective in reducing recurrence and death. So, we are using a similar tactic but selecting for patients with hypermutated colon cancer and applying this strategy to earlier-stage, nonmetastatic disease.

The ATOMIC trial is evaluating the standard chemotherapy regimen FOLFOX, which is a combination of fluorouracil, leucovorin, and oxaliplatin, and randomizing patients to either this regimen alone for 6 months or to this regimen combined with the anti–programmed death ligand 1 (PD-L1) immune checkpoint antibody atezolizumab. Atezolizumab is given together with this chemotherapy for 6 months and then is continued as monotherapy for an additional 6 months. We are looking to see if atezolizumab will improve the survival of these patients. Again, the study is targeted towards the group of patients whose tumors have MSI due to mismatch repair deficiency.

It’s important to point out that it is now standard practice to test all newly diagnosed colon cancer patients for defects in mismatch repair. 

Harnessing the immune system of a patient to fight his or her own cancer has been studied for many years. A breakthrough in immunotherapy that revolutionized the oncology field was achieved only after the discovery of a means to modulate immune checkpoints: via a pathway that enables tumor cells to display a cell-surface profile that resembles that of their normal counterparts, despite their differences, therefore evading antitumor immunity.

In 2017, the US Food and Drug Administration approved pembrolizumab, a checkpoint inhibitor that targets the programmed death 1 pathway, as a second-line treatment for all metastatic solid tumor types classified as microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR), including this type of colorectal cancer.

In the United States, colorectal cancer is the third most common diagnosed cancer type, and the second deadliest, in both men and women. However, only a small subset of colorectal cancer patients with metastatic disease have tumors with MSI-H or dMMR characteristics and are candidates for immunotherapy. Only those patients with Lynch syndrome, and those who randomly acquire alterations in one of the MMR genes, are eligible for immunotherapy.

In this interview, Dr. Sinicrope nicely summarizes the background, successes, and challenges of immunotherapy for the treatment of colorectal cancer. As the lead investigator of the phase III ATOMIC trial (ClinicalTrials.gov identifier: NCT02912559), he explains how this research builds on very positive survival data seen with immunotherapy in metastatic MSI-H/dMMR colorectal cancer, and aims to expand the utilization of immunotherapy for additional colorectal cancer patients.

While the trial is still restricted to MSI-H/dMMR colorectal cancer patients, it is set to determine whether patients diagnosed with stage III colorectal cancer would benefit from the combination of atezolizumab with the current standard of care, defined as surgery and an adjuvant chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin (FOLFOX).

The ATOMIC trial is the only ongoing immunotherapy trial in stage III colorectal cancer patients. If successful, recurrence and death in stage III colorectal cancer patients with MSI would be reduced. Therefore, testing all patients for MSI is of interest, not only to increase patients’ eligibility for the trial, but also to raise awareness about Lynch syndrome and family medical history of colorectal cancer. If success is achieved, it may ultimately open the door for additional studies, such as those focusing on whether the efficacy of immune checkpoint inhibitors could be extended as a single agent for MSI-H/dMMR tumors.

Finally, multiple ongoing studies are investigating the expansion of immunotherapy beyond immune checkpoint inhibitors in MSI-H/dMMR tumors to the broader population of colorectal cancer patients.

**Financial Disclosure:** Dr. Yarden has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

**For references visit cancernet.com/ATOMIC-CRC-trial**

Dr. Yarden is Director of Medical Affairs for the not-for-profit Colorectal Cancer Alliance, and former Assistant Professor and Researcher at Georgetown University, both in Washington, DC.
This is done in pathology laboratories around the country where, typically, the tumor is tested for the expression of four proteins (MLH1, MSH2, MSH6, and PMS2) that govern the DNA mismatch repair system in the cell. A patient’s tumor tissue is stained for these proteins and if there is loss of one or more of these proteins, then this provides evidence for an inactivated or mutated gene, which can be a germline or heritable event (Lynch syndrome), or alternatively, inactivation of the MLH1 gene due to methylation, which is a sporadic event. Approximately 12% of stage III colon cancers show deficient mismatch repair—or MSI. The ATOMIC trial aims to accrue 700 patients total; we currently have 167 patients enrolled on the trial, so we are actively recruiting patients. An interim analysis for efficacy or futility is planned for when 50% of the projected outcome events have occurred.

**Q:** Are there other similar trials that are also testing novel adjuvant approaches for colorectal cancer that you could highlight?

**DR. SINICROPE:** The ATOMIC study is the only adjuvant trial in the United States that is currently looking at immunotherapy for the treatment of stage III colon cancer. There are ongoing discussions about evaluating molecularly targeted agents as adjuvant therapy for colon cancer, particularly for tumors with BRAF V600E mutations that are associated with worse prognosis in these patients. The ATOMIC study has the potential to be practice-changing in that it will determine whether immunotherapy is an effective treatment for the subset of colon cancers with MSI, where it has the best chance of being effective.

It is important to emphasize that immunotherapy has not been shown to benefit the majority of patients with colorectal cancer who do not have hypermutated tumors. Colorectal cancer is lagging behind some of the other tumor types in which immunotherapy has shown efficacy for a larger proportion of patients. This is a very active area of research, to understand the factors that determine both the likelihood of response and the mechanisms underlying treatment resistance, such that we can overcome them so that more patients can receive and benefit from this remarkable new treatment.

**FINANCIAL DISCLOSURE:**
Dr. Sinicrope is a consultant to Roche/Ventana Medical Systems, which has products for mismatch repair testing.

**MyPathway Subanalysis Backs Combination HER2–Targeting Antibodies in Colorectal Cancer**
Investigators studied a combination of pertuzumab and trastuzumab in patients with metastatic HER2-positive colorectal cancer. For references visit cancernetwork.com/MyPathway-study
State of Cancer Research Around the Globe

Mehmet Sitki Copur, MD

ABSTRACT: Cancer, the second leading cause of death globally, remains a significant challenge for societies, healthcare systems, and affected individuals worldwide. Adding to this challenge are complex disparities in access to and use of cancer care, basic and clinical research, and clinical trials, as well as disparities in cultural beliefs and genetics. To improve cancer treatment, it is essential that cancer investigators, cooperative groups, national research institutions, national governments, competent authorities, ethics committees, and pharmaceutical companies come together to strengthen global collaboration in cancer research. Once we reach this goal, the resulting data will be more broadly applicable to all patients. This article reviews the current state of cancer research around the world.

Introduction
Cancer is a significant challenge for society, healthcare systems, and the growing number of affected patients and their families. In 2018, out of the 18 million cases of cancer worldwide, 9.5 million were in men and 8.5 million were in women. Cancer is the second leading cause of death globally, with an estimated 9.6 million deaths.[1] The most common cancers are lung cancer (2.09 million), female breast cancer (2.09 million), prostate cancer (1.28 million), colorectal cancer (1.1 million), non-melanoma skin malignancies (1.04 million), and stomach cancer (1.03 million). Cancer-related deaths, from most to least frequent, are due to lung cancer (1.76 million), colorectal cancer (862,000), stomach cancer (783,000), and liver cancer (782,000). More than two-thirds of these cancer fatalities occur in low- and middle-income countries.[2]

High body mass index, low fruit and vegetable consumption, lack of physical activity, tobacco use, and alcohol use are the five leading behavioral and dietary risk factors for cancer-related deaths. It is estimated that tobacco use alone is responsible for approximately 22% of cancer deaths.[3] Some 25% of cancer cases in low- and middle-income countries stem from infections, such as hepatitis and human papillomavirus.[4] Beyond the risk factors and common causes of cancer, the economic impact of the disease is significant, and it is increasing. More than 90%
of high-income countries have cancer treatment services available compared with fewer than 30% of low-income countries. Only one in five low- and middle-income countries has the necessary data to drive cancer policy.[5,6]

No single country can successfully fight this global public health problem on its own. Science is collaborative in nature and international in scope. To effectively improve treatments and identify cures, it is essential to fund the most promising research from all corners of the globe. Translational cancer research covers the continuum of research, including basic, preclinical, early clinical, late clinical, and outcomes research. Basic/preclinical research serves as the foundation for early clinical research, bridging the gap between science and practice. A prime example comes in the form of progress made towards controlling the infectious diseases that are linked to certain malignancies, such as hepatocellular carcinoma, cervical cancer, and stomach cancer. Coordinated approaches in basic research, translational research, and clinical trials may be applied to fighting cancer worldwide. This article reviews the current state of cancer research around the globe.

Cancer Research in the United States and Canada

While 85% of cancer patients are diagnosed and treated at local, community-based clinical practices, cancer-related clinical research and clinical trials have traditionally been conducted at well-established academic medical centers in the United States. For the last 4 decades, the National Cancer Institute (NCI) has acknowledged the importance of community-based oncology research through several initiatives and programs. The significance of this research was validated in 1982, when the NCI initiated the Community Clinical Oncology Program (CCOP).[7]

The CCOP was designed to disseminate and implement advances in cancer care by linking cancer investigators and academic centers to community-based practices, thus expanding access to clinical trials and promoting cancer treatment innovations within the community populations that otherwise might not have had access. This collaborative partnership between research institutions and community physicians helped to facilitate phase III cancer prevention, control, and treatment trials in the local practice setting. Despite these efforts, community-based cancer research continued to face challenges as a result of the era of emerging science, technology, genomics, and molecularly targeted therapy, as well as a rapidly changing healthcare environment.

In 2007, the NCI further expanded its community-based efforts by launching the NCI Community Cancer Centers Programs (NCCCP), a public–private partnership with 21 community hospitals in 16 states.[8] The goals of the NCCCP were to enhance access to, and improve the quality of, cancer care by expanding the infrastructure to support a platform for basic, clinical, and population-based research, as well as informatics, biospecimen collection, and cancer care disparities in community hospitals. Self-reported data from NCCCP sites between 2007 and 2010, supplemented with data from the NCI Cancer Therapy Evaluation Program, showed that the availability of phase III trials and patient accrual increased by 16% and 133%, respectively, at NCCCP sites, compared with 8% and 30% nationally. In addition, enrollment of racial and ethnic minorities in oncology trials increased by 82%, from 83 to 151 patients; the accrual of patients age 65 years or older in oncology trials also rose by 221%, from 200 to 641 patients at NCCCP sites. The exact changes in trial portfolios and accrual differed by sophistication of the site and by prior experience conducting clinical trials at the site.[9]

In 2014, the NCI initiated a new community-based program, the NCI Community Oncology Research Program (NCORP), to align with and replace the CCOP and NCCCP programs. The goals of the NCORP are to support clinical trials on cancer control, prevention, treatment, and cancer screening in the community setting, as well as to expand the scope of research to include cancer care delivery. The NCORP initiative emerged around the same time as two other significant changes: 1) the transformation and condensing of nine long-standing NCI Cooperative Group Programs into four new groups under the National Clinical Trials Network (NCTN), and 2) the implementation of the NCI Central Institutional Review Board. Both of these changes helped to provide easier access to all NCI Cooperative Group clinical trials, with some reduced regulatory load.

The NCTN structure included five US Network groups and the Canadian Collaborating Clinical Trials Network (Figure). Membership in the individual NCTN groups is based on criteria that are specific to each group. Sites can belong to more than one group, and membership in at least one group allows a site to participate in the trials led by any NCTN group for which their investigators are qualified. Consequently, researchers from the Lead Academic Participating Sites, NCORP, other academic centers, community practices, and international members associ-
ated with the Network groups may all enroll patients onto NCTN trials. Clinical trials led by NCTN groups may receive support from the Imaging and Radiation Oncology Core Group, Clinical and Translational Science Awards, and tissue banks, according to the scientific needs of the trials.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) is the adult cooperative oncology group based in Canada committed to assessing all modalities of therapy across the spectrum of different types of cancer. The NCIC-CTG has been operational since 1980. The group’s activities have included leadership of, and participation in, large randomized clinical trials conducted in the United States and Canada by both the NCIC-CTG and US-based cooperative groups. The mission of the NCIC-CTG is to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer, with the ultimate goal of reducing morbidity and mortality from this disease. NCIC-CTG collaborates with the NCI’s Cancer Therapy Evaluation Program and US-based groups through its NCTN Program to develop new intergroup trials under NCIC-CTG leadership and to ensure more rapid accrual to trials led by US-based groups, thereby enhancing the overall clinical research program for adults and children with cancer.

Pharmaceutical companies may run international trials on their own or in conjunction with established clinical trials cooperative groups. Until the late 1990s, few pharmaceutical companies showed interest in oncology products. Most new anticancer drugs in development reached the cooperative group researchers through the NCI. Within the past 2 decades, however, a record number of pharmaceutical and biotechnology companies have come up with hundreds of novel agents, compelling cooperative group investigators to work directly with industry partners. Chronic underfunding of the cooperative groups by NCI, coupled with the opportunity to access novel compounds, inevitably led to the development of much closer relationships between the cooperative groups and the pharmaceutical industry. While some effective collaborations between industry and clinical trials groups have resulted in the successful completion of many important cancer trials, the potential conflict between the goals of government-funded cooperative groups vs pharmaceutical industry sponsors has raised concerns in some others. The primary importance to oncologists and patients may be of no interest to the pharmaceutical industry. The cooperative groups may also want to combine or compare agents from two different companies, which may not serve the interests of industry. [11] This is an ongoing challenge in the United States especially.

**Cancer Research in Europe**

While representing less than 10% of the global population, one-quarter of all cancers occur in Europe. Due to an aging population, these numbers are expected to increase, with an estimated 3.9 million Europeans diagnosed with cancer and 2 million cancer-related deaths in 2018 alone. Progress from basic research to patient treatment has historically been a long and fragmented process in Europe. At the 2000 European Council meeting in Lisbon, member states of the European Union signed on to an ambitious program aimed at helping Europe to become the most competitive and dynamic knowledge-based economy in the world by 2010. The cornerstone of the Lisbon Agenda was the creation of a European Research Area. [12] These activities led to the establishment of the European Research Council in 2007, which helped...
In 2017, a goal of achieving long-term clinical outcomes of cancer prevention policies. These protocols were established by the merger of the International Agency for Research on Cancer and the United States. Culprit is to create a sustainability of high-level, shared research infrastructure platform. Cancer Core Europe is now a legal entity hosting research collaborations. Cancer Core Europe (CCE) in 2014. The main goal of CCE is to create a sustainable, high-level, shared research infrastructure platform hosting research collaborations. Cancer Core Europe is now a legal entity including seven large European cancer centers, most of which are Comprehensive Cancer Centers. They operate with a single portal system to engage in various research projects with partners. Motivated by the creation of CCE, the leaders of 10 research institutes with prominent cancer prevention programs in Europe (the International Agency for Research on Cancer in France, and institutes in the United Kingdom, Denmark, Netherlands, Germany, Sweden, and Italy) came together and established Cancer Prevention Europe (CPE).[16]

CPE is a consortium of multidisciplinary centers focused on reducing cancer mortality and morbidity through development of prevention policies. These infrastructures are intended to serve as a hub to connect and interact with other centers across Europe and beyond, bringing innovative approaches to cancer research, links to healthcare systems, development of quality-assured multidisciplinary cancer care, and assessment of long-term outcomes. Presently, CCE and CPE are integrating therapeutics and prevention strategies to address worsening cancer burden as a central engine. In 2017, a goal of achieving long-term survival in 3 out of 4 cancer patients by 2030 was proposed as a mission. This was deemed to be possible through innovative prevention and treatment strategies in a virtual European cancer center/infrastructure.[17] In June 2018, a press release from the European Commission concerning Horizon Europe stated that "Examples of missions could range from the fight against cancer, to clean transport or plastic free oceans."[18]

**Cancer Research in the Asia-Pacific Region**

Cancer is one of the leading causes of death in South Korea, Taiwan, Singapore, and Hong Kong, as well as in urban China. The incidence of cancer has increased significantly over the past several years in the Asia-Pacific region, becoming a major concern for many healthcare systems. During the 1980s and 1990s, impressive economic growth in the East and Southeast Asia countries and China has improved standards of living and healthcare systems, leading to fewer deaths from infectious diseases. The increase in cancer deaths has been attributed to the enormous economic successes, longer life spans, and a population that is expanding far more rapidly than those in Europe and the United States. Furthermore, the proportion of people older than 65 years of age has been increasing. Over the last 25 years, while the total population of China has increased by 31%, the number of people over age 65 years has increased by 81%. [19,20] The number of cancer cases in Asia is expected to rise to 8.1 million by 2020 if the current management strategies are not changed. Much of the Asia-Pacific population has certain characteristics that increase their cancer risk. In men, the smoking rate is about twice that seen in Europe and the United States. Culprit infections are much more common in Southeast Asia, including *Helicobacter pylori*, which increases the risk of stomach cancer by 5 to 6 times, and hepatitis B, which increases the risk of liver cancer. Nasopharyngeal cancer is a very common disease in Asia, predominantly affecting people of southern Chinese descent. The global UV index for Asia is about twice that of the countries in the Northern Hemisphere, further increasing cancer risk in this population.[21]

While cancer research is in great demand across the Asia-Pacific region, the infrastructure and resources to conduct clinical trials can be variable. Australia, Japan, South Korea, Hong Kong, Taiwan, and Singapore have adequate resources to conduct clinical trials efficiently. Countries such as China and India have built institutions that can provide infrastructure and access to clinical trials for large populations of cancer patients, which has been a good resource for industry clinical trials. With the advent of immuno-oncology and the number of new agents undergoing testing, a multitude of centers and studies have cropped up to meet demands in the region. Challenges to participation in clinical trials in the Asia-Pacific region include specific inclusion/exclusion criteria of these trials, unavailability or irrelevance of the standard care arm (if a trial has one), and the lack of genetic biomarker testing in these developing countries. Another challenge, which at times can be an advantage in the Asia-Pacific region, is the genetic makeup of this population, which may display a difference in the incidence of the mutation being studied.[22]

**Cancer Research in the Middle East**

Similar to the incidence of the most common cancers worldwide, breast cancer, lung cancer, colorectal cancer, and prostate cancer are the most frequent cancers in the Middle Eastern and North African countries. Bladder and stomach cancers, however, constitute the fifth and sixth...
most common cancers in this region.[23]
Cancer incidence rates vary widely within and between Arab populations. There are few population-based cancer registries in Arab countries, with only 2% to 5% of populations reporting high-quality incidence data. National and regional spending on research and development has been relatively modest. In 2013, the regional gross expenditure on research and development by all Arab states was $15.5 million, compared with $282 million and $427 million by the European Union and North America, respectively.[24]

Conducting research in this region of the world has been more challenging due to language barriers and lack of research infrastructure for reliable and valid data collection, as well as too few researchers and too little networking among them.[25] Furthermore, constant political instability in this part of the world has adversely affected the number of research publications in circulation.[25-28] Due to weak infrastructure, low research spending, and the cultural attitudes of physicians and patients towards clinical research, high-evidence analytical research studies—such as randomized clinical trials—have been very problematic to conduct.[29-31]

To reduce the incidence and impact of cancer in the Middle East, a regional initiative for cancer research and treatment, the Middle East Cancer Consortium (MECC), was established in 1996. MECC members include the United States, Cyprus, Egypt, Israel, Jordan, the Palestinian Authority, and Turkey.[32-34] The goal of MECC was to launch and sustain academic-based medical programs that bring together scientists, academics, and clinical professionals from its member countries. MECC has helped to establish a successful Middle Eastern Network of Cancer Registry Centers, and initiation of palliative programs in its member countries.

Global Collaboration in Cancer Research
International networks for research collaboration are not new for Europe and North America. The European Organisation for the Research and Treatment of Cancer (EORTC) has been around since 1962, with its top 35 accruing institutions located in 11 European countries, as well as Turkey and Egypt. Likewise, the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Children's Oncology Group have brought cancer researchers from Canada and the United States together for many years. The NCIC-CTG has worked closely with investigators in the United States, Europe, and Australia. Advantages of international collaboration include faster accrual for both common and uncommon tumors, broader applicability of research results, fewer duplicative trials, and rapid dissemination of innovations.[35] Thus, the need for global partnership in cancer research is crucial to maximize resource utilization, permitting cancer researchers around the world to complete high-priority trials in a timely manner. There are, however, several challenges to this approach. Regulatory, logistical, and financial hurdles often hamper the conduct of clinical trials even at the individual country level. One can only imagine the hurdles that can be faced when international collaboration is sought. Disadvantages of international collaboration in cancer treatment trials include differing regulations among countries, disparate levels of clinical trial support infrastructure, contrasting processes and schedules for scientific review, longer lead time for concept and trial development, various licensing arrangements and distribution issues for specific drugs, and incongruent contractual issues with pharmaceutical companies in different countries.[35] Despite these challenges, there have been some successful examples of effective international interchange between clinical trials groups. The Breast International Group and the International Breast Cancer Study Group bring together 41 member groups from Europe, Canada, Latin America, Australia/New Zealand, and Asia, in addition to those from North America. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial, sponsored by the NCI, the Breast International Group, and GlaxoSmithKline, is an example of a worldwide trial made possible through international collaboration and industry partnership.[36]

With the steady increase in global cancer burden and the unprecedented pace of discoveries in basic cancer science, it is clear that cancer investigators, cooperative groups, national research institutions, national governments, competent authorities, ethics committees, and pharmaceutical companies need to get together, now more than ever, to strengthen global collaboration in cancer research.

Integration of cancer investigators and cooperative groups in Latin America, Asia, Africa, the Middle East, and Europe into the existing cancer research networks is critical if research is to become more representative of the entire globe. Once we reach that goal, the resulting research will be more broadly applicable to all patients. ■

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For references visit cancernetwork.com/global-research

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ONCOLOGY DRUG UPDATES

FDA Approves Two New Indications and Dosage Form for Pembrolizumab

Traci DeVito and Naveed Saleh, MD, MS

The US Food and Drug Administration (FDA) recently approved a new dosage form and two new indications for pembrolizumab (Keytruda) in non–small-cell lung cancer (NSCLC) and renal cell carcinoma (RCC).[1,2] Key information about these updates is highlighted below.

New Indication for NSCLC

In April 2019, the FDA approved pembrolizumab for the first-line treatment of stage III NSCLC patients who are not candidates for surgical resection or definitive chemoradiation, and for those with metastatic NSCLC. Patients’ tumors must have no EGFR or ALK genomic aberrations, and must express programmed death ligand 1 (PD-L1; Tumor Proportion Score [TPS] ≥ 1%), per an FDA-approved test.[1]

This approval was based on KEYNOTE-042, which evaluated 1,274 patients with stage III or IV NSCLC who had not received systemic treatment for metastatic NSCLC. Participants received 200-mg intravenous (IV) pembrolizumab every 3 weeks or investigator’s choice of a carboplatin-based regimen with pemetrexed or paclitaxel. Statistically significant improvements in overall survival (OS) were seen with pembrolizumab in all three populations studied. Median OS was as follows for the pembrolizumab vs chemotherapy arms, respectively: TPS ≥ 1%: 16.7 vs 12.1 months (hazard ratio [HR], 0.81; 95% CI, 0.71–0.93; P = .0036); TPS ≥ 20%: 17.7 vs 13.0 months (HR, 0.77; 95% CI, 0.64–0.92; P = .004); and TPS ≥ 50%: 20 vs 12.2 months (HR, 0.69; 95% CI, 0.56–0.85; P = .0006).[1,3]

Adverse reactions (≥ 10% of patients) with pembrolizumab were fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pyrexia, and weight loss. The recommended dose of pembrolizumab for NSCLC is a 200-mg IV infusion over 30 minutes once every 3 weeks.[1,3]

New Indication for RCC

The FDA also approved pembrolizumab plus axitinib for the first-line treatment of advanced RCC last month.[2,4] This approval was based on KEYNOTE-426, which evaluated 861 patients who had not received systemic therapy for advanced RCC. Participants received 200-mg IV pembrolizumab every 3 weeks plus 5-mg oral axitinib twice daily or 50-mg oral sunitinib once daily for 4 weeks followed by no therapy for 2 weeks. A statistically significant improvement in OS was seen with pembrolizumab/axitinib (HR, 0.53; 95% CI, 0.38–0.74; P < .0001). The 12-month OS rate was 90% vs 78% for pembrolizumab/axitinib vs sunitinib.[2,4]

Grade 3/4 hepatotoxicity occurred in 20% of patients, 13% of whom discontinued pembrolizumab or axitinib. Common adverse reactions with pembrolizumab/axitinib (≥ 20% of patients) were diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. The recommended dose for RCC is 200-mg pembrolizumab every 3 weeks plus 5-mg oral axitinib twice daily.[2,4]

New Dosage Form

Lastly, the FDA approved a new dosage form for pembrolizumab: 50 mg of lyophilized powder shipped in a single-dose vial to be reconstituted and used as an injection solution.[5]

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For references visit cancernetwork.com/onc-drug-update-may
The Role of Primary Tumor Treatment and Metastasis-Directed Therapy in Oligometastatic Prostate Cancer

Abhinav Gupta, Thomas J. Pugh, MD, Elaine Lam, MD, Alison D. Sheridan, MD, and Sameer Nath, MD

An otherwise healthy 59-year-old man who was recently diagnosed with American Joint Committee on Cancer (AJCC) 8th edition clinical stage IVB (T3aN1M1b) prostate adenocarcinoma presents to the radiation oncology clinic for consideration of radiation therapy. After he was found to have an elevated prostate-specific antigen (PSA) level of 16.7 ng/mL, he underwent a standard transrectal ultrasound-guided biopsy that revealed a prognostic grade group 4 (Gleason score 4+4) in 7 of 12 core biopsies, with lower-grade adenocarcinoma present in the remaining 5 core biopsies. A multiparametric prostate MRI revealed a large (4 cm) Prostate Imaging Reporting and Data System (PIRADS) 5 lesion with extracapsular extension, as well as pelvic lymphadenopathy, including a 2.2-cm left internal iliac node (Figures 1 and 2). A staging bone scan showed focal uptake in the seventh right rib (Figure 3), corresponding to a sclerotic lesion on follow-up CT, which was deemed highly suspicious for metastatic prostate cancer after careful review in multidisciplinary conference. He was started on upfront systemic therapy with leuprolide, abiraterone acetate, and prednisone. Three months later, his PSA level had decreased to 0.03 ng/mL, and 1 month after that, imaging showed a mixed response to systemic therapy with reduced bilateral pelvic lymphadenopathy and persistent focal uptake in the seventh right rib metastatic lesion. No new lesions were identified.

What is the most appropriate management for this patient?

A. Radical prostatectomy with pelvic lymph node dissection
B. Pelvic external beam radiotherapy (EBRT) and stereotactic body radiation therapy (SBRT) to the bony metastatic lesion
C. Continue with current systemic therapy
D. Intensify systemic therapy with 6 cycles of docetaxel

FIGURE 1 Axial; (A) T2 weighted; (B) diffusion b-value, 1,000; (C) ADC map; and (D) dynamic post-contrast images showing a PIRADS 5 lesion in the right lateral peripheral zone in the mid gland, with markedly increased signal on high b-value diffusion, markedly hypointense on ADC, and early enhancement on dynamic post-contrast images. Capsular bulging and irregularity of the capsule consistent with extracapsular extension is noted (arrow).
Discussion
Cancer is thought to progress in an orderly stepwise fashion, from a primary organ, to regional metastatic sites, and then to distant metastatic sites. In the past, cancer was traditionally viewed as a systemic disease when it spread to distant organs, and local therapy was deemed unlikely to improve outcomes or render cure. However, pioneering work from Hellman and Weichselbaum in 1995 led to the hypothesis that cancers may instead fall along a continuum between localized and systemic disease. They proposed that a transitional stage between local and metastatic cancer exists, known as “oligometastatic cancer.”[1] In this intermediate state, metastases are initially more limited before becoming widespread, and local therapies could still provide a benefit, perhaps even cure. Many experts have explored this hypothesis in a variety of solid tumor sites.[2-4] The exact definition of oligometastatic disease remains controversial, but studies have typically included patients with one to five metastatic sites identified on standard imaging. [5,6] With the advent of novel molecular imaging, including prostate-specific membrane antigen (PMSA) PET, carbon-11/fluorine (F)-18 fludeoxyglucose PET, and F-18 fluciclovine PET,[7,8] we can now detect disease spread at lower PSA levels than ever before. As a result, the prevalence of oligometastatic prostate cancer has increased, as have discussions of whether or not these patients should be treated differently than those with overtly widespread metastatic disease.

Metastatic prostate cancer has traditionally been treated with androgen deprivation therapy (ADT), with an initial goal of lowering serum testosterone to castrate levels.[9] The optimal form of ADT has not been determined with level 1 evidence, and options include medical castration with gonadotropin-releasing hormone agonist (GnRH) agonists/antagonists or surgical orchiectomy. Treatment-related side effects of ADT can adversely impact quality of life, and include fatigue, mood changes, hot flashes, decreased libido, bone fracture, cardiovascular disease, and metabolic changes. [10] Recent clinical trials have shown the benefit of adding other systemic therapies to standard ADT in patients with metastatic prostate cancer. In particular, the addition of abiraterone acetate or docetaxel to standard ADT has been shown to improve overall survival in select high-risk men.[11,12] There are limited data comparing these two regimens, and both appear to be associated with the same magnitude of survival benefit.[13] Interestingly, the extent of survival improvement has been shown to differ between low- and high-burden metastatic disease. For example, adding docetaxel to ADT fails to improve survival outcomes in low-burden disease or oligometastatic disease, while demonstrating improved outcomes in those with high-burden disease.[14] This also supports the notion that low-burden disease metastases may behave differently than a more widespread disease process.

Treatment of the primary tumor in metastatic prostate cancer was always considered a palliative measure for patients suffering from medically refractory local symptoms. However, this changed when a benefit from local therapy was observed in other types of metastatic cancers, sparking an interest in local therapy as a potentially life-prolonging treatment for metastatic prostate cancer. Cytoreductive therapy for stage IV malignancies has been associated with improved outcomes in several solid cancer types, including colon,[15] ovarian,[16] and renal cell carcinoma.[17]
The underlying theory is that cyto-reduction can help eliminate the original source of tumor spread and highest concentration of tumor clonogens, which may improve disease control when combined with effective systemic therapy to treat the remaining microscopic distant disease. Recently, a growing body of retrospective studies has indicated a potential benefit of local therapy in metastatic prostate cancer. [18-22] In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, Culp et al identified 8,185 men with documented stage IV (M1) disease, of whom 245 underwent definitive prostatectomy and 129 underwent brachytherapy. Patients undergoing local therapy had improved survival compared with those without any local therapy. Factors associated with increased cancer-specific mortality in patients undergoing local therapy included T4 disease, high grade, and PSA level > 20 ng/mL.[18] In a follow-up SEER analysis, the benefit of local therapy was highest in patients with a cancer-specific mortality risk of < 40%.[20]

Two recent analyses of the National Cancer Database have also found that local therapy was associated with improved overall survival compared with ADT alone. Rusthoven et al identified 6,382 men in this database who were diagnosed with metastatic prostate cancer between 2004 and 2012 and were treated with ADT with or without radiation. [23] Only a small number of men (8.4%) received prostate-directed radiation. After a median follow-up of 5.1 years, the 5-year overall survival rate was 49% with the addition of radiation compared with 33% with ADT alone after adjusting for covariates with propensity score matching. Secondary analysis showed that men treated with ADT plus prostatectomy also had superior survival compared with men treated with ADT alone; there was no difference between the radiation or prostatectomy cohorts in terms of survival. These results were validated in a separate analysis of the National Cancer Database.[24]

Finally, a variety of additional retrospective and post-hoc studies have also indicated a benefit of local therapy in stage IV prostate cancer patients. In particular, in node-positive (stage IV) disease, the addition of radical prostatectomy to conventional treatment has been associated with improved clinical outcomes in several studies.[25-28] A post-hoc analysis of the Southwest Oncology Group 8894 trial showed that patients with metastatic prostate cancer who underwent radical prostatectomy prior to systemic treatment had improved cancer-specific survival.[29] Similarly, using a case control design study, Heidenreich et al found increased time to castration resistance, freedom from clinical progression, and improved overall survival in men who received a radical prostatectomy in the setting of low-volume skeletal metastases.[30]

Although these studies provide promising data for the potential role of prostate-directed therapy in the setting of metastatic prostate cancer, they were retrospective in nature and are therefore limited by the possibility/likelihood of selection bias. There are two recently published randomized trials evaluating the impact of prostate radiation therapy in M1 patients. The HORRAD trial[31] is a multicenter randomized controlled trial conducted in the Netherlands, which began in 2004. Men with newly diagnosed prostate cancer, bone metastases, and a PSA level > 20 ng/mL were randomized to ADT alone or ADT plus radiotherapy to the prostate. The primary endpoint was overall survival; the investigators ambitiously estimated a 10-month absolute improvement in overall survival with the addition of prostate EBRT to ADT. After a median follow-up of 47 months, prostate EBRT significantly improved PSA failure-free survival (hazard ratio [HR], 0.78; 95% CI, 0.63–0.97; P = .02). However, prostate EBRT was not associated with a statistically significant improvement in median overall survival (43 months with ADT alone vs 45 months with prostate EBRT and ADT). There are several important considerations when applying HORRAD to current medical practice. First, the relatively large estimated survival impact from prostate EBRT likely underpowered the trial to detect smaller, yet clinically significant, differences in overall survival between the two groups. Secondly, the median PSA level for the entire cohort was 142 ng/mL, and there was no limit to the number of allowable metastatic lesions detected on bone scan. Furthermore, a staging CT scan was not required, meaning the presence of nodal or visceral metastases was unknown. Therefore, patients enrolled in HORRAD had a disproportionately
high metastatic burden and may not be representative of the oligometastatic patient population. Interestingly, on subgroup multivariate analysis, there was a trend towards an overall survival benefit for patients with <5 bone lesions (HR, 0.68; 95% CI, 0.42–1.10). Considering the inherent limitations of unplanned subset analyses, these data should be considered hypothesis generating only.

The second published randomized trial was an analysis of STAMPEDE participants.[32] These investigators actually prospectively tested whether or not prostate radiotherapy improved overall survival over systemic therapy alone in M1 patients and specifically in those men with low metastatic disease burden (as defined in the CHAARTED trial). In the M1 cohort at large, STAMPEDE showed similar results to HORRAD, in which progression-free survival was improved with the addition of prostate radiation therapy, without a statistically significant improvement in overall survival. However, in those men with low metastatic disease burden, prostate EBRT significantly improved overall survival compared with systemic therapy alone (HR, 0.68; 95% CI, 0.52–0.90).

We now have level 1 evidence demonstrating improved progression-free survival with the addition of prostate EBRT to ADT in M1 patients and, more specifically, an overall survival advantage in M1 patients with low metastatic disease burden as determined by appropriately powered a priori hypothesis testing. Furthermore, these benefits are highly consistent in both outcome and magnitude with the preceding hypothesis-generating data.

A growing number of patients may present with either synchronous or metachronous oligometastatic disease, and the optimal management of these patients is unclear. SBRT is a highly conformal mode of radiation therapy that has been associated with high rates of local control. It is a particularly attractive option due to its favorable toxicity profile and short treatment duration. Two recent clinical trials provide supportive data for metastasis-directed therapy for patients who present with limited metastatic disease.

The STOMP trial was a multicenter phase II trial that randomized patients with biochemical recurrence after systemic therapy, three or fewer extracranial metastatic lesions on PSMA PET imaging, and serum testosterone levels greater than 50 ng/mL to either metastasis-directed therapy (including SBRT or surgical extirpation) to all active lesions or surveillance. PSA surveillance was conducted every 3 months, and
biochemical progression prompted repeat imaging. Patients who developed symptomatic disease, locoregional tumor progression, or more than three extracranial metastatic lesions were started on ADT. The primary endpoint was ADT-free survival. A total of 62 patients were enrolled. After a median follow-up of 3 years, the median ADT-free survival was 13 months in the surveillance group vs 21 months in the SBRT group. Treatment was well tolerated, and there were no grade 2 to 5 toxicities.[33]

A similar clinical trial, POPSTAR, recently corroborated these findings. In this prospective trial, 33 patients with 1 to 3 oligometastases were treated with a single fraction of SBRT to each lesion. In all, SBRT was feasible for 97% of putative targets. After a median of 2 years’ follow-up, the local progression–free survival rate was 93% and the distant progression–free survival rate was 39%. Of the 22 men not on any form of ADT, the 2-year rate of freedom from ADT was 48%. There was one grade 3 complication (vertebral body collapse). No differences in quality of life were found. [34] Overall, these small prospective studies provide compelling evidence for the use of metastasis-directed therapy as a safe and effective option for those with low-volume metastatic disease to decrease the risk for disease progression and delay the use of ADT.

Outcome of This Case
After a discussion of the pros and cons of various management options, the patient elected to proceed with fractionated radiotherapy to the pelvis and SBRT to the bone lesion (Figures 4 and 5), along with continuous GnRH agonist therapy with abiraterone acetate plus prednisone. The patient tolerated radiotherapy well, with no significant toxicity. At this time, he is still receiving adjuvant ADT, with a PSA level < 0.01 ng/mL. We plan to discontinue ADT and allow testosterone recovery after completion of 24 months of continuous therapy.

Key Points
• Oligometastatic prostate cancer may be a biologically unique entity.
• Select patients with limited sites of metastatic disease benefit from prostate–directed and metastasis–directed therapy.
• Two randomized controlled trials support a progression–free survival benefit with the addition of prostate radiation therapy to systemic therapy; this benefit has translated into an overall survival advantage in select patients with low–burden metastatic disease.
• Future trials are needed to better elucidate the risks and benefits of other local therapies, such as surgery. Understanding the role of local therapy in the setting of multiple systemic therapy options will also require additional study.

Conclusion
In summary, oligometastatic prostate cancer is increasingly viewed as a unique entity separate from widely spread metastatic disease. A growing body of evidence now supports a role for local ablative therapy to the primary tumor and metastatic sites to improve disease control and potentially delay the use of ADT and its associated side effects. Novel imaging modalities will likely increase the detection of limited metastatic sites, demonstrating the importance of understanding the benefits of local or ablative therapy in this clinical scenario. Overall, radiation therapy offers a noninvasive approach that can be used to treat both the primary tumor site and metastatic sites, with a favorable toxicity profile. At present, select patients with a good performance status, limited disease sites amenable to SBRT, and a strong desire to avoid the side effects of long-term ADT may be considered for consolidative therapy after a discussion of goals of care, treatment alternatives, and shared decision making. In the future, more granular risk stratification with next-generation imaging and the integration of genomic results may help determine exactly which patients with metastatic prostate cancer will benefit most from local therapy.

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For references visit cancernetwork.com/oligometastatic-pca
**Case Presentation**

A 21-year-old woman presented in 2006 with a persistent nonproductive cough and exertional shortness of breath. Further workup of her cough revealed a mediastinal and right hilar mass. A core needle biopsy of the mass was performed, which showed dense inflammatory cells with a few Reed–Sternberg cells. Immunophenotyping revealed CD15-positive, CD30-positive, CD20-negative cells with weak PAX5 staining, suggesting a diagnosis of classical Hodgkin lymphoma. Staging workup was consistent with stage II Hodgkin lymphoma. The patient was treated with a Stanford V regimen (doxorubicin, vinblastine, etoposide, vincristine, bleomycin, mechlorethamine, and prednisone) with consolidation radiation therapy. She achieved a complete remission with therapy and did well for 8 years.

In 2013, the patient presented to the clinic with prolonged upper respiratory tract infections despite antibiotic use. She also reported fatigue, night sweats, and low-grade fevers. A 7.5-cm mediastinal mass and bilateral lung lesions were found. She underwent video-assisted thoracic surgery and wedge resection of the lung lesions. Their pathology was consistent with relapsed nodular sclerosing Hodgkin lymphoma. A pretreatment PET/CT scan revealed a hypermetabolic mediastinal mass and bilateral lung lesions, with a maximum standardized uptake value of 9.0. The patient was enrolled into a clinical trial and received a combination of bendamustine and brentuximab vedotin for 2 cycles. Following 2 cycles of therapy, a PET/CT scan reported a Deauville score of 2, consistent with a complete response. Stem cell mobilization was done after 2 cycles of therapy.

**Hope After Salvage Therapy Fails: Novel Agents for Relapsed/Refractory Hodgkin Lymphoma**

Avyakta Kallam, MD, and Julie M. Vose, MD, MBA

**ABSTRACT:** Hodgkin lymphoma is a highly curable malignancy, with an excellent prognosis. However, around 10% to 25% of patients will have primary refractory or relapsed disease, despite using risk-adapted strategies. The standard of care for patients with relapsed/refractory Hodgkin lymphoma has been cytodestruction using salvage chemotherapy, followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSTC). Studies have shown that AHSTC produces a durable response rate of 50%, and that patients achieve a complete response with salvage chemotherapy. The outcomes for patients who do not respond to salvage chemotherapy or relapse after an AHSTC have been poor, with a median survival of 25 months. However, with the approval of novel agents over the last decade, the outcomes for patients with relapsed/refractory Hodgkin lymphoma have improved significantly. In this article, we present a case of a patient with relapsed Hodgkin lymphoma who responded to salvage chemotherapy incorporating brentuximab vedotin, a novel agent.

**Perspective**

John W. Sweetenham, MD, FRCP, discusses chemotherapy-free regimens for HL on page 194.
Salvage chemotherapy was followed by an autologous hematopoietic stem cell transplantation (AHSCT). In July 2013, the patient underwent conditioning with BEAM (carmustine, etoposide, cytarabine, and melphalan), followed by autologous stem cell infusion. Following the AHSCT, she was placed on maintenance therapy with brentuximab vedotin. She received a total of 14 cycles, with subsequent cycles being held for peripheral neuropathy. She continues to do well and has been in complete remission for over 5 years.

Introduction
Hodgkin lymphoma is a highly curable malignancy, with an excellent prognosis. [1-4] Combination chemotherapy has been shown to cure 85% to 90% of patients with early-stage disease and 70% to 80% of patients with advanced disease. [2,3] However, around 10% to 25% of patients will have primary refractory or relapsed disease, despite using risk-adapted strategies. [5] The standard of care for patients with relapsed/refractory Hodgkin lymphoma has been cytocidal reduction using salvage chemotherapy, followed by high-dose chemotherapy and AHSCT. [6] Studies have shown that AHSCT produces a durable response rate of 50%, and that patients achieve complete response with salvage chemotherapy. [6,7] The outcomes for patients who do not respond to salvage chemotherapy or relapse after AHSCT have been poor, with a median survival of 25 months. [8] However, with the approval of novel agents over the last decade, the outcomes for patients with relapsed/refractory Hodgkin lymphoma have improved significantly. This article will focus on the roles of AHSCT and novel therapies in the setting of relapsed/refractory Hodgkin lymphoma.

Current Standard of Care
High-dose chemotherapy and AHSCT
High-dose chemotherapy followed by AHSCT has become the standard of care in patients with relapsed/refractory disease, based on the findings of two landmark phase III clinical trials. The BNLI study compared conventional doses of chemotherapy (mini-BEAM: carmustine 60 mg/m², etoposide 300 mg/m², cytarabine 800 mg/m², and melphalan 30 mg/m² once every 3 weeks) vs higher doses of the same chemotherapy (BEAM: carmustine 300 mg/m², etoposide 800 mg/m², cytarabine 1,600 mg/m², and melphalan 140 mg/m² once every 3 weeks). Patients who received BEAM then underwent an AHSCT. This study reported superior event-free survival rates in the BEAM plus AHSCT arm compared with the mini-BEAM arm (35% vs 10%; P = .025). [9]

The HD-R1 study randomized 161 patients with relapsed Hodgkin lymphoma to high-dose chemotherapy with AHSCT or chemotherapy alone. All patients received 2 cycles of Dexe-BEAM (BEAM regimen plus dexamethasone) and were then randomized to AHSCT or 2 additional cycles of chemotherapy. [10] The 3-year survival rate in the AHSCT arm was 55% vs 34% in the chemotherapy arm. The study did not show a statistically significant benefit in overall survival; however, this was thought to be due to low patient numbers. [10]

Role of salvage chemotherapy
Response to salvage chemotherapy is a strong prognostic marker for predicting long-term outcomes with AHSCT. Studies have shown that patients with a negative PET/CT scan at the time of AHSCT have far superior outcomes compared with patients with a positive PET/CT scan following salvage chemotherapy. [7,11,12] Moskowitz et al evaluated patients treated with sequential salvage therapy and reported a 5-year event-free survival rate of 31% in patients with a positive PET scan vs 75% in patients with a negative PET scan. [7] In patients with primary refractory disease, the 10-year event-free survival rate following salvage therapy was 68% in patients with a negative PET scan vs 33% for patients with a positive PET scan. [11] A meta-analysis of 745 patients with Hodgkin lymphoma reported an overall survival rate of 17% to 77% in patients who were PET-positive at the end of salvage chemotherapy compared with 78% to 100% in PET-negative patients. [12] The varying results were due to different criteria used for determination of disease status and varying salvage chemotherapy regimens.

The optimal salvage chemotherapy regimen in patients with relapsed/refractory Hodgkin lymphoma has been debated. Several options have been proposed, such as Dexe-BEAM [10] or a combination of dexamethasone, high-dose cytarabine, and cisplatin (DHAP). [13] with...
In recent years, the development of front-line treatment strategies for Hodgkin lymphoma has been based on two main—and to some extent—competing principles: improving disease control and reducing the potential for long-term toxicity. The latter is incredibly important in this predominantly young patient population. The emergence of early “interim” functional imaging has allowed for the development of protocols aimed at maintaining efficacy while de-escalating treatment in those with favorable-risk disease to reduce the potential for late toxicity. For those with poor-risk disease, identified by persistently positive interim imaging, various strategies are under investigation, some of which involve the use of more intensive chemotherapy regimens, and others that introduce novel agents early in the course of treatment.

As Dr. Kallam and Dr. Vose describe in the accompanying article, agents now being evaluated as part of front-line therapy for Hodgkin lymphoma have emerged from studies of patients with relapsed and refractory disease. Until recently, treatment options for patients with relapsed and refractory Hodgkin lymphoma were very limited. Salvage chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT) has been the standard of care for more than 20 years (and still is), resulting in long-term disease-free survival for about 50% of patients.

With an improved understanding of the biology of Reed–Sternberg cells and of the unique tumor microenvironment in Hodgkin lymphoma, many new targeted therapies have been shown to have clinical activity. For some agents, such as brentuximab vedotin, this has led to new US Food and Drug Administration-approved indications, such as maintenance therapy after ASCT for high-risk patients. This treatment, as well as other new treatments, are being investigated as components of front-line therapy based on promising phase II trial results, and the prospect of chemotherapy-free regimens for Hodgkin lymphoma is now closer to becoming a clinical reality.

The outcome for patients with relapsed disease is improving. The use of brentuximab vedotin as maintenance therapy for high-risk patients undergoing high-dose therapy has resulted in improvements in progression-free survival for certain patients, although the effect on overall survival has not yet been reported. It also remains unclear whether this approach is beneficial to patients who are PET-negative immediately prior to transplant. The remarkable activity of checkpoint inhibitors and the promise of several other agents have allowed some patients to avoid or delay the necessity for ASCT.

Acknowledging the importance of achieving PET negativity following salvage therapy, several regimens incorporating novel agents are under investigation to achieve a better response before proceeding with high-dose chemotherapy and AH SCT. A review of novel agents and several combinations follows.

comparable outcomes. In the United States, the most common regimen is ifosfamide, carboplatin, and etoposide (ICE). Studies evaluating this regimen have reported overall response rates ranging from 84% to 88%.[14,15]

Radiation therapy is often overlooked as a salvage regimen in the setting of relapsed disease. However, it can induce durable remission and should be explored as a treatment option in patients with localized relapses. Studies have shown a survival benefit with involved-field radiation therapy in patients with residual disease after salvage therapy.[16,17]
Novel Agents Under Investigation
Brentuximab vedotin

Brentuximab vedotin is a CD30-targeted antibody–drug conjugate. The CD30 antibody is conjugated to monomethyl auristatin E (MMAE), an anti-microtubule agent.[18] Upon binding with the CD30 receptor on the Reed–Sternberg cells, the antibody–drug conjugate gets internalized. Once internalized, MMAE is released, causing apoptosis.[19]

In 2011, the US Food and Drug Administration (FDA) approved brentuximab vedotin for relapsed/refractory Hodgkin lymphoma based on the results of a pivotal phase II trial, in which the agent was given to 102 patients with relapsed/refractory disease who progressed following an AHSCST. The overall response rate was 75%, with a complete response noted in 34% of patients.[20] A subsequent 5-year follow-up study by Chen et al showed a 5-year overall survival rate of 41%. With a median 35-month follow-up, the estimated progression-free survival and overall survival were 9.3 and 40.5 months, respectively.[21] In a study by Gopal et al, it was shown that, of the patients who achieved a complete response, 47% remained in remission at a median follow-up of 53.3 months, establishing the durability of response.[22] The most common adverse reactions noted were peripheral neuropathy, neutropenia, fatigue, and diarrhea.[21] These promising results led to the exploration of brentuximab vedotin in different clinical scenarios in patients with relapsed Hodgkin lymphoma.

Brentuximab vedotin as a first-line salvage regimen. Single-agent brentuximab vedotin was evaluated in patients with relapsed/refractory Hodgkin lymphoma as a salvage therapy, prior to proceeding with high-dose chemotherapy and AHSCST. Brentuximab vedotin was administered weekly at 1.2 mg/kg for 3 weeks. Following 2 to 3 cycles, a PET scan was completed, and patients who had achieved PET negativity underwent AHSCST. Patients who had a positive PET received ICE prior to AHSCST. The 3-year progression-free survival rate was 79%. [23] When brentuximab vedotin was administered at a standard dose of 1.8 mg/kg every 3 weeks, 35% of patients achieved a complete response after brentuximab vedotin alone, with minimal side effects.[24]

Brentuximab vedotin with bendamustine. Bendamustine is a nitrogen mustard derivative with partial cross-resistance to other alkylating agents, thus giving it the potential for use in the refractory setting. Single-agent bendamustine was evaluated in 36 patients with relapsed/refractory Hodgkin lymphoma who had progressed through multiple lines of therapy. The overall response rate was 53%, demonstrating that bendamustine is an active agent in heavily pretreated patients. Thrombocytopenia was the most common toxicity, with 20% of patients experiencing grade 3 or 4 thrombocytopenia.[25]

In another trial, bendamustine was combined with brentuximab vedotin as first salvage therapy in patients with relapsed/refractory Hodgkin lymphoma. [26] Fifty patients were enrolled and received 1.8 mg/kg brentuximab vedotin on day 1, with bendamustine 90 mg/m² given on days 1 and 2 of up to 6 total 3-week cycles. The complete response rate was 74%, with an overall response rate of 93%. Stem cell collection was successful in 93% of patients. The estimated 2-year progression-free survival rate was 70% in patients who underwent AHSCST. Infusion reactions were seen in 56% of patients, which were then mitigated by premedications.[26]

Brentuximab vedotin is also being studied in combination with standard chemotherapy combinations, such as ICE[27] and DHAP.[28] Preliminary results are promising, with complete response rates of between 69% and 90%, which are comparable to response rates seen with standard chemotherapy regimens alone.[27,28]

Brentuximab vedotin as consolidation therapy post-AHSCST. Several studies have shown that AHSCST cures 50% of patients.[29,30] Since the prognosis for patients who relapse post-AHSCST is poor, identification of patients at a high risk of relapse is important. Primary refractory disease, extranodal disease, relapse within 12 months of front-line therapy, and residual disease at the time of high-dose therapy have consistently been identified as poor prognostic factors.[14,31,32]

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Phase</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV + ICE</td>
<td>NCT02227199</td>
<td>Phase I/IIa</td>
<td>Salvage therapy at first relapse</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>NCT01902160</td>
<td>Phase I</td>
<td>Relapsed HL</td>
</tr>
<tr>
<td>BV + gemcitabine</td>
<td>NCT01808662</td>
<td>Phase I/II</td>
<td>Salvage therapy at first relapse</td>
</tr>
<tr>
<td>BV + temsirolimus</td>
<td>NCT01412307</td>
<td>Phase Ib</td>
<td>Relapsed HL, post-AHSCST</td>
</tr>
</tbody>
</table>

ASCT = autologous stem cell transplantation; BV = brentuximab vedotin; ICE = ifosfamide, carboplatin, and etoposide; NCT = National Clinical Trials.
AETHERA was a multicenter study that randomized 320 patients with high-risk relapsed/refractory Hodgkin lymphoma who had undergone an AH SCT to receive 16 cycles of brentuximab vedotin or placebo.[32] High-risk disease was defined as patients having one of the following risk factors for progression: primary refractory disease, progression within 12 months of initial therapy, or extranodal involvement. The progression-free survival rate was superior in patients who received brentuximab vedotin vs placebo (43 months vs 24 months; hazard ratio [HR], 0.52; 95% CI, 0.37–0.71). A 5-year follow-up showed a continued benefit, with a 5-year progression-free survival rate of 59% in the brentuximab vedotin arm vs 41% in the placebo arm (HR, 0.521; 95% CI, 0.379–0.717).[33]

**Checkpoint inhibitors**

Hodgkin lymphoma is histologically characterized by Reed–Sternberg cells, which are surrounded by inflammatory T-cell infiltration. Alterations in chromosome 9p24.1 within Hodgkin lymphoma cells lead to upregulation of programmed death ligand 1 (PD-L1) and 2 (PD-L2) on the surface of the Reed–Sternberg cells, thus making checkpoint inhibitors a potential therapy.[34] Anti–PD-1 antibodies, such as nivolumab and pembrolizumab, have been evaluated in patients with relapsed/refractory disease in two pivotal studies, with promising results.[35,36]

In the first such study, nivolumab was evaluated in patients who had progressed following AH SCT and brentuximab vedotin, a group associated with poor prognosis.[35] A total of 80 patients were enrolled, and nivolumab was administered every 2 weeks until disease progression occurred. The overall response rate was 66%, with a median duration of response of 7.8 months. The promising results of this study led to the FDA approval of nivolumab in this setting in 2016. The second pivotal study, KEYNOTE-087, was a single-arm phase II study of pembrolizumab in patients with chemotherapy-refractory disease or those who had progressed following an AH SCT. The overall response rate was 69%, with a complete response rate of 22%.[36] The median progression-free survival exceeded 1 year, which led to the FDA approval of pembrolizumab in this setting in 2017.

Both nivolumab and pembrolizumab are well tolerated; immune-related adverse events include: hypothyroidism/hyperthyroidism (12% to 16%), rash (6% to 9%), hepatitis (5%), and pneumonitis (3%). Grade 3/4 adverse events are rare, including gastrointestinal toxicities and neutropenia (both < 5%).[35,36]

Avelumab, an anti–PD-L1 monoclonal antibody, has also shown promising activity in Hodgkin lymphoma. A phase I study of avelumab in 31 patients with relapsed/refractory Hodgkin lymphoma showed a 42% overall response rate and a 16% complete response rate.[37] Further studies involving PD-L1 antibodies are ongoing.

Across the board, a remarkable feature of checkpoint inhibitors is the continued clinical benefit seen with treatment that extends beyond disease progression.[38] In a phase II study, 70 patients who experienced disease progression on nivolumab were continued on the therapy for a median of 5.2 months.[39] Of the 51 evaluable patients, 60% had a decreased or stable tumor burden. The median time to the next systemic therapy was 8.8 months, with a 1-year overall survival rate of 84%.[39]

**Brentuximab vedotin and nivolumab**

Combination therapy with brentuximab vedotin and nivolumab is being evaluated as an initial salvage therapy in patients with relapsed/refractory Hodgkin lymphoma.[1] In a clinical trial, 62 patients were enrolled and administered up to 4 cycles of combination therapy. The complete response rate was 61%, with an objective response rate of 82%. This therapy did not impact stem cell collection and was fairly well tolerated, with grade 3 or higher immune events noted in 13% of patients. A phase III study evaluating the efficacy of this regimen in patients who are ineligible for AH SCT is ongoing (ClinicalTrials.gov identifier: NCT03138499).

Other checkpoint inhibitors are being evaluated in combination therapies, particularly with additional checkpoint blockade with cytotoxic T-lymphocyte–associated antigen 4 inhibitors or cytotoxic chemotherapy, in both the front-line and refractory settings.[40] Additionally, studies that combine different novel agents for the treatment of relapsed Hodgkin lymphoma are being designed (Table).

**Histone deacetylase inhibitors**

Panobinostat and mocetinostat target histone deacetylase, which plays a role in cell cycle progression, angiogenesis, and cell survival. In a clinical trial of 129 patients with relapsed/refractory Hodgkin lymphoma, patients received 40 mg of oral panobinostat 3 times a week.[41] A decrease in tumor size was seen in 74% of patients, with an overall response rate of 27%. The median duration of response and progression-free survival were 6.9 months and 6.1 months, respectively, thus making it an effective therapy for Hodgkin lymphoma. Panobinostat was reasonably well tolerated, with the most common side effects being grade 1/2 nausea and fatigue.

Relapses occur in 10% to 20% of Hodgkin lymphoma patients with favorable features and early-stage disease, as well as 30% to 40% of patients with advanced disease. Source: Ther Adv Hematol. 2017;8:293-302.
The most common grade 3/4 side effect was thrombocytopenia, which was easily regulated.[41]

Studies evaluating combination therapies with lenalidomide as a potential salvage therapy are ongoing. The results of one phase I study testing panobinostat and lenalidomide in heavily pretreated patients with Hodgkin lymphoma were promising, with an overall response rate of 30%.[42] A phase Ib/IIa study evaluated panobinostat in combination with ICE (P-ICE) vs ICE in patients with relapsed/refractory Hodgkin lymphoma. A complete response was seen in 82% and 67% of patients who received P-ICE and ICE, respectively. However, in the ICE group, grade 4 thrombocytopenia was seen in 100% of patients, and grade 4 neutropenia occurred in 55% of patients. [43] Further studies investigating a combination of panobinostat with less myelosuppressive agents are ongoing.

mTOR inhibitors
The phosphatidylinositol 3-kinase (PI3K)/ mammalian target of rapamycin (mTOR) signaling pathway has been found to be active in Hodgkin lymphoma, and is therefore a potential target for novel agents.[44] Everolimus is one such oral agent that targets the mTOR complex 1. A phase II study was conducted in 19 patients with heavily pretreated relapsed/refractory Hodgkin lymphoma.[45] These patients had received a median of 6 prior treatments, and 84% had undergone a prior AH SCT. The overall response rate was 45%, while 6% achieved a complete response and 39% achieved a partial response. The median progression-free survival and overall survival were 9 months and 36 months, respectively, thus making everolimus a potential agent for use in relapsed Hodgkin lymphoma.[45] The combination of everolimus with agents that specifically target other signal transduction pathways—such as the JAK/STAT pathway and the NF-kappa B pathway—may potentially prolong the duration of response.

**Lenalidomide**
Lenalidomide is an immunomodulatory agent that has additional antiangiogenesis properties. In a phase II study, the efficacy of lenalidomide was evaluated among 38 patients with heavily pretreated Hodgkin lymphoma who had received a median of 4 prior therapies before enrollment.[46] Patients received 25 mg/day of lenalidomide on days 1 to 21 of a 28-day cycle. The overall response rate was 19%; 1 patient achieved a complete response, 6 achieved a partial response, and 5 patients had stable disease. The drug was fairly well tolerated, thus confirming the moderate efficacy of lenalidomide in treating patients with Hodgkin lymphoma.[46]

**JAK inhibitors**
JAK is a family of tyrosine kinases that are involved in signal transduction from cell surface receptors. Phosphorylation of JAK results in recruitment of STAT proteins, which are involved in cell proliferation and survival.[47] The JAK/STAT pathway has been found to be activated in Hodgkin lymphoma, thus making it a potential target for therapy. Pacritinib is a JAK2 inhibitor that has been tested in clinical trials of patients with relapsed/refractory Hodgkin lymphoma. A total of 34 patients were enrolled, and an overall response rate of 14% was noted.[48] In light of this poor single-agent response, subsequent studies have looked at combination therapies. One such clinical trial evaluated the combination of an oral PI3K-delta inhibitor (INCB040093) and itacitinib, an oral JAK2 selective inhibitor.[49] Seventeen patients with relapsed/refractory Hodgkin lymphoma were enrolled. All patients were heavily pretreated, and 82% had undergone a previous AH SCT. The overall response rate was 67%, including 2 complete responses. The treatment was well tolerated, and further studies using this combination are ongoing.[49]

**ADCT-301**
ADCT-301 is an antibody-drug conjugate, with a CD25 antibody conjugated to a pyrrolobenzodiazepine toxin. CD25 is expressed on the surface of Hodgkin lymphoma cells, thus making it a potential therapy target.[50] Phase I studies have shown activity in heavily pretreated patients with relapsed/refractory Hodgkin lymphoma. In one such study of 22 patients, the progression-free survival rate was 64% and the complete response rate was 27%. The most common adverse events reported were fatigue, rash, nausea, and mucositis.[50] Further studies are ongoing based on the results from the early-phase studies.

**Chimeric antigen receptor (CAR) T-cell therapy**
Since success has been seen with CAR T-cell therapy in treating patients with relapsed/refractory non-Hodgkin lymphomas and leukemias, the use of CAR T cells that target the CD30 receptor on Reed–Sternberg Hodgkin lymphoma cells is being explored.[51] One phase I trial of CD30-specific CAR T cells enrolled 18 patients with relapsed/refractory Hodgkin lymphoma. The overall response rate was 39%, with 7 of 18 patients achieving a partial response.[52] Additional studies evaluating anti-CD30 CAR T cells in relapsed Hodgkin lymphoma are ongoing (ClinicalTrials.gov identifiers: NCT02690545, NCT02917083).

Brentuximab vedotin has led to the success of antibody-drug conjugates and has shown significant clinical activity in Hodgkin lymphoma.

Conclusion
The outcomes of patients with relapsed and refractory Hodgkin lymphoma have improved significantly with the advent of antibody-based therapies (eg, brentuximab vedotin) and immunotherapies. With several targeted therapies and CAR T cells showing promising results in early-phase trials, the future is bright for patients with Hodgkin lymphoma. Integrating these novel agents into existing treatment guidelines and developing safe and effective combination therapies are the next steps in optimizing the clinical outcomes in this disease.

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