

Kevin Oeffinger at the Duke Cancer Institute in Durham, North Carolina, advises a cancer survivor.

THERAPY

The cost of beating cancer

Children who survive aren't out of the woods — the treatment that saved them can cause major health issues.

BY MICHAEL EISENSTEIN

Beating cancer is supposed to be the hard part. And after vanquishing Hodgkin's lymphoma, many patients and their families are understandably eager to leave behind doctors and hospitals and move on with their lives.

Survivors often have most of their life still ahead of them, because Hodgkin's lymphoma is very much a disease of the young. In the United States, it is the most common cancer in people aged 15–19 according to the American Cancer Society, with a median age of diagnosis in the mid-20s. Fortunately, the odds of long-term recovery are excellent. “For early-stage disease, the cure rate is over 90%,” says Andrea Ng, a radiation oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts. “And for advanced-stage patients, it's probably still around 80%.”

But radiation and chemotherapy take a toll on the body. Survivors generally have an increased risk of other forms of cancer and greater vulnerability to heart problems. For example, studies

indicate that Hodgkin's survivors are 2–7 times more likely to die from cardiovascular disease than the general population. This means that oncologists face some difficult conversations during treatment. “I remember going through this with one mother, and she looked at me as if to say, ‘Can I see somebody else?’” recalls Melissa Hudson, director of the cancer-survivorship division at St Jude Children's Research Hospital in Memphis, Tennessee.

Oncologists are now aware of the long-term health risks of chemotherapy and radiation, and today's treatments have become safer and more precise. Nevertheless, young survivors often do not receive the targeted medical attention that they require in the decades after beating cancer, and some clinicians are concerned about missed opportunities to protect their patients. “They feel great and treatment is over and they don't want to think about these things,” says Kevin Oeffinger, a family physician at the Duke Cancer Institute in Durham, North Carolina. “But a proactive approach can avoid so much trouble and make a lifetime of difference.”

Hodgkin's lymphoma is sensitive to both

radiation and chemotherapy, and doctors have been achieving high cure rates for more than 50 years. However, it quickly became apparent that recovery carried a high cost. “By the early 1980s, we had an 82% cure rate,” says Oeffinger. “But as these patients got into their 20s and 30s, they started having major problems.”

Side effects were initially chronicled at a handful of centres, including St Jude, which established a programme for monitoring the long-term health of cancer survivors in 1984. The hospital's patient registry revealed a disconcerting trend: young adults who had been successfully treated for Hodgkin's lymphoma were developing secondary malignancies of the type that would usually only occur in late middle age. “We were receiving calls asking us, ‘I have breast cancer — could this be related?’” says Hudson.

OFF-TARGET EFFECTS

Because Hodgkin's lymphoma often affects upper-body lymph nodes, treatment has historically entailed bombarding the torso and neck with radiation. This ‘mantle-field’ radiotherapy approach can inflict considerable collateral damage on the lung and breast, and these are common sites for secondary malignancies. A 2003 study by paediatric oncologist Smita Bhatia and colleagues found that nearly one-quarter of Hodgkin's-lymphoma survivors out of a cohort of 1,380 had developed solid tumours in the 30 years after treatment (S. Bhatia *et al. J. Clin. Oncol.* **21**, 4386–4394; 2003). “These solid tumours have a latency of about 10–15 years post-treatment,” says Bhatia, now at the University of Alabama at Birmingham. “However, then the incidence climbs and climbs, and we haven't seen a plateau yet.”

Radiotherapy and chemotherapy can both contribute to heart problems. Doctors began seeing heart attacks and heart failure in Hodgkin's-lymphoma survivors in their 20s and 30s, says Oeffinger, much younger than the typical onset of such conditions. Anthracycline drugs — a core component of the drug cocktails administered for this cancer and other common malignancies — are particularly damaging to the heart and blood vessels. A 2017 study led by researchers in the Netherlands tracked survivors treated for Hodgkin's between 1965 and 1995, and found that combining anthracycline-based regimens with radiation nearly tripled the long-term risk of heart failure relative to radiation alone (F. A. van Nimwegen *et al. Blood* **129**, 2257–2265; 2017).

Several large-scale survivorship studies are now monitoring the long-term health of patients who were successfully treated for Hodgkin's and other cancers in their youth. For example, a team led by Flora van Leeuwen at the Netherlands Cancer Institute in Amsterdam has been studying a cohort of 7,000 European Hodgkin's survivors. And in the United States, Hudson is the principal investigator on the St Jude Lifetime Cohort Study (SJLIFE), another long-term cancer-survivorship study. It has been running for more than a decade and

has enrolled more than 4,000 people who have been successfully treated for various paediatric cancers.

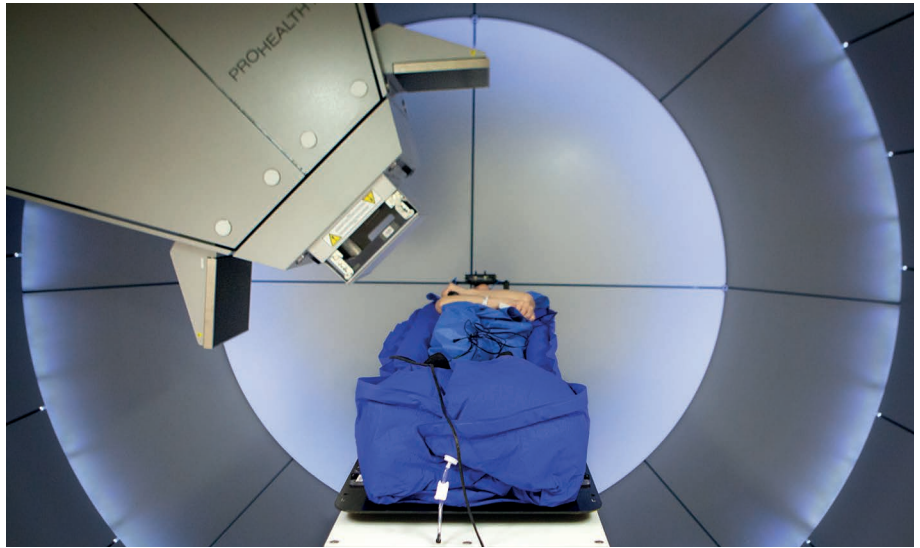
Hudson notes that findings from SJLIFE have confirmed previous observations about accelerated organ degeneration. “What we’re seeing is a clinical phenotype that is really more for people in their 60s or 70s in a population where the median age is people in their mid-30s,” she says. And the data have also yielded some unpleasant surprises. For example, the treatment of paediatric non-Hodgkin’s lymphoma — a much rarer disease than Hodgkin’s lymphoma in young people — often exposes the central nervous system to toxic chemotherapy. This can cause lasting cognitive and mental deficits, affecting survivors’ academic, career and social prospects. And even though the brain is generally not directly exposed to such toxic compounds during treatment for Hodgkin’s lymphoma, Hudson and her St Jude colleague Kevin Krull have observed evidence of similar cognitive problems in SJLIFE Hodgkin’s survivors that seem to be related to secondary effects of cardiac and pulmonary dysfunction.

ETERNAL VIGILANCE

Hodgkin’s treatment has evolved considerably, guided by lessons from survivorship studies. For example, mantle-field radiation has been replaced by more precise, imaging-guided strategies. “It’s now very focused on the tumour, minimizing the risk of collateral damage to the breast tissue and other areas,” says Bhatia. Treatment is also being personalized on the basis of a patient’s outlook, so oncologists can cut back on or even skip highly toxic regimens.

But low risk does not mean no risk — especially when the goal is curative treatment. Because many Hodgkin’s malignancies occur adjacent to the heart or lungs, it is almost impossible to protect these organs entirely. Omitting radiation often means a longer course of chemotherapy — substituting one source of toxicity for another. And although the potential damage from anthracyclines is well established, these drugs remain highly effective and will not be replaced any time soon. A watered-down treatment regimen also raises the risk of relapse. Recurrent disease is not a death sentence — Ng estimates a post-relapse cure rate of 60–70% — but it requires more-aggressive treatments that can have severe effects on long-term health.

The good news is that oncologists are aware of the health risks of lymphoma treatment, and now regularly screen survivors with tests for complications such as cardiovascular disease or breast or colorectal cancer. Cancer centres keep a close eye on people in the years immediately following treatment, and some survivorship programmes continue surveillance well into adulthood. “We typically try to see our childhood cancer survivors once a year,” says Bhatia. “We also ask them about school performance or problems with work, to see if that triggers any suspicion of cognitive



Proton-beam therapy might reduce the amount of radiation exposure that a patient receives.

impairment.” Monitoring also encompasses behavioural factors affecting long-term recovery. For example, obesity and smoking can dramatically increase the risk of complications such as lung cancer.

Unfortunately, most people who have survived Hodgkin’s leave the care of dedicated oncologists after five cancer-free years — a commonly used clinical milestone for a ‘cure’. This leaves them with community practitioners who are unfamiliar with their particular health risks, and thus may be ill-equipped to guide them. To fill this void, some survivorship specialists encourage their patients to take the initiative. For example, Bhatia prepares brief ‘cheat sheets’ that enable patients to relay details of

“They feel great and treatment is over and they don’t want to think about these things.”

their treatment history and recommended screening tests to their health-care providers. Such efforts can help, but they also require a collaborative doctor–patient relationship. “Some doctors accept patients’ advocacy,” Hudson says. “But others just look at them like ‘what are you talking about?’”

The oncology community is exploring options that might broaden access to care — for example, Bhatia envisions close partnerships between dedicated cancer-survivorship programmes and community practitioners. In the ongoing EMPOWER-II clinical trial, Oeffinger is investigating the use of smartphones to relay important information about medical care to patients and doctors in the form of text messages and video vignettes. “We’re learning how to ‘activate’ primary-care practices, and get the right information at the right time to the right physician,” he says.

Cancer doctors still see considerable opportunities to eliminate, or at least reduce, the cost of a cure. Several studies have found genetic factors that predispose certain patients to particular complications. Research by Bhatia

and colleagues, for example, indicates that pre-existing mutations might render some patients especially vulnerable to damage from radiation. Her team is now looking for genetic and physiological signatures that might lead to personalized treatment regimens. “If I know that 10% of kids who are exposed to anthracyclines are going to develop heart failure,” she says, “can I identify that 10% up front and use some other treatments to prevent that from happening?”

A HEALTHIER FUTURE

Advanced treatment options could also contribute to healthier survivorship. A radiotherapy approach called proton-beam therapy, for example, might enable more precise killing of cancer cells, although the technique is still too young for long-term survivorship data to be available. “On paper, at least, it seems to result in lower radiation doses to organs-at-risk in most patients,” Ng says. Likewise, people with recurrent Hodgkin’s lymphoma now have access to therapies that target molecular features of the tumour, as well as drugs that can stimulate an aggressive immune counter-attack against cancer. These might prove safer than conventional chemotherapy, but this remains to be demonstrated over the long run.

For now, the hard conversations will continue — although there are ways to make them easier. Oeffinger cites the importance of countering what he calls Damocles syndrome, a reference to the legendary Ancient Greek courtier who sat through a feast under the shadow of a sword suspended by a single hair. Fortunately, the knowledge that researchers and clinicians have accrued can confer considerable agency to survivors, enabling them to make informed decisions to safeguard their own health. “We present it as cause for celebration,” says Bhatia. “You’ve finished your treatment, and we now need to turn your attention to the rest of your life.” ■

Michael Eisenstein is a freelance science writer in Philadelphia, Pennsylvania.