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About the Cover

The term metastasis brings to mind the migration or spread of cancer cells from one part of the body to another. The effects of cancer are equally complex and far reaching, as patients and families navigate through the process of diagnosis and treatment. Artist Laura Reed of Albuquerque, New Mexico, portrays the uncontrolled, dynamic nature of cancer in her cover illustration inspired by the Directed Reading that begins on Page 17.
Stay Tuned!
More Classics will be coming your way.
Lean Management Improves Patient Care

Kim Harrison, R.T.(R)(T)

ThedaCare is a community health system comprised of 4 hospitals and 20 physician practices in Wisconsin. With nearly 5400 employees, it is the third largest health care employer in the state and is dedicated to delivering world-class care for its patients. With a focused commitment to improvement, 6 years ago ThedaCare hired Simpler Healthcare to teach hospital staff how to apply lean management, a practice that eliminates wasteful processes that do not increase value to the customer. Implementing lean strategies hospital wide would relieve overburdened employees, improve patient care and decrease costs.

Focusing on Patient Care

Radiation therapists at ThedaCare have been an instrumental part of the radiation oncology department’s lean management team, which has experienced breakthrough results since implementation. Simpler Healthcare senseis, or lean management coaches, began the lean transformation by helping hospital staff identify which parts of the treatment process were of greatest value from the patient’s perspective. ThedaCare examined each step in the patient’s experience, from checking in with the receptionist to receiving treatment to getting test results.

The Problem

ThedaCare discovered that patients only found value in one-tenth of their current treatment process and that patients found the most value in face-to-face interactions with hospital staff. ThedaCare needed a solution that would focus on patient care and help relieve overburdened staff.

The Process

The 8 therapists in the ThedaCare radiation oncology department work as a team to seek improvement daily. To help facilitate this process, the radiation oncology department initiated an actionable item log for radiation therapists and staff to record wastes and defects they see in their daily tasks. Wastes are discussed each morning during the department’s “leadership huddle.” In the huddle, the lead radiation therapists, physicist and nurses meet with the department’s managers and lean facilitor for 30 minutes to discuss action plans, productivity and current lean management projects.

The forum allows the lead radiation therapists daily interactions with management to discuss where the department needs improvement, how managers can provide resources to implement the improvements and what solutions have been successful. Suggestions such as moving equipment or furniture out of the way to improve workflow and redirecting resources as demand changes are a few examples of the ongoing improvements employees are encouraged to recognize and suggest.

Radiation therapists also participate in rapid improvement events. In a rapid improvement event, the sensei leads selected members of the radiation oncology unit, administration and patients in an intensive forum in which new ideas to eliminate waste are tested and put in place.

The Results

The radiation therapists have been empowered to work as a team, which has fostered a community of problem solvers and a culture of no fear. By implementing lean management, the radiation oncology department can provide employees with a forum to understand glitches in processes and develop a plan to remedy those defects.

The results consistently have been significant. In 2008, the radiation oncology department improved productivity by 30%, increased gross revenue by 24% and reduced the time from patient referral to treatment by 44%. In addition, lean management has helped relieve overburdened staff, allowing them to focus on patient care.
The outcomes of radiation therapy treatments depend on the accuracy and precision of the treatment. Several technological advancements, such as the introduction and evolution of record and verify software systems, have improved patient outcomes and reduced treatment errors. It is important that radiation therapists are aware of the history and future of radiation therapy and oncology systems software and the impact it has on the profession.

More than 1.4 million people are diagnosed with cancer each year in the United States. Approximately 60% of these patients will receive radiation therapy as part of their treatment plan. The outcomes of these treatments depend on the accuracy and precision of the radiation fields. Information technology has improved the accuracy of radiation treatments, with the most significant advancements occurring within the past 3 decades. As software systems developed in the 1970s evolved, technological advancements followed, which led to improved patient treatment processes and outcomes. These technological advancements necessitated creation of new software applications. The most noticeable software evolution was the transformation of the original record and verify software systems to computer-based integrated oncology management systems in which the software actually controlled the treatment parameters. The introduction and evolution of these systems has influenced how radiation therapists deliver treatment. More than 12,000 radiation therapists have entered the profession since commercial record and verify systems became available. Although it is important that these therapists learn the historical aspects of these systems, it is also imperative that the profession realizes the changes new oncology management systems will bring.

System History
Modern radiation therapy treatment machines were developed in the 1950s. The introduction of megavoltage treatment machines transformed the radiation therapy field. Although there were many benefits, a major advantage to radiation therapy treatments was that the equipment enabled patients to be treated easily from multiple angles, which allowed for an increase in dose and, ultimately, an increase in tumor control. Patients received more fractions of radiation from more treatment fields. Although patient outcomes improved, the development of these treatment standards increased the opportunity for error.

In the late 1970s, delivery of radiation treatment required radiation therapists to set between 15 and 20 parameters manually per patient, including field size, collimator angle and gantry angle. Because the potential for random treatment errors was substantial, equipment vendors and radiation therapy institutions developed record and verify software systems. Record and verify systems are software programs that "detect and prevent treatment mistakes by inhibiting the radiation beam when the parameters set on the treatment machine do not agree with the prescribed deviations." Simply, record and verify systems do not allow the radiation therapist to enable the equipment and treat a patient if the parameters are set incorrectly.

The initial record and verify software systems were institution specific. Software was loaded on microcomputers and each treatment machine had its own system. Patient data were stored on secondary media, such as cassettes, diskettes, paper tape or paper cards. Although this was the first step to decrease treatment errors, the programs were limited in function. Verification was restricted to an individual treatment machine, and the system could not generate reports for scheduling, billing or research. In addition, the media that patient data were stored on were unreliable.

The software evolved in the 1980s to a centralized record and verify system networked to numerous treatment machines. Memorial Sloan-Kettering Cancer Center in New York City, New York, was 1 of the first radiation therapy departments to publish its experience with a centralized radiation therapy record and verify system. The software had many benefits, including creation of reports that required data from the entire patient population, statistical analysis of these reports to use for research purposes, the ability to transfer patients between treatment machines, and increased disk space to...
save patient data. The greatest setback occurred in the communication between treatment machines. Although each machine would communicate to a central computer, the machines did not communicate in the same format or level of data. To overcome initial difficulties, interfaces between the machines and host computer were developed. Communication standards also were developed to normalize data transmission and prevent “beam on” when the parameters were not within limits.7

With a central computer system, reports that were impossible to generate with the initial system became possible. Patient demographic data and the treatment prescription now were entered into the system. Patient treatment and verification failure records also were captured. Retaining standardized data in a central, secure location allowed many reports to be created (see Box 1).7

Radiation therapists at Milwaukee Regional Medical Center in Wauwatosa, Wisconsin, published the details of a networked record and verify system implementation. A Metamatic III Record and Verify System (Siemens Healthcare, Malvern, Pennsylvania) was installed at the facility in January 1984 and offered many benefits (see Box 2). Using the record and verify system was simple. First, the patient’s hospital identification number was entered to display his or her treatment setup information on the computer monitors. Because of networking capabilities, monitors could be used in the treatment and control rooms to expedite patient setup. After the patient was aligned for treatment, the software took 1 minute to verify treatment parameters. After treatment, the system recorded the treatment data and printed a card, with abnormal treatment parameters printed in red ink. This card was a backup for the manual treatment chart.8

Commercialization

Over the next 10 years, there were several technological advancements, such as multileaf collimators (MLC), dynamic wedges and asymmetric jaws, and an increase in available commercial record and verify software systems. Because of 3-D treatment planning and MLC, radiation treatments became more complex and the opportunity for errors increased. These factors encouraged the widespread adoption of record and verify software systems.9

By the mid-1990s, commercially available record and verify systems evolved to a networked client-server environment. Microsoft Windows-based operating systems (Microsoft Corporation, Redmond, Washington) were integrated, and the client network used Transmission Control Protocol/Internet Protocol (TCP/IP) addressing. Interfaces existed between treatment planning equipment, treatment machine workstations, MLC workstations, linear accelerators and the network.9

Prior to record and verify systems, treatment with an MLC field was a complex process. Without the interfaces, a therapist had to go to the separate MLC workstations to select each field and send the leaves into position. Another therapist would need to go into the treatment room to check the light field on the patient. Checks between the therapists were required in the treatment room and at the console. Even with the cross-checks, treatments were susceptible to error. With the record and verify system, the computers automatically communicated with each other. MLC leaves automatically would drive into place for each field. Automated record and verify software also had preset functions for the jaw, collimator, gantry and table, all of which could be controlled by the pendant.9

In addition to the complex issues with MLC, another flaw with early record and verify systems was the amount of data that needed to be entered manually. The manual process allowed numerous opportunities for transcription errors.2 Commercial record and verify systems allowed for direct download of simulation data to the treatment field; however, no data transfer interface yet existed for 3-D treatment planning systems.9

Klein et al reported that implementing a commercial record and verify system positively affected a radiation oncology department.9 Integrating the MLC and the preset features allowed 2 therapists to control and complete patient treatments efficiently.
rather than 3. Staffing decreased by 1.5 full-time therapists without increased errors in treatment. Klein et al also reported that the software system significantly reduced the amount of data entry errors. 9

The evolution to the integrated and interfaced record and verify software system actually transformed the systems into computer-control systems because the record and verify system controlled the treatment parameters.8 As with the initial record and verify prototypes, computer-controlled treatment delivery systems were designed to improve efficiency of treatments, which led to decreased costs, reduced errors and increased accuracy and complexity of the treatments.

Researchers from the University of Michigan Health Systems in Ann Arbor, Michigan, published a study documenting the effect of a computer-controlled treatment delivery system on treatment delivery errors.10 Within 15 months, the researchers analyzed 34,463 treatments, including 114,083 individual treatment fields, on 4 different treatment machines. The majority of the 152 documented errors occurred on the treatment machines that still had the manual treatment delivery mode. These machines had an error rate of 0.21 % per segment; the error rate on the machines with computer-controlled treatment delivery was only 0.085 % per segment. It also is important to note that the machines equipped with computer-controlled treatment delivery software provided patients more complex treatments in the same time as the machines with manual treatment delivery.10

The introduction of computer-controlled treatment delivery software systems had a profound impact on the field of radiation therapy. The system design that allowed networking of computers through vendor-provided interfaces propelled the invention of technologies and innovative treatment techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). Treatments became more complex, while efficiency and safety remained consistent. Like the original record and verify systems, computer-controlled treatment delivery software systems decreased random treatment errors. An unintended consequence was the increase in susceptibility to systemic errors. Macklin et al published findings that 15 % of treatment delivery errors could be attributed to the use of a record and verify system.11 Paton et al reported that in a 1-year period, 23 % of the documented errors were related to the software system.12 Fraas et al suggested that a complete re-evaluation of a department’s quality assurance (QA) testing and evaluation process could minimize these errors.10

There are specific QA issues that a radiation therapy department must pay attention to in order to decrease opportunity for errors.2 The first involves data transfer. As treatment techniques become more complex, the amount of data and different types of data systems that interface also have increased. QA programs must adapt and review information and images from all data sources in weekly chart rounds. Another QA issue that needs to be defined is how to verify accuracy of complex treatment parameters. Fraas suggested using the computer-controlled treatment delivery software system to run reports of the recorded treatment parameters and any abnormal variations from the planned treatments.2 Fraas further emphasized that QA procedures need to be developed to ensure that human review is not lost to automation.2

Goldwein et al suggested that record and verify or computer-controlled treatment delivery software systems improve patient safety as long as they do not replace common sense and clinical judgment.13 Simply stated, “technology should not be blamed for its misapplication any more than a safe automobile should be blamed for car wrecks.”15 Although information technology is designed to improve safety of health care applications, it does not replace safety checklists and procedures.

Recent Innovations

In addition to record and verify software systems, other recently developed information technology applications include the computerized physician order entry system (CPOE), integrated radiology information management systems and the electronic medical record (EMR). The evolution of information technology in the radiation oncology department integrates all of the systems to improve patient safety. Oncology information management systems have been developed to manage the complexities of cancer care. These systems are similar to EMRs. They have the ability to manage patient schedules, as well as administrative, financial and clinical information.12

It is necessary for radiation therapy departments to transition to an oncology management system to meet the demands of today’s health care consumers and stakeholders. Managing oncology patient data is more complex than in other specialties. For example, chemotherapy regimens must be calculated and monitored closely; radiation treatment must be planned, verified and recorded; and the data must be readily available and stored for long periods.14 Oncology management systems have many benefits (see Box 3). In 2000, the Institute of Medicine published Enhancing Data Systems to Improve the Quality of Cancer Care and stated that adopting an information technology system “can improve the timeliness and accuracy of information on the quality of cancer care.”16 An integrated oncology management system is needed to maintain excellent communication among the
entire oncology treatment team and provide efficient, quality care for patients.

There are several components to an oncology management system. Based on facility needs, the software system can be purchased from vendors as a complete package or separate applications. Oncology management systems are designed to provide information technology applications for all aspects of the cancer center, from diagnosis to long-term follow up. Many departments can benefit from this type of system, such as medical oncology, radiation oncology, oncology clinical laboratories, pathology laboratories, medical imaging and cancer registry. Although there are several commercial oncology management systems available, the applications that they offer are similar (see Box 4).15,17-18

Commercial Systems

An important aspect of the commercial systems is the interface to external software systems. The interfaces are designed to communicate with Health Level 7 (HL7) compliant software systems. HL7 defines electronic data exchange standards to maintain data integrity as it is transferred between software systems.19 Incorporating the interfaces in the software system design facilitates the exchange of patient information between all health information systems, such as laboratory information systems, admission, discharge and transfer systems, CPOE systems and billing and accounts receivable.15,17,19 Another characteristic of the interface design is the accommodation of open architecture software systems that simplify data transfer between systems.15,17

The oncology management system MOSAIQ (IMPAC Medical Systems Inc., Mountain View, California) has a component labeled the external system interface (ESI) manager.15 This element manages and administers the interchange of data, manages multiple interfaces at the same time and executes user-defined data mapping. The ESI manager uses TCP/IP protocols, which allow the software to coexist in any health care environment. IMPAC also has created a virtual interface for certain classes of software systems or equipment, which allows quick conformity to new devices.15 This option also is available with the LANTIS oncology management system (Siemens Medical Solutions, Malvern, Pennsylvania). Their Gateway module creates interfaces with other HL7 systems.18

One of the major components of oncology management systems is the central EMR with scheduling capabilities. With interfaces, users can view patients’ complete schedules throughout the cancer center and other facilities. Most scheduling views can be customized for the patient or the user.15,17 The ARIA oncology management system (Varian Medical Systems, Palo Alto, California) can synchronize with Microsoft Outlook’s calendar to manage user schedules.17

Documentation and electronic note creation is another major aspect of the system’s EMR component. Users have 2 primary options for this module to meet the needs of their organization: traditional dictation and transcription or predefined note applications. With the use of document import, providers can use traditional dictation and transcription methods, either from an onsite or offsite transcription agency. Once the transcribed documents are imported into the information management system, providers can complete online review, editing and approval. The process is easy to use and allows efficient document distribution to referring providers.15 Providers also can choose to use predefined, structured note applications. This helps eliminate transcription costs and decrease coding errors.15,17 Another advantage of oncology management systems is the easy handling

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**Box 3**

**Benefits of an Oncology Management System**

- Increased efficiency
- Improved productivity
- Ability to mandate stricter accountability
- Increased medical record security
- Increased cost containment
- Streamlined workflow
- Data reporting
- Ensured accuracy of oncology treatment

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**Box 4**

**Common Commercial Oncology Management System Features**

- A central EMR with scheduling functions, note and documentation applications
- CPOE applications
- Billing and account receivable functions
- Remote access resources
- Advanced reporting capabilities
- Advanced imaging storage
- Radiation oncology record and verify applications, including computer-controlled applications
and accuracy of patient documents. Transcriptions, consent forms and scanned external documentation can be stored digitally.18

A third component of the oncology EMR is the patient assessment tool. Commercial systems are equipped with standard patient assessment tools that include chemotherapy and radiation therapy side effects plus quality of life indicators. These features can be customized for treatment site or treatment regimen.15,17 MOSAIQ alerts providers with laboratory results or assessments that are not within the preset limitations.15 ARIA can graph changes in vital signs and laboratory results to help identify trends in patients or patient populations. Toxicities also can be managed with the customized graphs or groupings.17 The HL7-compliant interfaces allow data from other information systems to be imported and integrated in the oncology management system.

CPOE and Integrated EMR

An oncology CPOE system is an important element in the oncology management system. Radiation therapy and chemotherapy prescriptions are very complex. Oncology CPOE not only provides a venue for ordering the primary treatment plan, but supportive treatments as well. A customizable treatment calendar helps manage all patient appointments.15 ARIA offers a rule-based decision engine for medical oncology applications, which has automatic safeguards to check drug contraindications and dose limits of medication.17 Using the EMR and standardized care plans allows oncologists to ensure patients are receiving evidence-based treatment regimens.20

Although the integrated EMR is important for clinical functions, the billing component of the oncology management system equally is important for administrative functions. This application helps organizations track insurance authorizations, referral expiration dates and visit limitations. The system can alert users when referrals or visit limits need to be renewed. The capability of advanced charge capture helps reduce coding inconsistencies, redundant charges or lost charges.15 For example, after incorporating IMPAC’s software system charge audit process, South Carolina Oncology Associates found $750,000 in missed charges.14 ARIA minimizes lost charges by tracking all completed activities to export charges and relative value units. This system also has the ability to separate technical and professional charges.17

Another important application that oncology management systems offer is the remote access function. Wireless technology allows for portability of the EMR.15 Thin client workstations or tablet computers can be used in exam rooms or at the point of care to decrease intrusion on patients.17 MOSAIQ offers an internet portal for users to access the EMR remotely in real time. This allows access to patient information anytime, anywhere.15 A Web-based portal can be used for telemedicine and teleconsultation services.21 LANTIS can use a single database for multiple satellite clinics, which improves providers’ access to patient information.18

Box 5

Report Benefits

Prevent lost charges with charge audits
Study referral patterns to develop marketing plans
Examine payer mix before expanding programs
Improve patient outcome reporting
Identify root causes for problematic situations
Scrutinize workflow trends to determine staffing needs

Reporting

One of the most beneficial applications for oncology operations is the advanced reporting functions the system offers. The system is a data clearinghouse where everything that a patient experiences or reports is captured.22 Oncology management systems can take the raw data and interpret it to create reports that can be used for decision making. Tools can represent data graphically for users to depict trends. The data also can be exported to spreadsheets or word processing applications for further analysis or distribution. The reports offer several benefits (see Box 5).15,18 The robust database also can be used for benchmarking or research. Third-party payers for health services likely will demand outcome assessment and performance improvement that only comprehensive information systems can offer.22

Data mining within the data repository also may prove beneficial. Johnstone et al described using data mining techniques to review electronic portal image reviews by physicians.23 From the data reports, they developed a quality improvement tool to facilitate the review and approval of portal images. Each week, the tool analyzed the data in the repository and calculated the percentage of electronic portal images that had been reviewed, including specification per oncologist. This report then is sent by e-mail to the entire faculty, so individual physicians can compare their performance with their peers.23

Information Management

Although all aspects of cancer care would benefit from implementing an oncology management system, the dramatic evolution of the technological innovations in radiation therapy demands it.
EVOLUTION OF ONCOLOGY MANAGEMENT SYSTEMS

Radiation therapy requires precise setup, consistent delivery and accurate documentation. Oncology management systems integrate record and verify software with image management and EMR. IMRT and IGRT rely on computers and mandate effective image management and data storage. IGRT alone has added perhaps gigabytes of data to an individual patient treatment record and all related information must be accessed efficiently and securely.

To maintain data integrity for future needs, data is stored in Digital Imaging and Communications in Medicine (DICOM) or Extensible Markup Language (XML) formats. To manage the increase in images used specifically for radiation therapy treatment management, oncology picture archiving and communication systems (PACS) are being developed. Oncology PACS storage area networks start with a minimum storage of 2 terabytes. Facilities can purchase PACS as part of their oncology management systems or use an interface to communicate with an independent system. Oncology PACS are single, central data repositories specially designed for oncology data. One PACS requirement is that they communicate in a DICOM language. Like HL7, DICOM provides communication standards for sharing electronic data. DICOM3 is the most recent version of the standards and describes the types of information that should be in a DICOM format. These are called information object definitions (IODs) and there are several specific to radiation oncology (see Box 6). The DICOM communications interface allows all important radiation therapy information, such as recorded treatment parameters, treatment fields, MLC plans and radiation therapy treatment plans, to be imported into the patient’s electronic chart. The IODs can be stored in a variety of file formats (eg, BMP, JPG, MP3, PDF and TIF). The administrator can configure rules for storage, data management and security levels based on facility needs.

Box 6

IODs Specific to Radiation Oncology

- Simulation images
- Digitally reconstructed radiographs
- Portal images
- Isodose lines
- Dose-volume histograms
- Computed tomography, beam definitions
- Data from the record and verify system
- Radiation treatment summary

Moving Forward

Imaging for daily treatment verification has allowed an increase in complexity in radiation therapy treatments. As the complexity increases, the need for accurate QA measures also increases. Oncology management systems have radiation therapy QA aspects integrated within the software applications. MOSAIQ can capture and document QA of the treatment beams prior to treatment. The test can be reviewed through the system at any time and is stored in the patient’s chart. ARIA has a similar feature for IMRT plans.

A major barrier to adopting EMRs is the concern that more work will be created; however, Pizziferri et al documented that the EMR does not require more time than traditional paper charting methods. Han et al shared this conclusion in a paper that also investigated the impact implementation would have on radiation oncology department team members in a Japanese radiation oncology department. The nursing and clerical staff had an average decrease in workload of 85.7%; simulation therapists decreased their workload by 61%; and the treatment therapists experienced a 20% decrease in workload. Dosimetry and physics staff had a workload increase of 21% because of increased double checks after data transfer.

Further studies should be completed in the United States to understand the impact of oncology management systems on staff workload.

A final application that will help radiation therapy treatment outcomes and research is the use of oncology management systems for managing clinical trials. Up-to-date records and patient contact information enhance the accuracy of documentation. Oncology management systems also can document whether the patient is enrolled in a clinical trial, and this information is accessible to all users. MOSAIQ offers Trial Check, which automatically screens patient data and advises users about possible clinical trials the patient qualifies for. The potential use of this application will transform oncology patient treatment. A recent study at the University of Wisconsin Paul P Carbone Comprehensive Cancer Center found that 60% of newly diagnosed cancer patients reported that they were never informed that clinical trials were a treatment option for them.

Oncology management systems will continue to evolve and improve integration between other programs and systems. According to Heather Davis, Midwest sales manager for IMPAC:

As technologies evolve, the EMR is becoming more and more an integral part of the clinical workflow and a critical component of patient outcomes. IMPAC’s oncology software already accommodates a full billing and accounts receivable section, electronic prescriptions that can be sent...
to neighborhood pharmacies, hospital/lab orders and also the introduction of self-assisted patient kiosks (September 2008).

Davis added, as radiation oncology continues to experience technical and treatment innovations, the need for oncology management systems will continue to evolve to improve experiences for users and patients alike (written communication, September 2008).

Conclusion

Record and verify systems have changed the way radiation therapy is delivered and facilitated many innovations. The field of radiation oncology will continue to experience technological advancements, but will be successful only if information technology keeps pace. Oncology management systems and other information technology applications will ensure the accuracy and safety of patient treatments, as they transform the way in which the treatments are delivered. The widespread adoption of EMRs and integration of information technology programs and systems will continue to evolve and change many processes in health care. Radiation therapists should play an important role in the selection and implementation of these systems, as well as appreciate and embrace the changes that they bring.

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20. With IMPAC’s EMR we give better care, save money, operate more efficiently.
EVOLUTION OF ONCOLOGY MANAGEMENT SYSTEMS


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The Metastatic Process
Teresa G Odle, BA

After completing this article, readers should be able to:

◆ Discuss theories concerning metastatic pathways and mechanics.
◆ Explain the role of metastasis in cancer staging and prognosis.
◆ Describe how metastasis is somewhat site specific and why.
◆ Discuss the basic biology and molecular biology of metastasis.
◆ Summarize diagnosis and treatment strategies for metastasis and the role of radiation therapy in treating metastasis.

When a patient receives a cancer diagnosis, concern first focuses on arresting growth and effects of the primary tumor. Despite improved diagnosis and treatment techniques for cancer patients, most deaths from cancer result from metastases. Metastasis is the leading cause of cancer morbidity, as well as mortality. From the Greek meta- for “after, beyond or over,” the prefix of metastasis signifies change or transformation. Stasis denotes “stand or stationary.” Together, the word metastasis means a change in the location of the disease and transferring of the disease from one organ or part of the body to another.

As early as the 16th century, French surgeon Henry LeDran first noted that breast cancer that had spread to axillary lymph nodes resulted in much poorer outcomes than localized tumors. In 1889, Stephen Paget published the definitive article on metastasis, espousing his “seed and soil hypothesis.” Over the years, other researchers have studied the metastatic phenomenon to learn how to better detect and arrest the process. Isaiah J Fidler spent many years studying metastasis, first demonstrating that it is a nonrandom process and later demonstrating the varying metastatic potential of cancer cells. With several decades of research now reviewed on the genetic basis of cancer, scientists are just beginning to understand the molecular biology of metastasis.

Metastasis is the final step in progression of neoplastic disease and although metastases might not be evident for many years following diagnosis and treatment of the primary tumor, the metastatic process can begin before a primary tumor is diagnosed. About 50% of patients already have metastases by the time their primary cancer is detected, thus leading to arguments and difficult decision processes regarding treatment. Is it too late to treat metastases because the cells already have escaped? Metastasis is a complicated process involving the growth and characteristics of the primary tumor, migration of cells and proliferation and survival of the cells in a distant organ or body part. Metastasis is also the most important factor in determining a cancer patient’s survival.

The involvement of lymph nodes in the metastatic chain and detection of metastatic cells in regional or sentinel lymph nodes is critical to cancer management and prognosis for a cancer patient. Adding to the complexity of the process and dormancy of metastatic cells is that some tumors are highly aggressive and likely to metastasize, while others remain locally invasive but have low metastatic potential.

Biology of Metastases
Beginning with the primary tumor, the progression of cancer is a complex biological process and our understanding of
THE METASTATIC PROCESS

this process has evolved considerably in recent years.\textsuperscript{1,12} Progression to metastasis involves multiple sequential steps; these steps are wellorchestrated but dependent on a number of intricate and distinct events involving the cancer cells and the “host” environment.\textsuperscript{11} Each of the steps is considered “rate limiting,” meaning that if a tumor cell fails to complete any step, the metastatic process effectively terminates.\textsuperscript{1} The steps include intravasation, circulation, arrest in a new organ, extravasation, local migration and growth in the new organ (see Figure 1).\textsuperscript{6,13}

Models and Theories of Metastasis

Paget’s original 1889 seed and soil hypothesis was based on the theory that cancerous cells that were disseminated needed an appropriate host environment.\textsuperscript{9} He published the following question and hypothesis:

What is it that decides what organs shall suffer in a case of disseminated cancer? If the remote organs in such a case are all alike passive and, so to speak, helpless — all equally ready to receive and nourish a particle of the primary growth which may “slip though the lungs” and so be brought to them — then the distribution of cancer throughout the body must be a matter of chance. But if we can trace any sort of rule or sequence in the distribution of cancer, any relation between the character of the primary growth and the situation of the secondary growths derived from it, then the remote organs cannot be altogether passive or indifferent as regards embolism…. Every single cancer cell must be regarded as an organism, alive and capable of development. When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil….\textsuperscript{3}

As Paget observed the frequency with which metastases occurred in lymph nodes and certain organs vs others, he noted the inconsistencies in blood supplies to favored and unfavored sites. Metastasis thus required a willing seed, or certain cellular characteristics, and hospitable soil, or a compatible host organ.\textsuperscript{3} Paget’s seed and soil hypothesis was challenged in 1928 by James Ewing, who favored mechanical factors brought about by vascular system reorganization in the anatomy. Later, Schackert and Fidler experimented with injecting melanoma cells into the bloodstream of mice and observed that different cells formed or did not form tumors in the meninges. Everett Sugarbaker reported that common regional metastases could be attributed to mechanical and anatomical explanations, but distant metastases from various cancers were site specific. For many years, researchers have continued to study the preferential growth of metastases in specific organs and environments.\textsuperscript{1} Although research continues today to further explain the entire metastatic process, including its nonrandom nature, numerous studies support the basis of Paget’s 19th century hypothesis.\textsuperscript{9}

In the past, a primary tumor’s metastatic potential was believed to relate to its size and the number of cell population doublings. Sometimes referred to...
as the “classic hypothesis” of how tumor metastasis occurs, it failed to explain metastases from small tumors, slow-growing tumors and those limited by anatomical boundaries. Bert Vogelstein and colleagues championed this theory into the early 1990s. However, more recent data emerged to suggest that primary tumors with characteristics once considered noninvasive could contain cells that lead to metastatic tumor development. Today, scientists are identifying tumor-encoded genes that enable the transition of cells to metastases.

Researchers now accept that there are elements of various theories to consider in understanding the metastatic process. The classic hypothesis includes the established seed and soil theory, host climate also is important to metastatic growth, and as molecular genetics studies continue, more proof emerges of gene expression patterns in some primary tumor cells that predispose them to metastasis.

**Role of the Primary Tumor in Metastasis**

Understanding and managing the primary tumor are critical to managing metastases because the process begins in the primary tumor. Under the classic hypothesis of tumor metastasis, clinicians believed strongly in eradicating the local and regional cancer. An improperly managed primary tumor can result in recurrence, which studies have shown results in higher rates of metastases than is the case with locally controlled primary tumors.

In situ cancers are some of the earliest tumors detected. These small, localized tumors might be only a few millimeters in size and usually are avascular. Several factors lead to triggering of angiogenesis, or development of new and differentiated blood vessels. The vascularized tumor grows more rapidly, leading to breaching of basement membranes and other natural barriers. The newly formed vascular system also can serve as the vehicle for disseminating cells from the primary tumor. A larger tumor normally serves as a clinical marker for increased risk of metastasis. The causal relation is not clear, however. A simple explanation could be that larger tumors can disperse more cells, increasing chances that a viable metastatic tumor will form. Genetic expressions might explain the correlation.

It also is likely that rapidly growing malignancies are highly vascular. This increases the probability that tumor cells will gain access to the systemic circulation and disseminate to distant organs. Research has shown that “hot spots” of highly intensive vascular development can indicate prognosis in tumors of the prostate, breast, bladder, stomach and colon. Tumors can outgrow their blood supply and become hypoxic, or oxygen deficient. When this occurs, the microenvironment of the tumor changes, altering its malignant and metastatic potential. Research also has shown that certain tumors can continue growing without angiogenesis, relying instead on nearby pre-existing blood vessels. But formation of a new vascular system might closely relate to tumor cell entry to the bloodstream.

Normal cells go through the process of apoptosis, or programmed cell death. In most solid cancers, mutations alter the cell’s ability to undergo apoptosis, so the cancerous cells continue to proliferate instead of dying. Cancer cells also can develop resistance to apoptosis, a special form of apoptosis in which cells lose adhesion to the extracellular matrix on which they are growing and maintain a state of suspension. Metastatic cells must be resistant to both of these processes so they can survive to travel to and re-establish in distant sites.

Most cells in a solid tumor cannot cause metastasis, but a small group of cells possesses metastatic potential. Work in the past few decades has identified genes and sets of genes within primary tumors most likely to overcome barriers in the metastatic process. Among these are genes prone to initiating metastasis. Signatures have been identified for breast, ovarian and prostate cancers. The CD44 + surface marker is an example of a subset of breast tumor cells associated with poor prognosis.

Research also has shown that the role of the primary tumor in metastasis might go beyond providing cells that disseminate to form tumors elsewhere. Kaplan and colleagues reported in 2005 that primary tumors can communicate with metastatic host environments before the cancerous cells reach the distant site, preconditioning the new environment to more suitably “welcome” and accommodate the cells. Scientists are attempting to decode the language used to enable the tumor-host dialogue. Investigations involve the potential role of stem cells and the theory that only mutated cancer stem cells migrate and give rise to metastasis.

**Pathways to Metastatic Invasion**

A primary tumor can spread and invade regional tissues, such as when cervical cancer extends to the bladder. Often, these early-invading tumors are accompanied by higher mortality risk because they metastasize early in their development. Some tumors metastasize across body cavities or along the spaces between the endothelium and basement membrane. For example, ovarian cancer can spread through the abdomen’s peritoneal cavity to the peritoneal surface of the intestine; pancreatic cancers can spread along neurons.

The dissemination of metastatic cancer cells typically involves the lymphatic system and the hematogenous system, or more specifically the veins. It begins with intravasation, or entrance of the cells into the blood or lymphatic systems.
cells can be shed per gram weight of a solid tumor into the bloodstream or lymphatic system per day; they travel through the blood system from the primary site to secondary sites in a matter of seconds. Not all of these cells will survive and colonize in a distant site. Studies show that most metastatic cells that enter the bloodstream are eliminated rapidly and fail to form metastases.1,8 Lymphatic channels are thin walled and venous and offer little resistance to tumor cell penetration.1 Some reports suggest that certain types of cancers more likely metastasize through blood or lymphatics. For example, it has long been reported that carcinomas primarily metastasize through the lymphatic system and sarcomas are more likely to spread via the blood system. Dividing the 2 systems is generally an arbitrary exercise because the disseminating cells can pass from one to another.1,8

How tumors shed their cells and invade these systems is not understood completely. Mechanically, tumor growth enables breaches of the basement membranes and surrounding tissues, capillaries, lymph vessels and similarly penetrable structures.8 Mechanics alone do not explain the cells’ motility; the cells not only must penetrate these barriers but assemble enough force to propel from the extracellular matrix to the cytoskeleton, the network responsible for organizing and moving cells. Naturally occurring proteinases, chemokine gradients and other motility mechanisms help the cells enter and exit the circulation.3,9 Once in the bloodstream, tumor cells can grow within the blood vessel or traverse the vessel wall and access underlying tissue.

Platelets play a role in hematogenous metastasis. Research has shown a number of ways in which these colorless bodies in the blood that aid in clotting also may aid in metastasis. Examples include the release of mediators that might augment expression of integrin receptors on tumor cells and the tendency of some primary tumor cells to express receptors that recruit platelets. The gathering of platelets increases potential for tumor cells to survive on vascular surfaces and to adhere at a new site.1 Lymphatic vessels help regulate interstitial fluid volume and absorb dietary fat. They also serve immune system functions and as a transmission route for cancer metastasis. The first layer of lymphatic vasculature is located in the superficial dermis layer of the skin. Also referred to as lymphatic capillaries or initial lymphatics, they can be penetrated and take in fluid easily. The next layer is precollecting lymphatic vessels, which are located in the deep dermis. They drain into the collecting lymphatics, which are located in the subcutaneous layer of tissue. They flow efficiently, and recent research has shown that the lymphatic vessels can dilate in response to certain tumor growth factors, making them more efficient at transporting tumor cells to lymph nodes throughout the body.4

Precisely why tumor cells move toward a preferred lymph node or group of nodes is not understood clearly. Passive drainage once was believed to be the reason, as the invading tumor eroded vessel walls. Recent evidence points to a cellular interaction between the tumor cells and the lymphatic endothelium.4 Tumor markers can alter normal lymphatic vessel growth, a process called lymphangiogenesis.8,9 It still is unclear whether metastasis through lymphatics is an active molecular process or is due to the passive transport to draining nodes.9

In traditional research on drainage of tumor cells into lymph nodes, much attention has focused on regional and sentinel nodes. The sentinel node is believed to be the first node to receive tumor cells in lymphatic drainage from a tumor.1,8,9 Micrometastasis to lymph nodes usually occurs before most primary tumors can be detected clinically.4 Once the tumor cells invade the lymphatic channels, tumor emboli can become trapped in the first lymph node they encounter. It also is possible that tumor cells will bypass these regional lymph nodes and move on to distal nodes, a metastatic indicator. There is debate about whether the regional lymph nodes can trap tumor cells, thus functioning as a temporary barrier to further tumor cell dissemination.1

Lymph node status is critical to staging, prognosis, forming disease management strategies and, ultimately, to the patient’s survival. Use of the sentinel lymph node in evaluation of cancer has become commonplace.19,20 In staging of breast cancer and melanoma, lymphoscintigraphy has replaced lymphadenectomy in some cases. For the most part, lymphatic drainage patterns in breast cancer are consistent. Wall et al reported on the complications of predicting lymphatic drainage patterns from truncal melanoma, which are less predictable than patterns for melanoma of the extremities (see Figure 2).21 Patients with melanoma on the trunk and with multiple channel drainage to multiple nodal basins have poorer prognoses, although the literature provides mixed data on the impact of multiple channel drainage on survival. Wall and colleagues reported that multiple lymph channels facilitate the metastatic process and are an independent risk factor for mortality in melanoma and suggested that these findings could be applicable to other cancers that tend to spread via lymphatics.21

The survival of tumor cells in the metastatic cascade — whether through lymphatic or hematogenous dissemination — depends on their ability to elude natural immune and inflammatory cells and processes. Tumor cells also must resist shear forces, such as turbulence within vessels, as well as other forces. Their predetermined metastatic potential extends to
this step in the process, as cells that successfully navigate from the primary tumor to the new metastatic site have been shown to express progression genes that mediate their survival in the circulation.6,9

**Extravasation and Colonization**

The success rate for each circulating cancer cell is <0.1%. This has been termed “metastatic inefficiency.” To form a metastatic tumor, cells first must survive in circulation, and then form emboli that lodge in the distant organ’s capillary bed. The emboli adhere to the capillary endothelium at the distant site. As these arrested cells develop, subtle microenvironmental changes that support metastatic tumor development occur.8,22

Characteristics of the primary tumor cells can trigger many of these actions, including attachment to the endothelium and cooperation against the host organ microenvironment. Research shows the primary tumor also can activate recruitment of bone marrow cells that facilitate metastasis.22 The cells leave the circulation by migrating through the vascular wall, a process called extravasation. They can become established quickly in the new local environment and proliferate, forming a lesion in the host organ. This often is called colonization.6,9 How this early growth is regulated remains unclear. Some tumor cells or emboli arrest at different sites and remain dormant or do not replicate appreciably; the dormancy phase can last several years. Other cells might proliferate actively if the host tissue changes or a suitable environment develops.9,22

As researchers begin to understand the genetic basis of cancer and the metastatic process, they also are beginning to classify metastasis virulence genes. These genes may be responsible for the selective advantage that benefits metastatic cells at the distant site. Virulence genes might explain why circulating cells can perform the mechanical action of arresting in an organ’s capillary bed, although the growth of the metastatic lesion depends on the host site’s ability to support tumor growth.6 Adhesion molecules are particularly important because metastatic cells must adhere to other cells to arrive at the host organ site, as well as to cells of the host organ’s extracellular matrix when they arrive.3 Metastases are unicellular in origin, much like primary tumors. The more metastatic the tumor cells, the more likely the lesion is to grow in a supportive microenvironment.1

**Metastatic Site Selection**

In addition to the many barriers tumor cells must overcome to reach a distant site and form a metastatic tumor, they also can acquire the ability to colonize certain organs preferentially.2 Clinicians long have recognized that primary tumors arising in certain organs tend to metastasize to particular distant sites (see Table). Some of the correlations can be explained by the nature of a tissue’s venous structure, lymphatic drainage pattern or other natural channels. For example, a tumor near a pleural or peritoneal space may shed its cells directly into that space and spread to other organs connected to the cavity.6 Blood flow explains why the liver is a common metastatic site for primary colorectal cancers.9 Other organ site patterns are less easily explained.

Paget weighed in on the predictable distribution of metastases and compatibility of primary and
host organ with his seed and soil hypothesis, stating that tumor cells only will grow in the appropriate tissue microenvironment. Subsequent research has supported his theory, as the adhesion molecule receptors on the host organ’s endothelial cells and mechanisms to encourage response to organ-specific growth factors engage. As with other steps in the metastatic process, genetic markers, such as chemokine receptors, likely play a role in the link between the primary tumor site and the metastatic secondary tumor site and in the subsequent survival and growth of the tumor.3,9,10 Breast cancer cells express certain oncogenes known to generate central nervous system metastasis. The link might be explained by certain related growth factors at the cellular level. Likewise, colon and pancreatic carcinoma cells overexpress oncogenes that respond to a hepatocyte growth factor in the liver.9 Certain cell-bound and tissue-bound enzymes and adhesion and homing molecules are part of the intricate biological network of site-specific metastases.11 Tumor cells express some genes, such as osteopontin, that are common to metastases at all sites, while others are expressed selectively to grow in a particular tissue.9 Genetic profiling of lung, bone and adrenal gland metastases from human breast cancer cell lines that were injected in animal models showed a tendency to prefer the same organs.10 The genetic profiles of metastatic site selection are highly complex and most likely require a combination of site-specific genes for successful metastasis to occur. Scientists have identified the surface molecules and endothelial bed receptors on major organ systems in animal models for the lungs, joints and brain but still have much to learn.9,10

Lymph nodes are important to the cascade effect of organ-specific metastatic patterns and in the diagnosis and staging of metastatic disease. Although regional lymph node metastases can develop at a high rate from many primary cancers, the lymph nodes are not vital organs and their metastatic involvement will not cause mortality and morbidity. However, lymph node involvement might indicate probability of future loss of function and death. Researchers continue to debate whether metastatic disease in the lymph nodes spreads from node to node sequentially or as a result of additional shedding of cells from the primary tumor. The same concept could apply to multiple organ metastases.10

Research suggests that some metastasis suppressors might regulate metastasis to some sites but not others. There is variation in metastatic site patterns and much to learn.9 Following are examples of metastasis by primary tumor site:

■ Up to 75% of young patients with papillary thyroid carcinoma have regional lymph node metastases on routine nodal dissections, but their rate of distant metastasis is <3% and is confined entirely to the lung. They also have a 99% disease-free survival rate at the 20-year mark.

■ Duodenal carcinoid tumors ranging in diameter from 8 mm to 1.5 cm are shown to have a high lymph node metastatic rate but low mortality, even when the lymph node metastases are bulky, multiple or recurrent.

■ Patients with primary tumors in a variety of organs, but no lymph node involvement, die of metastases in systemic vital organs.10

■ Between 30% and 74% of patients with early-stage breast cancer have been found to have breast cancer cells in their bone marrow.7

■ Most long-term survivors of lung, gastric, colorectal or breast cancers who had lymph node metastases at the time of surgery to the primary tumor had 1, 2 or occasionally 5 positive lymph nodes.10

As demonstrated in the Table, several organs more commonly serve as sites for metastases. Tumors at these sites lead to considerable morbidity and mortality among cancer patients. Patterns vary but offer enough clues to help in evaluating metastases after identification of a primary tumor or to identify the primary site that may have led to a metastatic lesion if the metastasis was detected before the primary cancer. Following are brief descriptions of metastatic patterns from some common cancers.

### Table

#### Frequent Sites of Metastasis for Selected Primary Tumor Sites

<table>
<thead>
<tr>
<th>Primary Tumor Site</th>
<th>Metastatic Tumor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Bone, lung, liver, brain; contralateral breast through lymphatics</td>
</tr>
<tr>
<td>Lung</td>
<td>Brain, bone</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Liver, lung</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lung, liver, bone</td>
</tr>
<tr>
<td>Prostate</td>
<td>Bone</td>
</tr>
<tr>
<td>Ovary</td>
<td>Abdomen, liver, lung</td>
</tr>
<tr>
<td>Testis</td>
<td>Lung, liver</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Lung, liver</td>
</tr>
</tbody>
</table>

*Axillary or regional lymph node involvement not included.*
Breast Cancer

Patients who die from breast cancer die primarily from metastatic disease, often many years after successful treatment of the primary cancer.25 Once metastasis occurs, a patient’s chance of long-term survival plunges from 90% to 5%.26 Breast cancer tends to metastasize more frequently to certain organs, most notably the bone and lungs. The next most frequently colonized organs from the breast are the liver and brain.9,26 Early in the 20th century, William Halsted’s theory concerning distant metastasis from breast cancer prevailed. His theory centered on local spread of the disease in a contiguous manner from the primary site through the lymphatics. He therefore promoted aggressive local control of the disease, leading to radical mastectomy. A systemic approach soon arose to explain subsequent metastases in distant sites after aggressive local surgery.27 Halsted’s theory could not explain the common spread of breast cancer to the long bones, however.9

Bernard Fisher and other clinicians broke breast cancer metastases into 2 distinct groups: tumor cells that could metastasize to different sites and those that could not. Fisher et al promoted early systemic treatment based on the theory that the metastasis already had occurred at the time of primary tumor diagnosis. Most clinical trial evidence supported the systemic theory until recently. Some patients benefit from improved screening and earlier diagnosis, suggesting that dissemination of metastatic cells might be influenced by the timing of diagnosis. Trials also support a link between local control of the primary cancer and survival. It appears that a combination of systemic therapy and local control that includes radiation therapy addresses both possibilities.27 Several studies have identified the gene expression signatures in primary breast tumors that present highest risk for metastasis.26 Research continues into the host and tumor characteristics associated with breast cancer metastasis.25,27

Lung Cancer

In addition to local spread, lung cancer may spread regionally through the lymphatic system or to distant sites by hematogenous dissemination. Some lung cancers display a higher incidence of distant metastases. For example, undifferentiated small cell carcinoma, or oat cell cancer, metastasizes to distant sites more than nonsmall cell lung cancer (NSCLC). Of the NSCLCs, adenocarcinoma tends to spread to distant sites more than others.28 NSCLC carries a high risk of brain metastases; reports show a rate of up to 44% at autopsy. When lung cancer spreads to the brain, it often happens early relative to other primary tumors and causes neurological symptoms. Many patients with NSCLC have been reported to have overexpression of an epidermal growth factor receptor, an indicator of poor prognosis.29 Lung cancer metastases to the bone have been reported to be as high as 44%, with spinal metastasis rates of up to 26%. Oghihara et al retrospectively studied 144 patients with spinal metastases from lung cancer.30 Among patients with NSCLC with spinal metastases, 6-month survival rates were about 37%; at 2 years, survival was only 2.1%. Median survival time for these patients was about 4.5 months. Small cell lung cancer patients’ survival rates in the study were 37% at 6 months and 0% at 2 years, with a median survival time of 4.9 months.30

Up to 90% of patients with distant metastases from the lungs have been found to have lymphatic metastases. Hematogenous spread also has been reported, with multiple distant organs involved.28

Prostate Cancer

Prostate cancer is a leading cause of cancer deaths among North American men and the most common cancer among older men. Mortality from prostate cancer usually is a result of metastasis caused by hormone-refractory cells.1 Screening for prostate cancer with prostate specific antigen (PSA) tests has decreased the incidence of lymph node metastasis in patients with early-stage prostate cancers. Subsequent research has led to use of PSA score, Gleason grade and clinical stage to predict involvement of pelvic lymphatics. Prognosis is closely related to the presence of metastases in these regional nodes. Patients with positive pelvic nodes have a > 85% probability of distant metastases at 10 years compared with a < 20% chance in patients with negative pelvic nodes. Negative prognosis is based on multiple regional node involvement rather than single node involvement. When a single node is involved, 5-year survival rates might be as high as 60% to 80%; rates decrease to 20% to 54% with multiple node involvement.31

Blood flow might explain the propensity of prostate cancer to spread to the vertebrae.9 Research has focused on cytokine-inducible endothelial cell glycoprotein that prostate tumor cells may use to promote metastasis to bone; bone-derived chemokines, such as osteopontin, might explain the high colonization of bone in prostate and breast cancers.1 A number of genetic markers have been identified for prostate cancer as well as benign conditions of the prostate since the advent of PSA as an indicator for prostate cancer.9 Experimental models have looked at metastasis modifier genes in prostate cancer.9

Colorectal Cancer

Nearly 150,000 new cases of colon and rectal cancer are diagnosed in the United States each year.
THE METASTATIC PROCESS

and nearly 50,000 people die from the disease annually. The colon and rectum have different anatomies and offer different patterns of spread. The portal system offers direct access to the liver from the large bowel and therefore is the most common site of colorectal metastasis, the lung is the second most common site. Lymph node status is important to prognosis in colon cancer.

Among metastatic disease, tumors arising from colorectal cancer in the lung or liver can be resected with some success. Patients who have had surgical resection to the liver or lung for treatment of colorectal metastases have been reported to have 5-year survival rates averaging 20% to 30%. Resection rates for the liver alone range from 30% to 60%. Although scientists are beginning to understand the molecular basis of colorectal metastasis, research continues to show a relationship between prognosis and nodal status. Positive lymph node status in colon cancer decreases the 5-year survival rate by 20% to 30%. The fewer involved nodes, the higher and longer the survival rate after resection. The number of involved nodes also correlates to the number of involved metastatic sites. The nodes may serve more as an indicator of spread than a cause; recent reports might implicate migrating stem cells in colon cancer metastasis.

Melanoma

Melanoma is known as a highly aggressive cancer and can spread to nearly any organ or site in the body. Although the metastatic potential of melanoma varies, nodular types of malignant melanoma have a 50% metastatic potential. Truncal melanoma also carries a poor prognosis; it makes up about 42% of all primary tumor sites for the disease. Multiple lymph node involvement is a risk factor for decreased survival. Many studies have shown the logical flow from a melanoma primary tumor site into a regional lymph channel (see Figure 2) and the sentinel node. In addition to a strong regional lymphatic correlation in metastatic spread from melanoma, tumor markers similar to those on glioma and breast cancer cells indicating metastatic potential have been identified on melanoma primary tumor cells. Lymph node metastasis did not explain reports of liver metastases from melanoma to the uvea, the middle layer of the eye. Moreover, the actual route of spread to the most prevalent distant site — the lung — likely is hematogenous.

Evaluating Metastatic Disease

The diagnosis and management of metastatic disease varies according to primary cancer type, extent of disease, metastatic site and other factors. Patients with metastatic disease may be asymptomatic or the symptoms from the metastatic lesion may be the first sign that cancer exists. For example, bone pain from prostate cancer metastases might bring a patient in for examination before a prostate symptom.

Ultimately, management of metastasis begins with management of the primary tumor, as local control might prevent recurrence and arrest metastatic cells contained within the primary tumor. Managing, staging and providing a prognosis for the primary cancer have rested on evaluation of the lymphatics and imaging to detect metastatic spread. Today, managing metastasis begins with predicting which tumors will or won’t metastasize. Scientists identify the many types of metastatic genes and metastatic suppressor genes, they are developing gene expression microarray testing to determine a primary tumor’s metastatic potential.

Metastasis in Cancer Staging

Staging of cancer is more than 100 years old; the precursor to the modern-day system was developed by French surgeon Pierre Denoix between 1943 and 1952. The first international tumor-node-metastasis (TNM) system was published in 1958. The system has worked for decades to help clinicians manage cancer, as well as with research and prognosis. The TNM system has been criticized for being too simple because the biology of cancer is much more complex than the system. Recent changes have been made to allow for expanded staging of nodal involvement. For example, involvement of local and regional lymph nodes vs distant nodes may be an important factor in staging and was not distinguishable under the previous system. Sentinel node dissection in evaluation for many cancers has necessitated addition of a suffix, indicated as “sn.” Whether the node is negative or positive, the suffix helps distinguish the node from one evaluated during a complete regional lymph node dissection. Staging also is being redesigned to allow for isolated tumor cells identified in lymph nodes.

The staging system is based on anatomic factors (ie, size of primary tumor, presence of cancer in the lymph nodes and cancer in 1 or more distant sites). As nonanatomic factors begin to affect cancer management staging and strategies, the system could become more accurate, but too complicated. For example, instead of adding genes known to cause metastasis from breast cancer into the staging system, it is more likely these data will be fed into a database that is linked to the basic TNM system to provide more detailed therapeutic and prognostic information for patients and clinicians.

Lymph Node Evaluation

Micrometastasis to lymph nodes can occur before many primary cancers are detectable and often
signifies concurrent or future distant metastasis. The role of the lymph nodes in staging and prognosis remains critical. The sentinel lymph node (SLN) biopsy method has become a favored biopsy technique for lymphatics in evaluating many cancers. The method originally was developed for melanoma evaluation, but may best be known for its use in breast cancer evaluation. Mapping the lymph node or nodes to which a primary tumor drains helps surgeons identify the most likely location of metastatic cells. The surgeon then can remove the affected nodes and use the information for staging and prognosis. When metastases are found outside the regional nodes, they indicate likelihood of organ metastasis and poor prognosis.

If the finding is negative on SLN biopsy, the remaining nodes in the examined group are assumed to be free of metastasis. This can save the patient unnecessary ablation of lymph nodes. It does not necessarily mean the patient is free of metastasis. Although lymph node drainage patterns for major cancers have been studied and are somewhat predictable, as many as 30% of primary tumors contradict these patterns and fail to drain into the predicted SLN or regional node group. Techniques have been developed to map lymphatics for drainage. In cancers such as breast cancer and melanoma, the addition of a radiocolloid with blue dye has improved accuracy and detection rates. DeHaas et al studied SLN mapping techniques in colon cancer, a primary cancer in which lymphatic drainage patterns vary, making SLN prediction difficult. A systematic literature search reflected a lack of standardization in technique and in definition of SLNs for colon cancer. In the future, these methods may be less invasive and more accurate. In particular, evaluation of lymph nodes that are located in deeper viscera has been debated, as clinicians weigh the morbidity resulting from biopsy techniques with the clinical benefits.

Predicting Distant Metastases

The detection of metastatic spread is complex and to date has been based largely on the site-specific patterns primary cancers exhibit. Finding a metastatic lesion is critical to therapeutic or palliative care, reduction of further spread, decreased morbidity and lengthened survival. Once metastasis has occurred, more aggressive treatment is necessary. The key to managing metastatic disease is detecting the propensity of a primary tumor to spread before metastasis can occur. This involves not only identifying genes with metastatic potential, but those that may suppress metastasis.

Clues from genetic research are unfolding daily. Researchers are attempting to identify the various metastatic phenotypes. Gene expression microarrays have been used to compare and contrast metastatic and nonmetastatic cells and already have shown promise as a method to identify which tumors will metastasize and which do not have metastatic potential (see Figure 3). Similar to the findings regarding site-specific gene signatures vs genes, such as osteopontin, that express a tendency for metastasis to all organs, research with microarrays has identified prognosis markers, molecular portraits and cancer signatures. These advances will help determine the course of action for preventing or managing metastases early in treatment of the primary tumor. The use of microarray data also is debated among some researchers because of questions regarding the prognostic value of circulating cells. Once refined, detection methods aimed at predicting the metastatic potential of the primary tumor can prove more successful as efforts to detect primary cancers in early stages also meet with success.

Imaging techniques have revealed steps in the metastatic process to disclose metastatic potential. Researchers have used magnetic resonance (MR) imaging to help evaluate the metabolic state of tumor cells. MR-compatible assays have assessed cellular interactions and the effects particular therapeutic.

Figure 3. Microarrays, sometimes called gene chips, provide snapshots of all the genes that are active in a cell at a particular time. Image courtesy of the National Institutes of Health, National Human Genome Research Institute.
agents may have on metastatic potential and invasion. A recent study reported the use of in vivo MR imaging to track labeled cancer cells in an animal model of human breast cancer metastasis to the brain. Positron emission tomography (PET) imaging with clinically available radiopharmaceuticals can be used to monitor tumor metastatic potential. Current radiopharmaceuticals support imaging of tumor glucose metabolism and hypoxia, new products that target angiogenesis are emerging. Preclinical evaluation is being conducted on classes of radiopharmaceuticals that may more directly target metastasis. For example, a number of PET and single photon emission computed tomography-based radioligands use the arginine-glycine-aspartate (RGD) motif to bind to proteins (see Figure 4).6,37

Common Distant Metastases

Several major organs and anatomic areas are more frequent metastatic sites and are reviewed below.

Brain

As cancer survival and imaging techniques have improved, the incidence of metastases to the brain has increased.36,58 Estimates of new cases of brain metastases each year in the United States range from 170,000 to 500,000.48 Nearly 40% of all intracranial tumors are of metastatic rather than primary origin. An additional reason that the brain has been documented as a preferred site for metastasis may be that many therapies have been considered unable to cross the blood-brain barrier, or even the blood-tumor barrier after a tumor has formed.5

Lung cancer is the primary cancer that metastasizes to the brain.38 As many as 25% to 30% of patients with newly diagnosed NSCLC have brain metastases at the time of their diagnosis.39 Most brain metastasis diagnosis and treatment involves patients with lung and breast cancer.41 Melanoma, renal cancer and colon cancer are the next most common.38 However, many other primary tumors can cause brain metastases, 20% to 40% of patients with systemic cancer will develop either a single metastatic lesion in the brain or, more likely, multiple brain metastases. Quantity also seems to be linked to the primary tumor, as patients with melanoma, lung cancer and breast cancer are more likely to experience multiple brain metastases.40 In 5% to 10% of cancer patients, detection of brain metastasis is the first sign of systemic disease.38 Metastases in the brain can cause neurologic symptoms such as headache, hemiparesis, mental status changes and visual field defects. Patients might experience hemorrhage and acute symptoms that mimic a stroke.38 They also experience emotional distress and are at high risk for mortality; brain metastases can be difficult to treat.38,58,59 Brain metastases normally occur late in the progression of cancer and often are asymptomatic.51 Retrospective studies have shown that as many as 64% of lung cancer patients with brain metastases were asymptomatic when the metastases were found on computed tomography (CT) scans.41 Brain metastases also may not be detected until they are large enough to be seen on imaging. Even micrometastases, which are barely

visible with today’s advanced imaging techniques, can contain millions of cells.2

Patients with brain metastases may be evaluated because they have systemic cancer and evaluating for spread to the brain is part of the staging investigation or because they have an identified primary tumor and neurological symptoms.36,41 If a patient might undergo surgery or stereotactic radiosurgery (SRS) to treat brain metastasis, contrast-enhanced MR imaging normally is chosen for evaluation. Contrast-enhanced CT will suffice in many other instances, but is not as sensitive as MR.41

Liver

The liver provides an excellent blood supply and other factors that support metastatic spread and growth; metastatic lesions are more common in adults’ livers than are primary tumors. Any primary tumor can produce liver metastases, but the eye, colon, stomach, pancreas, breast and lung are the most common in adults. Children more commonly experience liver metastases from a Wilms tumor, neuroblastoma and leukemia. Incidence of patients who have liver metastases is based largely on autopsy results, but these studies show that from 30% to 70% of people who died from cancer had liver metastases.42

In most cases, liver metastases are multiple and involve both lobes. Often, patients are asymptomatic, but once metastases become large or tumors form near the bile ducts, patients might experience jaundice. Hepatomegaly (enlarged liver) and ascites can make the patient’s abdomen appear larger.42

Sonography may be used for initial evaluation of the liver. However, if metastastic disease is suspected, dynamic multidetector helical CT or gadolinium-enhanced multiphase MR imaging often is used. Use of PET-CT imaging is increasing and is indicated in some cases, particularly if its use may change management. Additional imaging and biopsy may be used to distinguish a primary liver lesion from metastasis.43

Lung

Autopsies have revealed that the lung is the second most common site for metastases. Primary tumor sites that tend to metastasize to the lungs include the breast, colon, kidney, head and neck, bladder and skin (melanoma).1 However, while most pulmonary metastases arise from common tumors, the lungs can be the site of distant metastases from a number of primary cancers.44 The lungs are highly vascular at the surface. Recent evidence also suggests that the pulmonary circulation may be important to supplying blood to some primary tumors.1 Autopsies reveal that as many as 20% to 54% of people who die of cancer have lung metastases.45

Dormancy might explain why some metastatic cells remain in the lungs undetected for as long as decades.9,10 It has been reported that heart and lung transplant donors who had been cured of cancer from any number of primary sites have passed pulmonary metastases to nearly 50% of transplant recipients.10 Many studies are underway to explain the molecular biology of pulmonary metastases and the role of the pulmonary vasculature in metastasis.1 In general, pulmonary metastases carry a poor prognosis, as they indicate disseminated disease. But prognosis varies based on the primary site. For example, patients with carcinoma of the pancreas who have pulmonary metastasis have a 5-year survival rate of <5%. Patients with tumors that are chemosensitive, such as testicular teratoma, have better prognoses. Patients with pulmonary metastases generally have known primary tumors. If not, clinicians may suspect a primary tumor that is clinically silent, such as pancreatic or biliary cancer. Patients who have multiple pulmonary metastases usually have no pulmonary symptoms. However, a large metastatic tumor can lead to airway obstruction or pleural effusion, causing difficulty breathing.44

Chest radiography with posteroanterior and lateral images is recommended in screening for pulmonary metastases. If patients have a high probability of pulmonary metastases, they should undergo more frequent screening chest radiography or be screened by CT scanning. CT is more sensitive than radiography in detecting pulmonary nodules and will be used to follow up after detection of pulmonary metastases or if there is a negative finding but high probability. CT scanning also is used before planned biopsy or therapies for multiple nodules.45 MR imaging is not particularly sensitive for detecting metastasis to the lungs but can be indicated in cases in which the patient should avoid repeated exposure to radiation from screening exams.

Imaging with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can detect occult pulmonary metastases. The American College of Radiology (ACR) has developed criteria to address screening for pulmonary metastases based on the primary tumor site.45 In addition to imaging, sputum cytologic analysis or bronchial brushings might reveal malignant cells, but do not distinguish between primary and metastatic cells. Bronchoscopy can be used to evaluate some pulmonary metastases.44

Bone

Metastatic tumors outnumber primary malignancies in the bone by a wide margin.46 From autopsy reports, estimates reveal that more than 350,000 people in the United States die each year with bone metastases.1 Actual incidence is difficult
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to predict, evaluation of bone metastases generally occurs only if a patient has a known cancer and when the primary cancer has a tendency to metastasize to the bone.46 Breast and prostate cancers have the highest incidence of bone metastases, each averaging an incidence rate of about 70%. Lung and kidney cancer incidence rates for bone metastases are about 40%.1 Incidence is higher among middle-aged and older adults and much lower in children. When bone metastases occur in children, they are widespread in nature and most likely result from neuroblastoma or leukemia.46

The mechanism by which bone metastases develop is complex, involving tumor cells, osteoblasts, osteoclasts and endothelial cells, as well as several regulatory proteins.1 As many as 65% to 75% of patients with bone metastases experience a great deal of pain and reduced mobility.46,47 Resulting bone weakness makes bones more susceptible to fracture or spinal cord compression.46 As many as 10% to 20% of patients with bone metastases will experience pathological fractures of weight-bearing bones.47 Bone metastases take 2 forms: osteolytic or osteoblastic. The category depends on the type of cells involved in forming the metastases. Primary tumor type has some effect, as breast cancers tend to lead to osteolytic metastases and prostate tumors lead to osteoblastic tumors. Most patients show some evidence of elements of both types of lesions.1

Skeletal pain in cancer patients suggests possible bone metastases.46 Although several imaging methods can detect metastatic bone lesions, radionuclide bone scanning is the primary imaging examination used to detect bone metastases. The exam is advantageous because it allows for a total-body survey. which is important because most metastatic lesions are symptomatic and can appear in several areas of the skeleton. The ACR has developed appropriateness criteria with several scenarios for detection of single and multiple lesions from various cancers, as well as follow-up studies. These scenarios might involve use of MR, CT and FDG-PET. For example, CT scans are used to aid diagnosis and to localize placement for fine-needle aspiration or core biopsy.46

Recent research has demonstrated some of the molecular biology behind metastasis to the bone. Osteopontin and other bone-derived chemokines appear to act as chemoattractants for breast and prostate cancer cells, explaining the high incidence of bone metastases from these primary cancers. Evidence is gathering on the expression factor responsible for bone destruction from breast cancer metastases and endothelial factors associated with prostate cancer metastasis to bone.1

Metastatic Disease Management

In 1981, Suit addressed the American Society of Therapeutic Radiologists and emphasized the importance of local and regional control of the primary tumor.15 In current medical practice, elimination of all risk of spread usually is the preferred course of treatment. The most aggressive treatment based on possible metastasis and the extent and location of metastasis normally is advocated.9,15 This can subject some patients to unnecessary cytotoxic treatments because most cells that disseminate from the primary tumor do not cause metastases. It is therefore important to identify genuine metastatic cells.9

Current Treatments

Currently, when a patient first receives a cancer diagnosis — or there is suspicion of cancer based on a physical or screening examination — he or she often already has symptoms. This begins a cycle of diagnosis, staging and treatments that already may be too late to arrest much of the metastatic process.1,4 Generally, patients are referred for biopsy, from which staging information helps a multidisciplinary team plot a course of treatment that consists primarily of surgery, chemotherapy and radiation therapy, often in some combination.3,8 Other treatments might be used in place of surgery, including cryotherapy and radiofrequency ablation.3,8,41 Some therapies can affect the primary tumor and the metastatic tumors differently.3,8 Each of these treatments can produce a range of side effects and can be geared toward local/regional control or systemic/metastatic control. The success of treatment is measured by 5-year survival rates. If cancer recurs and metastases are detected, patients face the process again, perhaps with different details of treatment.3,8

Choice of metastatic treatment depends on the primary cancer’s size and stage and the location of metastasis, as well as patient factors such as age and general health.23 Although chemotherapy at times helps control local tumors, the main reason for its use is to control systemic disease, aiming to eradicate cancer cells that have disseminated from the primary tumor that can cause distant metastases.3 Radical surgical resection largely has been replaced by combination treatments that involve less radical surgery and radiation or chemotherapy or both to control the local tumor adequately and to clear the tumor margin and regional lymph nodes of cancer cells.3

Strategies such as chemotherapy and hormone therapy have been used to control metastases for many cancers, but they do not always work.23 NSCLC is less responsive to chemotherapy than other primary tumors that metastasize to the brain. In fact, the brain was once believed to be a pharmacologic sanctuary site for metastases, unreachable by systemic therapies because of the blood-brain
The Role of Radiation Therapy

Treatment methods for primary cancer have evolved to recognize the balance between local control and patient morbidity and cosmetic concerns. At the same time, techniques and technology have improved. Clearly, evidence has supported a link between local control of many cancers and overall survival. Radiation therapy plays a role in local control of the primary cancers and in control of the metastatic lesion or relief of symptoms caused by metastases.3,27

Use of whole-brain external beam therapy, for example, can extend median survival of patients with brain metastases by several months.40 The use of whole-brain radiation therapy (WBRT) traditionally has been recommended for most patients with metastatic brain lesions instead of surgical resection. Some literature has suggested that the use of WBRT can result in lowered performance status measures such as cognitive function.39 The decision to use radiation or any intervention for brain metastases is based on projected survival and Karnofsky performance status.52 Surgery is reserved for patients with high performance status and longer projected survival who have a solitary lesion that is easily accessed.53

These treatments often are used in combination. There is some debate over use of WBRT in patients who have surgical resection or SRS and prognosis for long-term survival. However, WBRT likely increases the chance of eliminating occult metastases and treatment with 3 Gy daily fractions has not been shown to lead to risk of dementia.53

SRS first was reported as a treatment for brain metastases in the late 1980s. No anesthesia is required and the technique is minimally invasive;40 it allows for delivery of a large dose while sparing surrounding normal tissues. The nature of metastatic lesions in the brain facilitates SRS treatment planning and fall-off of dose to surrounding tissue.55 The technique also allows for treatment of multiple metastases in a single session.40

Technological advances have improved radiation therapy techniques for treating liver metastases. Image-guided radiation therapy, gating techniques and real-time tumor or dynamic targeting techniques have helped eliminate past problems associated with substantial breathing motion. It is essential to check the position of the liver in relation to the vertebral bodies before each daily fraction. Stereotactic radiation therapy can deliver high doses with accuracy and precision and is particularly suited to liver metastases because the organ can regenerate following injury. Caution must be taken if the metastases closely border the stomach and small intestine because the high doses from this technique can cause late toxicity effects in these adjacent organs.54

Radiation therapy may be used for therapeutic or palliative treatment of lung metastases. Procedures for treating metastatic lung nodules often are similar to those for treating primary lung lesions. Patient selection decisions differ based on staging and prognosis for patients with pulmonary metastases.3,44,49 SRS has been used with some success in patients who are considered high risk for surgical resection of pulmonary metastases. Pneumothorax is a morbidity associated with the procedure.54

Radiation therapy can control pain from bone metastases; these patients are the largest group to receive palliative radiation therapy. The exact mechanism of how half-body radiation works in controlling

barrier. Observation of brain metastases using contrast-enhanced CT and MR imaging, as well as documentation of tumor responses to systemic treatment, have shown that many therapies might indeed cross the blood-brain barrier.39 Chemotherapy toxicity and side effects remain high and timing of chemotherapy can affect success of radiation therapy. With the introduction of new drugs, clinicians have had to fight the tendency to subscribe to a “more is better” philosophy in use of therapeutic agents.5,51 Many of today’s therapies for metastasis have improved survival by months, not years, and have introduced treatment complications.50

Treatment also involves local therapy for the metastatic presentation. The therapies vary widely based on a number of factors, including metastatic tumor site and size, as well as prognosis. For example, patients with colorectal cancer who have metastases confined to the liver may experience 5-year survival rates of 50% to 60% with surgical resection.34 About 50% of colorectal and renal cell carcinoma patients with liver and lung metastases experience recurrence from microscopic metastases that were established before resection of the metastatic lesions but were undetected.50 In most patients with colorectal cancer and liver metastasis, surgical resection is not possible because the patient has medical contraindications or extrahepatic disease, the metastases are diffuse or the lesion is unresectable. Radiation can reduce tumors to make resection possible.34 The decision to use surgical management of bone metastases requires weighing expected patient survival time, comorbidities and hematologic and hepatic status.47

Studies on women treated with adjuvant or neoadjuvant systemic therapy for breast cancer have demonstrated improved survival based on the number of women remaining disease-free at the 5-year mark. Generally, patients who are premenopausal cease tamoxifen therapy after a 5-year period and no proven therapeutic options exist for extending the therapy. But patients with early-stage breast cancer have a high risk of recurrence, which includes metastasis by definition.53 Rarely can metastases be eradicated completely.9

The Role of Radiation Therapy

Radiation therapy can control pain from bone metastases; these patients are the largest group to receive palliative radiation therapy. The exact mechanism of how half-body radiation works in controlling
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pain is not fully understood. Radiation also can be used to treat pain in patients with vertebral metastases resulting in cord compression. Exceptions include patients who have received full doses of radiation previously and those with spinal instability.47

Chow et al reviewed the literature to compare a single fraction with multidose fractions for treatment of painful bone metastases.55 For the most part, there was no difference between the 2 types of treatment in pain relief, but there was less burden of treatment for a single fraction. The single fraction carries a higher possibility of retreatment, however. This was particularly true for patients who had poor performance status or estimated survival.55 Most patients with bone metastases benefit from a brief, low-dose course of radiation therapy.55

The techniques for radiation therapy vary widely, depending on the patient, the primary and metastatic tumor characteristics and available and emerging technologies. Radiation therapy can be used at various stages in the metastatic process and in various combinations, including postoperatively to eradicate lymph node metastases and other occult foci of tumor cells remaining in the tumor bed, in combination with chemotherapy to reduce residual cell burden, preoperatively to reduce a tumor to facilitate resection or as a stand-alone treatment.3

Emerging Therapies

The classic chemotherapy and radiation therapy treatments for metastatic spread attack disseminating cells by inhibiting deoxyribonucleic acid replication, repair or the cell cycle. In recent years, targeted therapies have emerged. Agents such as imatinib, trastuzumab, erlotinib and gefitinib are based on oncogenic signaling pathways.9 Bevacizumab is an antiangiogenic agent that primarily has been used to target the vascular endothelial growth factor antibody in colorectal cancer.9,51

The most exciting advances will be those that target various steps in the metastatic process and then are customized to stop cancer spread in its tracks. For example, the endothelial receptor ET1 can be targeted with an antagonist called atrasentan.9 As scientists identify receptors and antagonists for various primary tumors and host-specific sites, disseminating cells may no longer find a suitable “soil” in which to grow.4,9,9

Although targeting the primary tumor to control its metastatic potential and prevent intravasation are essential, Steeg and Theodorescu recently reported that the final steps in the metastatic process — those involving colonization — might offer the most therapeutic potential.50 The authors stated that from 20% to 40% of patients with many common cancers already have passed the point of metastatic colonization by the time their cancer is diagnosed. Continued development of therapies, such as bevacizumab, that target angiogenesis in combination with other targeted antimetastatic therapeutics offers promise. Bevacizumab has been paired with epidermal growth factor receptor tyrosine kinase inhibitors; this combination therapy may target both endothelial and tumor cells.

In addition to therapies specific to the original tumor, targeted therapies also might attack site-specific metastases. Clinical testing has begun on molecular therapeutics that may inhibit bone metastases. A microarray signature has been identified for lung-specific metastasis and administration of a cocktail of inhibitors for the identified proteins has shown success.50 Much of the current research focuses on the role of stem cells in cancer development and migrating stem cells in metastasis. Stem cells’ role in metastasis remains controversial, but if proof emerges that a unique group of stem cells is responsible for primary and metastatic tumors, it might be possible to target specific cells that are distinct from common tumor cells to halt metastatic progression. Because the expression profiles and molecular pathways of primary and metastatic tumors differ, it is essential to include metastasis models in clinical trials for development of new cancer drugs.9,50

Conclusion

Just as the past few decades have shown tremendous progress in cancer screening, prevention, diagnosis and treatment, the future holds great promise for understanding cancer at the molecular level. Each new discovery conveys questions and new challenges. Most notably, how can we improve early detection of metastasis and halt the process? The answers are closer than before; they may lie in stem cells or in a number of genetic profiles yet to be unearthed. Along the way, each step in the process becomes clearer and therapies more effective.4,9,10

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Teresa G Odle, BA, has worked in health care communication for more than 17 years and is a member of the American Medical Writers Association. In addition to continuing education manuscripts, Ms Odle has written and edited medical essays for consumers and medical professionals and has edited national newsletters for managers in radiation oncology and other medical practice managers. She is a former business development director for a large radiology practice and the recipient of health care writing awards. She recently joined the ASRT staff as a scientific journal editor.

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The Metastatic Process

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1. Stephen Paget’s 1889 article on metastasis espoused the _____ hypothesis.
   a. classic
   b. seed and soil
   c. rate limiting
   d. hot spot

2. At the time of primary cancer detection, about _____ % of patients already have metastases.
   a. 20
   b. 30
   c. 40
   d. 50

3. If a tumor cell fails to complete any step in the metastatic process, the process:
   a. effectively terminates
   b. is slowed
   c. remains dormant for as long as 10 years
   d. is unaffected

4. _____ is a term used to describe a tumor that has outgrown its blood supply and become oxygen deficient.
   a. Apoptopic
   b. Hypoxic
   c. Intravasated
   d. Angiogenic

5. _____ is a state of suspension for cells that have lost adhesion to the extracellular matrix.
   a. Angiogenesis
   b. Hypoxia
   c. Anoikis
   d. Extravasation

6. Cells that are shed from solid tumors into circulation move from a primary site to a secondary site in a matter of:
   a. seconds
   b. minutes
   c. days
   d. weeks

7. Lymphatic channels are:
   a. thick walled, venous and easily penetrable by tumor cells
   b. thin walled, easily penetrable by tumor cells but low in vasculature
   c. thick walled, venous and impenetrable by tumor cells
   d. thin walled, venous and easily penetrable by tumor cells
8. The _____ is the network responsible for organizing and moving cells.
   a. cytokine
   b. osteopontin
   c. cytoskeleton
   d. router

9. The first layer of lymphatic vasculature is located in the:
   a. superficial dermal layer of skin.
   b. deep dermal layer of skin.
   c. subcutaneous layer of tissue.
   d. glandular layer.

10. The _____ lymph node is believed to be the first node to receive tumor cells in lymphatic drainage from a tumor.
    a. regional
    b. sentinel
    c. distal
    d. channel

11. _____ has replaced lymphadectomy in staging of breast cancer and melanoma.
    a. Fine-needle biopsy
    b. CT
    c. PET-CT
    d. Lymphoscintigraphy

12. According to this Directed Reading, the success rate for each circulating cancer cell is _____ %.
    a. 100
    b. > 10
    c. 1
    d. < 0.1

13. When cells leave the circulation and migrate through a vascular wall, the process is called:
    a. colonization
    b. intravasation
    c. extravasation
    d. virulence

14. According to this Directed Reading, colon and pancreatic carcinoma cells may overexpress oncogenes that:
    a. suppress metastases
    b. respond to a hepatocyte growth factor
    c. increase likelihood of osteolytic bone metastases
    d. represent multiple lymphatic drainage patterns

15. Between _____ % and _____ % of patients with early-stage disease may have breast cancer cells in their bone marrow.
    a. 10, 34
    b. 20, 54
    c. 30, 74
    d. 40, 94

16. The most common sites for metastases from breast cancer are the _____ and _____.
    a. bone, liver
    b. liver, brain
    c. bone, lungs
    d. brain, lungs

17. According to this Directed Reading, nonsmall cell lung cancer carries a high risk of _____ metastases.
    a. bone
    b. lung
    c. brain
    d. liver

18. According to this Directed Reading, poor prognosis in prostate cancer is related to:
    a. Karnofsky performance scale rating only.
    b. Gleason grade only.
    c. single regional lymph node involvement.
    d. multiple regional lymph node involvement.

19. The most common site of metastasis from colorectal cancer is the:
    a. lung
    b. liver
    c. brain
    d. bone.
20. The **most** common site of metastasis from melanoma is the:
   a. lung.
   b. liver.
   c. brain.
   d. bone.

21. Today, managing metastases begins with:
   a. predicting which tumors will or won’t metastasize.
   b. watching and waiting.
   c. immediate chemotherapy to ward off potential metastatic spread.
   d. radiation of the primary tumor.

22. The first international tumor-node-metastasis (TNM) staging system was published in:
   a. 1958.
   b. 1968.
   c. 1978.
   d. 1998.

23. The traditional TNM cancer staging system is based on ____ factors.
   a. genetic
   b. environmental
   c. anatomic
   d. nonanatomic

24. Of all intracranial tumors, nearly ____ % are of metastatic origin.
   a. 10
   b. 20
   c. 40
   d. 60

25. Liver metastases usually:
   1. are multiple.
   2. are symptomatic.
   3. involve both lobes.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2 and 3

26. ____ cancer and ____ are the 2 common cancers that metastasize most frequently to the bone.
   a. Prostate, melanoma
   b. Breast, lung cancer
   c. Breast, prostate cancer
   d. Lung, melanoma

27. Treatment success generally is measured by:
   a. complete eradication of metastatic cancer.
   b. partial eradication of metastatic cancer.
   c. 5-year survival rates.
   d. 10-year survival rates.

28. Patients with brain metastases are candidates for surgery if they meet certain conditions, including:
   1. high Karnofsky performance status.
   2. projected long-term survival.
   3. a solitary, easily accessible lesion.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2 and 3

29. ____ is (are) a risk of stereotactic radiosurgery for treating lung metastasis.
   a. Pneumothorax
   b. Late toxicity in the small intestine
   c. Poor accuracy
   d. Repeated low doses

30. ____ is a new agent that is used to target the vascular endothelial growth factor antibody.
   a. Imatinib
   b. Erlotinib
   c. Bevacizumab
   d. Arginine-glycine-aspartate
Hodgkin Lymphoma
Adi R Ferrara, BS, ELS

Hodgkin lymphoma is a malignancy of white blood cells with an impressive cure rate. However, many patients die years later from the long-term effects of treatment so researchers and clinicians must balance effective treatments and reduced toxicity with higher cure rates for patients with relapsed and refractory disease.

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The blood and its components can develop several types of malignancies, generally divided into leukemias, lymphomas and myelomas. Leukemias originate in the bone marrow and the blood. Lymphomas start in the lymphatic system, and myelomas start with abnormal plasma cells, which are part of the immune system. Certain types of leukemias can have symptoms also seen in lymphomas, such as enlarged lymph nodes or spleen.

In 1832, physician Thomas Hodgkin published the first modern description of the cancer that bears his name. Hodgkin lymphoma (HL), also known as Hodgkin disease, is a malignancy of lymphocytes. Lymphocytes are white blood cells that play a crucial role in defending the body from infection. These cells are divided into subcategories, including T lymphocytes and natural killer cells, but, with HL, the malignant cells most often are B lymphocytes. HL typically begins in a single lymph node and spreads to other nodes throughout the body (see Figure 1).

The incidence of HL is relatively low; it accounts for less than 1% of cancers worldwide. For 2008, the American Cancer Society estimated 8220 new cases and 1350 deaths from the disease. In addition to low occurrence, HL has a high cure rate of at least 80%, depending on the disease stage and the presence of certain risk factors. However, cases of relapsed or refractory disease have a cure rate approaching only 50%.

Several epidemiologic features point to a possible infectious origin of HL; however, this does not mean HL is contagious. There is also a strong genetic component to HL, and relatives of HL patients are 3 to 9 times more likely to develop HL. However, the exact mechanism of inheritance is unclear. It is possible that the genes involved have to do with an immune response to infectious organisms.

Systemic symptoms that appear in many HL patients, often called B symptoms, are consistent with infection and indicate a potentially poorer prognosis. Systemic symptoms include persistent fever (temperature more than 38°C), unexplained weight loss (more than 10% of total body weight in 6 months) and drenching night sweats. In addition, laboratory tests often find signs of immune response to infections in HL patients, such as inflammatory markers and high erythrocyte sedimentation rates. There may be several infectious agents responsible for different types of this cancer, which account for the varied behavior of HL in patients at different ages and geographic locations.

In developing countries and in lower socioeconomic areas of developed nations, HL is a childhood disease. In regions with higher socioeconomic and educational standards, the disease occurs more often in teens and young adults who grew up in a single-family house with few siblings or playmates. Children in developed countries who attended daycare and lived in multifamily housing seem to be
HODGKIN LYMPHOMA

Types of Hodgkin Disease

HL is divided into 2 main types, lymphocyte-predominant Hodgkin lymphoma (LPHL) and classic Hodgkin lymphoma (CHL). The main differences between the types are histological. However, LPHL also behaves differently than CHL, and, consequently, their early-stage treatments differ.

Classic Hodgkin Lymphoma

According to the National Comprehensive Cancer Network (NCCN), CHL accounts for 95% of HL cases in Western countries, with nodular sclerosing HL being the most common of the 4 subtypes. The other subtypes are mixed-cellularity, lymphocyte-depletion and lymphocyte-rich HL. CHL usually is detected in a group of lymph nodes. The appearance of a mediastinal mass is common in CHL patients.

CHL is characterized by abnormal cells called Reed-Sternberg cells (see Figure 2). These cells usually have more than 1 nucleus (or 1 nucleus with several lobes), and are found surrounded by inflammatory cells. Although the source of Reed-Sternberg cells was long unknown, the development of better histological and molecular techniques led to the discovery that they are B lymphocytes that should have undergone apoptosis (programmed cell death), but did not. The cell markers on Reed-Sternberg cells are not typical B-cell markers. For example, they do not express the CD20 marker found in LPHL cases.

Cases of CHL peak between ages 15 and 30 years, plateau and then peak again in adults older than 55 years in a phenomenon known as a bimodal age distribution.

Related Infections

Epstein-Barr virus (EBV) is the causative agent of mononucleosis. It is not always symptomatic, but can increase the risk of HL, especially the mixed cellularity kind. People with a history of infectious mononucleosis are up to 3 times more likely to develop CHL. In industrialized countries, at least 50% of CHL cases are EBV-positive (ie, the viral genome is found in the tumor cells). The percentage of EBV-positive cases varies by the type of CHL and the geographic location of the patient. It currently is unknown whether EBV is a single causative agent of some HL cases, or if the combination of EBV, environmental factors and a genetic predisposition act together to form CHL.

People who are human immunodeficiency virus (HIV)-positive are at much higher risk of developing

Figure 1. Major lymph node regions involved in HL. Reprinted with permission from Dasher B, Wiggers N, Vann AM. Portal Design in Radiation Therapy. Columbia, SC: RL Bryan Co; 1994:68.

Figure 2. High magnification of bilobed and trilobed Reed-Sternberg cells (center). Artwork courtesy of Michael M Quigley, MD, PhD, Naval Medical Center, San Diego, CA.
HL, although this cancer is not considered an acquired immunodeficiency syndrome-defining disease. In general, HL in the HIV-positive patient is more aggressive, carries a poorer prognosis and typically involves different areas of the body than those normally affected in the HIV-negative patient. Most HL patients who are HIV-positive have EBV-positive malignant cells.1

Lymphocyte-predominant Hodgkin Lymphoma

LPHL sometimes is referred to as having 2 forms, nodular and diffuse. The nodular form accounts for 80% of LPHL cases. However, according to the World Health Organization’s classification of lymphoma, a purely diffuse form of LPHL with no nodular masses does not exist. Such histological appearance is classified as a diffuse large B-cell lymphoma or T-cell rich B-cell lymphoma, both of which are types of non-Hodgkin lymphoma.8 (Non-Hodgkin lymphoma differs from HL in the type of malignant cells that are present. The difference is important because treatment for HL is different from treatment for non-Hodgkin lymphoma.) Unlike CHL, LPHL carries with it a high risk of transforming into non-Hodgkin lymphoma. Studies suggest there may be a common origin for these 2 types of cancer.

The malignant cells of LPHL are known as lymphocytic and histocytic cells, or “popcorn” cells because of their appearance (see Figure 3). They appear surrounded by small B lymphocytes or T-cell rosettes.1 Reed-Sternberg cells are rare in LPHL. LPHL is less aggressive than CHL and is characterized by long periods of remission between relapses. This leads some physicians to adopt a “wait and see” strategy in certain early-stage patient populations, especially pediatrics, rather than starting toxic therapies right away.8

LPHL usually is detected in 1 node, and the appearance of a mediastinal mass is rare. The malignant cells in LPHL usually express the typical active B-cell marker CD20 and are therefore designated CD20+. There is a monoclonal antibody, rituximab, against the CD20 marker. Tests of rituximab therapy in LPHL patients are showing promising efficacy and safety results.1

In addition to the CD20 cell marker, several other markers are present on the lymphocytic and histocytic cells that are missing on the Reed-Sternberg cells associated with CHL. Lymphocytic and histocytic cells usually are found surrounded by small B and T lymphocytes. Unlike CHL, there is no evidence of EBV involvement in LPHL. All LPHL tumor cells are EBV negative.1

In LPHL, the peak incidence is unimodal, occurring between 30 and 40 years of age.1 The difference in incidence between men and women is significant; approximately 75% of LPHL patients are men.

The frequency of early-stage disease is higher in LPHL than in CHL. The German Hodgkin Study Group (GHSG) found that 63% of its LPHL sample (n = 394) was in the early favorable stage of the disease (ie, without complicating factors), and 16% were in the early unfavorable stage. In the CHL sample (n = 7904), 22% were in the early favorable stage, and 39% were in the early unfavorable stage.8

Diagnosis and Staging

Approximately 90% of early HL cases appear above the diaphragm, and the disease spreads into contiguous nodes or nodal regions. A mediastinal mass, when present, can cause symptoms ranging from coughs to apnea, depending on the mass’ size and location in the mediastinum.4,5 Barring the existence of systemic symptoms or a mediastinal mass, the first symptom a patient notices is usually an enlarged gland in the neck. A peculiar sign of HL in some patients is pain in the affected nodal area following alcohol consumption. Depending on the patient’s age, a medical workup for HL may include questions regarding alcohol intolerance. Another unique sign of HL that some patients experience is pruritus, or intense itching, that is resistant to topical treatment.4

A physical exam, laboratory tests and medical history, including family history of HL, should be part of the workup. The physician also will ask the patient about the presence or absence of systemic symptoms, an important prognostic factor. Laboratory tests include a complete blood count and differential, liver function tests, erythrocyte sedimentation rate, albumin levels and creatinine levels.6 The NCCN recommends positron emission tomography and computed tomography (PET-CT) and contrast-enhanced diagnostic CT scans of the chest, abdomen and pelvis as part of the diagnostic workup.4,5
Diagnosis of HL requires an open biopsy because the number of malignant cells in the tumor can be low. Fine needle aspiration may not capture these cells and will not provide enough information to determine the particular HL subtype, which is needed for treatment decisions. With current imaging techniques, especially CT and PET-CT, patients do not require staging surgery (laparotomy).4,5

The presence of systemic symptoms or abnormal levels of white blood cells, platelets or hemoglobin indicates possible bone marrow involvement and requires a bone marrow biopsy.5,7

After beginning in the lymphatic system, which includes the spleen, HL typically invades only the bones, bone marrow, lungs and liver. The presence of a malignancy elsewhere may indicate a concurrent HIV infection. In cases of unusual disease presentation, an HIV test should be performed.

The HL staging criteria, which take into account the size and number of tumors, their location and the presence of distant metastases, were established in Ann Arbor, Michigan, in 1971 and modified in Cotswolds, England, in 1988.9,10 The current staging system (see Table 1) is known as The Modified Ann Arbor System or The Cotswolds Classification System. Each HL stage can have several additional designations, including:

- A – Absence of systemic symptoms.
- B – Presence of systemic symptoms (hence the name “B symptoms”).
- X – Bulky disease, which is “a mediastinal mass with a maximum width that is equal to or greater than one-third of the internal transverse diameter of the thorax at the level of T5/6 interspace or > 10 cm maximum dimension of a nodal mass.”10
- E – Involvement of extranodal regions or organs.

If certain organs are involved, a separate designation is added to the stage (see Box 1). For example, in a patient with stage III disease, if both extranodal and splenic involvements occur, the stage is IIIE+S.

Unfavorable Indicators

Studies of HL patient outcomes identified several factors that signified a worse prognosis, regardless of the cancer’s clinical stage. The presence of these signs and symptoms designates the patient’s HL as unfavorable, and treatment is modified accordingly. Unfavorable symptoms in early-stage HL (stage I or II) are different from those in advanced HL.

According to the NCCN, unfavorable indicators for HL stage I and II include:

- A mass anywhere in the body > 10 cm, or a mediastinal mass with a width of at least one-third the maximum intrathoracic diameter as seen on a chest radiograph.
- The presence of systemic symptoms.
- Erythrocyte sedimentation rate ≥50 mm/h, if no systemic symptoms are present.
- Cancer outside the lymph nodes in 2 or more sites.
- Cancer in 3 or more nodal and extranodal sites.5

The definition of unfavorable symptoms in early-stage disease differs slightly among the major HL study groups in North America and Europe. For

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**Table 1**

**Description of Hodgkin Lymphoma Stages**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The tumor is localized to only 1 lymph node region or 1 extranodal area or organ, such as the spleen or thymus, without lymph node involvement.</td>
</tr>
<tr>
<td>II</td>
<td>Tumors are evident in 2 or more lymph node regions on the same side of the diaphragm, either above or below it.</td>
</tr>
<tr>
<td>III</td>
<td>Tumors are evident in lymph node regions above and below the diaphragm.</td>
</tr>
<tr>
<td>IV</td>
<td>There are several tumors in 1 or more organs outside the lymph nodes. The associated lymphatic regions may or may not have cancer in them. Alternatively, there may be cancer in an extranodal organ and in a nonrelated (distant) lymph node region.</td>
</tr>
</tbody>
</table>

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**Box 1**

**Organ Designations**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>liver</td>
</tr>
<tr>
<td>L</td>
<td>lung</td>
</tr>
<tr>
<td>M</td>
<td>bone marrow</td>
</tr>
<tr>
<td>S</td>
<td>spleen</td>
</tr>
<tr>
<td>P</td>
<td>pleura</td>
</tr>
<tr>
<td>O</td>
<td>bone</td>
</tr>
<tr>
<td>D</td>
<td>skin</td>
</tr>
<tr>
<td>N</td>
<td>nodes</td>
</tr>
</tbody>
</table>
instance, the National Cancer Institute of Canada lists age ≥ 40 years as an unfavorable symptom. The GHSG and the European Organization for Research and Treatment of Cancer list erythrocyte sedimentation rate ≥ 30 mm/h as unfavorable if systemic symptoms are present.5

The International Prognostic Factors Project on Advanced Hodgkin’s Disease developed the international prognostic score (IPS) based on a study of more than 5000 patients.11 It is used widely to make treatment decisions for patients with advanced HL (stage III or IV). The IPS is based on 7 risk factors (see Box 2) that affect prognosis in patients with advanced HL. The presence of each factor in a patient receives 1 point. An IPS score of ≥4 earns the disease an unfavorable designation. In the original IPS study, the freedom from progression rate at 5 years for patients with a score of 4 was 51%. The rate dropped to 42% for patients with a score of 5 or higher. On average, each point reduces the freedom from progression rate by 7% to 8%.

### Treatment Options

An invariably fatal disease throughout the first half of the 20th century, HL is now considered a fairly curable cancer. Advances and successes in HL treatments, such as combined-modality therapy or prospective clinical studies, set an example that was copied in other oncology settings.4 Using a multidisciplinary team — an undisputed necessity in current treatment centers — started with the professional teams caring for HL patients.4

Successful treatments have existed for several decades because HL tumors are sensitive to chemotherapy and radiation. Because long-term survival is so common with HL, a major challenge is reducing adverse events from treatment, including heart disease, thyroid dysfunction and secondary malignancies. These events may appear years after the successful completion of treatment. In fact, starting 10 to 15 years after diagnosis, deaths from treatment toxicities outnumber deaths from HL itself.1 Another major challenge is finding an effective treatment regimen for patients with relapsed or refractory disease, for whom prognosis is still poor.

Response to HL treatment falls into 1 of 5 categories, including complete response (disappearance of all signs of disease), partial response, stable disease, relapsed disease or progressive disease.6 Lymphoma treatment can leave residual fibrotic tissue at tumor sites, which, when evident on imaging studies following treatment completion, could not always be identified as either scar tissue or a residual active tumor. However, in 2007, the International Harmonization Project recognized the advantages of PET scanning in determining whether masses were active tumors or scar tissue. The “complete response – unconfirmed” category that previously was used in such cases was officially eliminated.5

### Chemotherapy

Although researchers continue to test new drugs or treatment combinations, there are several common chemotherapy regimens on the market today (see Table 2). They can be used as stand-alone HL treatments or combined with other options.

#### MOPP

MOPP was the first multiagent chemotherapy regimen, but its detrimental effect on fertility and its tendency to induce leukemia or myelodysplastic syndrome led to this regimen’s abandonment. Sole use of MOPP results in 100% sterility in men and premature menopause in many women.12 To try to alleviate some of the more toxic aspects of MOPP, cyclophosphamide sometimes is used in place of the more toxic mechlorethamine; the regimen then is abbreviated COPP. MOPP still is used in hybrid regimens alternating cycles with ABVD or ABV (where dacarbazine is dropped from the regimen).

#### ABVD

ABVD is currently the gold standard in the first-line treatment of every stage of HL. Although the 2 sometimes are combined, ABVD was developed as an alternative to MOPP, “in an attempt to reduce some of the delayed sequelae associated with combined modality therapy in Hodgkin’s disease.”13 Administration of ABVD usually is followed by radiation treatment. However, a recent study showed that in early-stage favorable disease, the administration of 4 to 6 cycles of ABVD without radiation resulted in event-free and overall survival rates similar to the rates of a combined-modality regimen.14 Therefore, ABVD alone might be the preferred choice in some younger patients, in whom the late sequelae of radiation treatments might have significant effects on life expectancy or quality of life.
HODGKIN LYMPHOMA

BEACOPP
The BEACOPP regimen usually includes a dose-intensive or time-escalated treatment created by the GHSG to improve survival rates in patients with advanced disease. According to the initial publication that discussed the efficacy of BEACOPP, the freedom from treatment failure rate was 89% at a median follow-up of 40 months, which greatly exceeded the 50% best-case scenario of other advanced HL regimens. However, later studies found that the dose-escalated BEACOPP regimen induced leukemia in approximately 2.9% of patients. This led the GHSG to develop a time-escalated BEACOPP regimen given in 14 days instead of the original 21 days. In the pilot study of time-escalated BEACOPP, the freedom from treatment failure and overall survival at 5 years for patients with advanced disease were 90% and 95%, respectively. The hematologic toxicity, although still pronounced, was lower than that of the dose-escalated BEACOPP. A current GHSG trial is comparing the time-escalated BEACOPP to 6 or 8 cycles of the dose-escalated BEACOPP in a larger group of patients. Results are not yet published, but BEACOPP still is a common treatment option for patients with advanced HL and an IPS score of 4 or more.

Stanford V
The Stanford V regimen is another attempt to create a safer treatment for advanced and early-unfavorable HL and currently is listed as a treatment option in the NCCN guidelines for these types of disease. This regimen consists of weekly chemotherapy treatments, followed by consolidation radiation therapy of 36 Gy to any involved sites that were ≥5 cm at diagnosis. Consolidation therapy is treatment given to a patient who has completed primary treatments and achieved remission. This regimen’s advantages are reduced cumulative doses of radiation and individual drugs to the patient, which reduces the risk of late adverse events.

New Chemotherapy Drugs
New drugs are being investigated for use in HL patients. Currently, the one that generates considerable interest is gemcitabine. It is a nucleoside, the precursor to the basic units of deoxyribonucleic acid (DNA), and is used in lung and pancreatic cancers. When gemcitabine is incorporated into the cell’s DNA, replication cannot continue and the cell dies.

Radiation Therapy
In 1902, William Pusey released the first report of radiation treatment for HL. His first patient was a boy with a swollen gland on the left side of his neck that was “as large as a fist.” Pusey described the dramatic results achieved by treating this boy, and other HL patients, with radiation. Similar reports followed from other physicians, although treatment at that point was palliative rather than curative. Not until the work of Vera Peters and Henry Kaplan, in the second half of the 20th century, did radiation treatment for HL come of age.

For most of the 1900s, patients received high doses of radiation and no chemotherapy. These treatments resulted in often-severe late effects for survivors, including secondary malignancies and greatly increased rates of heart disease. Today’s treatment philosophy is to reduce the radiation dose and the size of the irradiated area as much as possible and allow chemotherapy to kill errant malignant cells throughout the body.

The radiation treatments normally used in HL are involved field radiation treatment (IFRT), extended field radiation treatment (EFRT) and subtotal nodal (or lymphoid) irradiation. IFRT is treatment given to the affected areas only. EFRT treats the “involved and immediately adjacent lymphoid regions.” Subtotal nodal irradiation includes all the areas at risk above and below the diaphragm, including the spleen (see Figure 4).

Radiation treatments in HL are given in a fractionated manner with a minimum 6 mV photon beam for areas above the diaphragm and 18 mV photons for areas below the diaphragm. CT simulation is used to mark the fields on patients prior to actual treatment. Treatment fields that include lymphoid regions often are large and irregular; any border separating fields should be placed away from the tumor to prevent underdosing in the tumor area. To ensure reproducibility of the

| Table 2 Common Chemotherapy Treatments for HL |
| Name | Drug Components |
| MOPP | Mechlorethamine, vincristine, procarbazine and prednisone |
| ABVD | Doxorubicin (Adriamycin), bleomycin, vinblastine and dacarbazine |
| BEACOPP | Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone |
| Stanford V | Doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin and prednisone |

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fields, the patient should be immobilized during simulation and treatments. The NCCN recommends that, whenever possible, high cervical areas and, in women, the axillae be excluded from the radiation fields.

Combined Treatments
Historically, initial treatments of HL consisted of high-dose radiation therapy, often exceeding 40 Gy, across extended fields with no shielding of major organs. With the advent of chemotherapy, reports of successful treatments using chemical agents, especially in patients who did not respond to radiation therapy, began to surface. Radiation and chemotherapy combined gained further popularity once the late effects of high-dose radiation treatments became apparent. The goal of combined-modality therapy today is to reduce the doses of radiation and toxic chemotherapy the patient receives, thus reducing or preventing their adverse late effects.

Because HL relapses often occur at the site of initial involvement, irradiating that area is important to eliminate the first tumor and decrease the chances of a recurrence, while chemotherapy destroys malignant cells that may have spread systemically.

Several studies have evaluated the efficacy of radiation treatments alone vs combined-modality treatments in HL. Press et al evaluated a regimen consisting of 3 cycles of vinblastine and doxorubicin followed by subtotal lymphoid irradiation, compared with subtotal lymphoid irradiation alone. All patients were in early-favorable stages of their disease. The study was aborted early because of obvious superiority of the combined-modality treatment. Failure-free survival in the combined-modality group was 94%, compared with 81% in the group receiving subtotal lymphoid radiation only.

A GHSG trial treated HL patients with either 30 Gy EFRT and 10 Gy IFRT or 2 cycles of ABVD consolidated with 30 Gy EFRT and 10 Gy IFRT. Although the overall survival rates were similar at a median follow-up of 87 months, freedom from treatment failure was significantly higher for the combined-treatment group than for the radiation-only group (88% vs 67%, respectively). Relapses also occurred sooner in the radiation-only group. Some patients who received radiation only relapsed within the first year of follow-up, whereas no patient in the combined-modality treatment group relapsed in the first 2 years after completing treatment.

The role of radiation treatment in advanced HL currently is unclear. An earlier GHSG trial evaluated consolidation with chemotherapy vs consolidation with 20 Gy IFRT in advanced-stage patients who achieved a complete response to 6 cycles of COPP/ABVD. The differences in the 5-year freedom from progression and overall survival rates between the 2 groups were not statistically significant.

The European Organisation for Research and Treatment of Cancer in collaboration with the Groupe d’Etude des Lymphomes de l’Adulte (trial No. 20884), looked at patients with stage III or IV HL. These patients were treated with 6 to 8 cycles of MOPP/ABV. Patients with complete response were randomized to receive IFRT or no further treatment. All patients with partial response received IFRT. In the complete-response group, there were no significant differences in event-free survival between the irradiated patients and those receiving no further treatment (79% and 84%, respectively, P = 0.35). However, the overall survival between the groups showed a statistically significant difference (85% and 91%, respectively, P = 0.07). The difference in survival was attributed to higher incidence of
leukemia and myelodysplastic syndromes in the patients receiving combined-modality therapy.

Conversely, the group of partially responding patients experienced a 5-year event-free survival of 79% and overall survival of 87%. Therefore, there may be a beneficial role for radiation therapy in patients with advanced disease who achieve a partial response to chemotherapy, even though such an advantage is not seen in patients achieving a complete response.

The current GHSG trial is treating only patients with PET-positive residual disease with radiation. The trial compares a variety of BEACOPP protocols in patients with advanced HL.

Based on existing data and member experience, the NCCN created guidelines for radiation therapy as part of a combined-modality treatment.

**Treatment Algorithms**

As is the case with all malignancies, clinical trials of HL treatment regimens most often look at 2 primary endpoints: freedom from progression (or freedom from treatment failure or event-free survival) and overall survival. In HL, however, overall survival is harder to evaluate for individual treatments because a variety of salvage therapies exist and their success may obscure any survival differences that are due to the treatment under investigation. These salvage therapies include high doses of potent chemotherapy drugs and an autologous stem cell transplant (ie, using the patient’s cells).

For example, according to Diehl et al, in a study of the Stanford V regimen, the overall freedom from progression rate for 162 patients at a median follow-up of 5.4 years was 89%, the overall survival was 96%. Effective salvage therapy led to the high overall survival rate compared to the freedom from progression rate.

The following treatment algorithms are based on the NCCN recommendations for each HL stage and risk category. If the patient fails to achieve a complete or partial response, salvage therapy is instituted. The particular salvage therapy depends on the initial therapy the patient had, the patient’s initial disease stage and possibly whether the site of relapse was treated previously. These recommendations are based on clinical study results and NCCN member experience, but clinicians will individualize treatments based on many factors that change from patient to patient. Clinical trials also constantly seek less toxic and more effective therapy combinations to help patients achieve a full recovery without delayed adverse events. As a result, radiation therapists might see different protocols than the ones described here. In general, however, the following protocols are the most common HL treatments in North America today.

**Early-stage CHL**

In early-stage favorable CHL, ABVD is administered for 2 or 4 cycles, followed by consolidation radiation therapy (30 Gy). Restaging with PET-CT is done after completion of chemotherapy and before consolidation. Patients who cannot withstand chemotherapy may receive subtotal nodal irradiation alone.

In early-stage unfavorable cases, 4 cycles of ABVD are followed by restaging with PET-CT. Patients who achieve complete or partial response receive 2 additional cycles of ABVD. IFRT follows these 2 additional cycles in bulky disease. For patients who cannot tolerate more chemotherapy but who had a complete response to the initial cycles, IFRT may replace the 2 additional cycles of ABVD.

If the Stanford V regimen is used, it is administered for 3 cycles, followed by restaging with PET-CT. Consolidation radiation therapy consists of 36 Gy to sites that were initially >5 cm and sites that showed PET positivity following completion of chemotherapy.

**Advanced-stage CHL**

If a patient is in stage III or IV, chemotherapy choices include ABVD, Stanford V and escalated BEACOPP. The latter is recommended for patients with IPS scores of 4 or above.

The treatment protocols for ABVD and Stanford V are essentially the same as the ones for early-stage unfavorable disease, except that patients with initial partial response to 4 cycles of ABVD may receive to 4 additional cycles, instead of the typical 2. For the Stanford V protocol, radiation treatments after completion of chemotherapy may include the spleen, if there is evidence of its involvement.

Escalated BEACOPP is given for 4 cycles, after which the patient is restaged with PET-CT. Patients achieving a complete response receive 4 baseline (nonescalated) BEACOPP cycles, followed by 30 Gy of radiation to sites that were initially >5 cm.

Partial responders are given 4 more escalated BEACOPP cycles following the initial 4 cycles, followed by additional restaging. Patients who still have a positive PET scan are either sent for high-dose chemotherapy with autologous stem cell transplant or receive 30 to 40 Gy of radiation to tumor sites that were initially >5 cm and 40 Gy to all other areas that still are positive.

**Refractory or Relapsed CHL**

As previously mentioned, the prognosis for patients with refractory or relapsed disease is poor. High-dose chemotherapy with autologous stem cell transplant is currently the standard treatment for these patients (see Figure 5), with the exception of patients who relapsed after receiving IFRT only because they can achieve a lasting remission with standard chemotherapy.
Advances in stem cell transplants, including the change from bone marrow transplant to peripheral blood stem cell transplants, have reduced the death rate from the procedure considerably, from 15% to less than 3%, according to one report. A disease that shows sensitivity to standard-dose second-line chemotherapy (SDSC) is required before patients receive the transplant option. Several studies have shown that patients without an SDSC-sensitive disease do not benefit from the more intense high-dose chemotherapy with autologous stem cell transplant therapies. There is currently no agreed-upon “gold standard” SDSC.

Figure 5. PET-positive residual mass in a patient with initial diagnosis of stage IIA nodular sclerosis HL. This patient underwent a restaging PET-CT scan 2 months after treatment with 6 cycles of ABVD. A. Fused PET-CT images show increased uptake clearly greater than that of mediastinal blood pool structures within the residual anterior mediastinal mass, consistent with persistent disease. B. Follow-up PET-CT scan performed 2 months later shows substantially more intense uptake in the same area, again suggesting persistent disease. C. A third follow-up scan performed 4 months thereafter also demonstrates intense uptake in the same area but now with additional new sites of disease in the right paratracheal, right hilar and subcarinal regions, indicating further disease progression. The patient then underwent high-dose chemotherapy and autologous stem cell transplantation. Reprinted with permission from Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25(5):571-578.
imaging in assessing HL treatment response has implications linked to a radioactive particle, such as $^{90}$yttrium. The particle emits low radiation, but it is enough to kill the cell the antibody targets and other nearby cells. Although this treatment is mainly in the anecdotal stage, it shows promise, especially in patients with refractory and relapsed disease.1

**Role of FDG-PET**

For the past decade, the importance of PET imaging in assessing HL treatment response has increased.2,3 It also is becoming apparent that early interim response to therapy, as assessed by $^{18}$fluorodeoxyglucose (FDG)-PET between treatment cycles, may serve as an accurate prognostic factor.3 Zijlstra and colleagues conducted a meta-analysis of studies that examined FDG-PET assessments of response to first-line therapy in HL and aggressive non-Hodgkin lymphoma.23 Using pooled results, the meta-analysis found the average sensitivity of FDG-PET in detecting residual disease at the end of HL treatments was 84% (95% confidence interval [CI], 71% to 92%), and its average specificity was 90% (95% CI, 84% to 94%).

FDG-PET increasingly is used between treatment cycles to assess a patient’s response and indicate whether treatment should be modified. For example, a patient showing a complete response to 2 cycles of ABVD might not need 6 full cycles of this regimen. Doxorubicin, which is part of the ABVD regimen, carries a risk of cardiotoxicity that depends on the drug’s cumulative dose, so the ability to reduce the dose, without sacrificing the patient’s chance of a cure, is important.

The prognostic value of interim FDG-PET has been demonstrated in several studies (see Figure 6). In a small study, Kostakoglu et al showed that FDG-PET after 1 cycle of therapy had a high predictive value and correlated well with FDG-PET after treatment completion.24 Of 31 patients who were PET-negative after 1 cycle of chemotherapy, 100% were in remission at a median follow-up of 28 months after treatment completion. There were 16 PET-positive patients after 1 cycle of treatment, 2 of them false positive (1 had an active infection at the biopsy site when the PET scan occurred). Of the 14 true-positive results, all patients either had refractory disease or relapsed at a median follow-up of 5.5 months (95% CI, 3 to 8 months).

In the repeat scanning performed at the end of treatment, 35 patients were PET-negative. Three were false negative, and their disease recurred 7 to 22 months later. In that study, the negative predictive value of FDG-PET after 1 cycle of therapy (100%) was higher than the negative predictive value at the end of treatment (91.4%), although the difference was not statistically significant ($P = 0.40$).

Gallamini et al studied 260 patients with advanced or early unfavorable HL.25 Most patients (n = 249) were treated with 6 cycles of ABVD, and 104 patients also received consolidation radiation therapy either for bulky disease (30 to 36 Gy) or for residual disease after treatment completion (36 Gy). Interim FDG-PET was performed after 2 cycles of chemotherapy (“PET-2”); however, treatment changes based on the results of PET-2 were not allowed in the study. The study showed that interim FDG-PET results were more predictive of progression-free survival than the IPS. At a median follow-up of 2 years, the progression-free survival for PET-2-positive patients was 12.8%, while the progression-free survival of
PET-2-negative patients was 95%. Multivariate analysis showed that when PET-2 results were added to the equation, the IPS had no value.

It is debatable how many cycles of therapy a patient should have before an interim FDG-PET scan is performed. In different studies, the timing ranged from 1 to 4 cycles.

The widespread use of PET and PET-CT created a need for standards that should apply in performing the scans, interpreting them and guiding patients’ treatments based on these interpretations. Standardization also is necessary to ensure reproducible results in clinical trials, thus ensuring that such study results are reliable, trustworthy and applicable to other patient populations.

**Standards**

In 2007, the Imaging Subcommittee of the International Harmonization Project in Lymphoma published its consensus paper for “performing and interpreting [PET] imaging for treatment assessment in patients with lymphoma both in clinical practice and in clinical trials.”

**Timing of Imaging and Patient Preparation**

To reduce the risk of false-positive results arising from inflammatory response to treatment, PET imaging should be done at least 3 weeks after completion of chemotherapy and at least 8 weeks after completion of radiation treatments or radioimmunotherapy. When used between treatment cycles, PET scans should be done within 4 days of the start of a new cycle. Currently, there is not enough information to standardize interpretations of interim PET studies. Therefore, the consensus paper recommends that interim PET scans only be used in clinical trials or as part of a prospective registry.

To assess treatment response, the patient receives a 3.5 to 8 MBq/kg FDG dose. The adult minimum dose is 185 MBq; for children, it is 18.5 MBq. The FDG tracer cannot be given to patients with blood glucose levels above 200 mg/dL.

Whole-body imaging should include, at minimum, the area from the base of the skull to midthigh. Image acquisition should begin 50 to 70 minutes (ideally 60 minutes) after FDG administration. PET or PET-CT data should be displayed on a computer screen on which images from all angles can be viewed together. Corrections for attenuation, coincidences and scatter should be done.

**Image Interpretation**

Typically, visual assessment is sufficient and images are not analyzed by computer. In most areas, PET-positivity is defined as uptake (either focal or diffused) above background in an area where such activity is not normal. If residual masses are ≥2 cm...
in diameter, the background activity is always that of the mediastinal blood pool, regardless of the mass’ location (see Figure 7). (Scans must be attenuation-corrected.) However, lesions in the spleen or liver ≥1.5 cm on CT should be compared to the background activity of the spleen or liver, respectively. Such lesions are only negative if their uptake is lower than that of the spleen or liver. For spleen or liver lesions <1.5 cm, the lesions are negative if their uptake is equal to or lower than that of the corresponding organ.

PET imaging cannot accurately assess bone marrow involvement; a bone marrow biopsy is required to rule out residual disease.

Avoiding False Positives

When using PET imaging, radiologic technologists should keep in mind that FDG activity is elevated under various conditions, such as infection or inflammation. Although the negative predictive value and sensitivity of PET are high, false-positive readings occur. Steps to minimize the risk of a false-positive scan include adhering to the timing guidelines for PET scanning at the conclusion of treatment, avoiding PET scans when the patient is known to have an active infection and obtaining confirmatory biopsies if unusual results appear on the scan. Unusual results include, but are not limited to, the appearance of high FDG uptake.

Figure 7. PET-negative residual mass in a patient with nodular sclerosis HL. This patient underwent a restaging PET-CT scan 1 month after treatment with 6 cycles of ABVD; the scan showed a residual mass in the mediastinum measuring 5.0 x 3.7 cm, with FDG uptake clearly less than that of mediastinal blood pool structures. The mass appears photopenic compared with surrounding mediastinal background activity. This patient was without evidence of disease after 25 months of follow-up post-therapy. A. CT images. B. PET images. C. Fused PET-CT images. Reprinted with permission of the American Society of Clinical Oncology. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25(5):571-578.
Special Considerations

Because HL treatment is difficult and toxic, special considerations are required for certain groups of patients. Future risks also must be assessed for patients who might develop late adverse sequela.

Pregnant Patients

Because the incidence of HL peaks during young adulthood, clinicians are bound to see the disease in pregnant women. In fact, HL is the fourth most common cancer during pregnancy.1 In many cases, pregnancy can be brought to term before treatment begins or with minimal chemotherapy, especially during the second half of the pregnancy. Pregnancy alone does not alter the clinical course of HL, nor does it seem to affect survival rates, when compared to women who were not pregnant at diagnosis.26 It is obvious, however, that the diagnosis and treatment of a malignancy during pregnancy presents special challenges.

Staging of HL in a pregnant woman should be done using magnetic resonance (MR) imaging and ultrasound imaging, as opposed to CT or PET-CT, to avoid exposing the fetus to radiation.

If the diagnosis of HL is made during the first trimester, women are advised to terminate the pregnancy. If a woman does not terminate the pregnancy and treatment cannot be delayed until the second trimester, treatment with vinblastine may be an option. Because most cases of HL begin above the diaphragm, radiation with fetal shielding at a dose <10 Gy is possible.1

In 1992, Woo et al outlined the outcomes of 16 pregnancies occurring in women with HL between 1956 and 1990 at The University of Texas M.D. Anderson Cancer Center.27 The women were treated with 6 mV photons or 60cobalt. Treatments ranged from the neck area only (35 Gy), neck and mediastinum (40 Gy) and mantle field radiation (40 Gy). All 16 women were past 8 weeks of pregnancy and delivered healthy babies at term. The estimated dosage to the shielded fetuses ranged from 0.014 to 0.055 Gy with photon treatment, and 0.1 to 0.136 Gy with 60cobalt treatments. No malignancies or other abnormalities were detected in any of the children throughout the study’s follow-up period.

Because chemotherapy drugs can pass through breast milk, new mothers should not breastfeed while receiving treatment.3

Elderly Patients

Elderly people with HL have lower survival rates than their younger counterparts. The reasons are related to the patient’s overall condition and disease presentation.1,6

HL in elderly patients typically presents at a later, more advanced stage and has a high frequency of relapse.1 Because many elderly patients suffer from other ailments, some treatment options may not be available to them. For example, patients with cardiac problems should not be treated with doxorubicin because it can cause heart damage. Similarly, patients with lung problems cannot be treated with bleomycin, a drug that is toxic to the lungs.

Some elderly patients are simply too frail to withstand the rigors of standard treatments, and some side effects are more pronounced in elderly patients. For example, a prolonged decrease in white blood cell count is common in elderly patients who receive ABVD for advanced HL. This may result in frequent infections.

In patients with early-stage disease who are not able to tolerate chemotherapy, radiation alone may be enough, although the dose may have to be reduced. Mantle field or inverted Y radiation may be necessary in these cases.

Elderly patients who are otherwise in good health and able to receive the standard recommended treatment for their stage and risk category do just as well as younger patients after treatments. Therefore, it is not the patient’s age, but rather his or her overall condition that causes the poorer outcome in elderly HL patients.6

Long-term Complications

As previously mentioned, the paradox of HL lies in the fact that many survivors face an increased risk of adverse consequences from the very treatments that saved their lives. The HL death rate decreases among survivors over time, but an increased risk of death from treatment toxicities remains significant even after 25 years of follow-up.28 Other long-term effects of treatment, such as infertility or psychosocial problems, may not be life threatening, but still can have a profound effect on the patient’s quality of life.

Perhaps the most frightening prospect for an HL survivor is the increased risk of secondary malignancies, especially lung, breast, gastrointestinal and hematologic cancers. With current treatment philosophies that limit or eliminate radiation treatments and reduce or eliminate the total dosage of certain chemotherapy drugs, the risks for patients receiving treatments today are lower than for those treated in previous decades. However, follow-up of clinical trials evaluating these new regimens is not yet long enough to assess the full long-term impact of these newer treatments. In addition, patients treated prior to 1990 are still fully at risk for the effects of older treatments.8 Follow-up care and monitoring is extremely important in HL survivors.
Additional Malignancies

Women who received radiation treatments for a mediastinal mass should have an annual screening exam for breast cancer starting 8 to 10 years after treatment is complete or at age 40, whichever comes first.\(^8\) Many young women have dense breasts, which may yield false-negative mammography findings. In 2 studies quoted by Hodgson, only 58% and 42% of breast cancers in HL survivors were detected by mammography.\(^8\) MR screening may be necessary in addition to mammography.

The American Cancer Society recommends an annual breast MR, in addition to mammography, starting 8 to 10 years post-therapy in women who received chest irradiation between the ages of 10 and 30 years.\(^8\) A mammogram in a woman with dense breasts still is important, as it may show microcalcifications or ductal carcinoma in situ, which MR imaging might miss.\(^8\)

It is important that women perform monthly breast self-exams. Studies have shown that a palpable mass can develop in HL survivors between the annual screenings.\(^8\)

Chest irradiation and treatment with alkylating agents, such as nitrogen mustard (mechlorethamine), also increase the risk of lung cancer. At highest risk are people treated with chest radiation and an alkylating agent at age 40 or older, especially if they are smokers. Compared with smokers who have no history of HL, HL survivors who smoke are at a significantly higher risk of developing lung cancer, and should be strongly encouraged to quit smoking. Currently, there is no clear advantage to CT or any other type of screening for lung cancer in low-risk patients.\(^2\) The NCCN recommends an annual chest radiograph or CT scan for patients at high risk.\(^5\)

Reproductive Damage

Infertility due to radiation or certain procarbazine-containing chemotherapy treatments may be helped by assisted reproductive technologies. Counseling is highly recommended for people experiencing infertility following HL treatment. In cases where pregnancy planning is possible prior to beginning of treatment, sperm or ovarian tissue can be preserved for later use. Reports of successful ovarian tissue transplants from a sibling also exist. In men, even if sperm were not preserved prior to treatment, the problems of very low sperm count or poor sperm motility can be overcome through the use of intracytoplasmic sperm injection.\(^8\)

In women, the risk of sterility because of radiation increases with age. For example, a dose of 2.5 to 5 Gy will sterilize up to 40% of women younger than 40, but more than 90% of women older than 40 years. Women in need of abdominal radiation treatments may want to consider laparoscopic transposition of the ovaries. Interestingly, women experiencing premature menopause as a treatment complication are more protected from breast cancer risks.\(^8\)

Additional Complications

People who received neck irradiation should be screened for hypothyroidism annually. Approximately 50% of such patients will develop hypothyroidism, which results in decreased metabolism and other complications.\(^7\)

Treatment with anthracyclines, such as doxorubicin, and chest irradiation without heart shielding can cause a variety of heart problems. The risk increases in patients who were younger at the time of treatment. The NCCN recommends “aggressive management of cardiovascular risk factors” (eg, cholesterol levels) and blood pressure monitoring. In addition, the guidelines recommend a baseline stress test and an echocardiogram 10 years after completion of HL therapy.\(^5\)

People who have had their spleen removed or irradiated are at high risk for severe bacterial infections. They should receive regular vaccinations, including vaccinations against meningococcal infections, pneumonia and *Haemophilus influenzae* type b.\(^5\)

Other potential complications of treatments include reduced lung function (from radiation or bleomycin-containing chemotherapy treatments), reduced levels of saliva leading to tooth decay (from radiation treatments in the high neck area) and bone damage (from radiation and, in women, premature menopause).\(^2\)

Conclusion

Hodgkin lymphoma has undergone a considerable transformation since its first description in 1832. From an invariably fatal disease, it has become a curable cancer for many patients. Along the way, HL changed the field of oncology considerably through the introduction of multiagent chemotherapy, combined-modality treatments and a growing understanding of the importance of a multidisciplinary team and prospective studies. In that respect, the story of HL is truly one of the best oncology success stories of the 20th century.

The story, however, still is being written. As clinicians learn more about the toll HL treatments take on survivors in the decades following recovery, they are changing these treatments to ensure a better balance between recovery and lasting good health. Better tools, such as FDG-PET and PET-CT, are enabling oncologists to tailor treatments to the patient’s individual situation, sparing some patients unnecessary toxicities and intensifying the treatments for others who
require it. Although survival rates of patients with relapsed or refractory HL still are poor, a growing arsenal of treatments, including monoclonal and radiolabeled antibodies, is improving the odds for these patients.

The role of radiation therapy, as well as its recommended protocol and doses, continues to change. Although it started as the only treatment for HL, radiation therapy now is mostly a companion to chemotherapy, and its role in advanced HL is unclear. However, as more studies of advanced-stage disease are completed, this role will be better defined.

Today, most HL patients can expect to be cured and those who are not still can expect to live longer than was historically possible. Whether the 21st century will see the conquest of HL is unknown, but it is certain that its treatment will only get better as time goes by.

References
HODGKIN LYMPHOMA


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Hodgkin Lymphoma

To earn continuing education credit for this Directed Reading, read the preceding article and circle the correct response to each statement. Transfer your responses to the answer sheet on Page 85, and then follow the directions for submitting the answer sheet to the ASRT. Members also may take quizzes online at www.asrt.org. Effective October 1, 2002, new and rejoining members are ineligible to take DRs from journals published before their most recent join date unless they purchase access to the DR quiz. Note: Readers who are not ASRT members can receive credit by joining the ASRT. To join, contact the ASRT Customer Information Department at 800-444-2778, Press 5, or join online at www.asrt.org.

*Your answer sheet for this Directed Reading must be received by the ASRT on or before this date.

1. Hodgkin lymphoma (HL) has a cure rate of at least 80%, depending on the disease stage and the presence of certain risk factors. However, cases of relapsed or refractory disease have a cure rate approaching only _____%.
   a. 65
   b. 60
   c. 55
   d. 50

2. Systemic, or B, symptoms for HL include ________.
   a. sleep apnea
   b. loss of appetite
   c. drenching night sweats
   d. chest pain

3. Classic HL (CHL) is characterized by abnormal cells called:
   a. Reed-Sternberg cells.
   b. popcorn cells.
   c. lymphocytic cells.
   d. histocytic cells.

4. Compared with CHL, lymphocyte-predominant HL (LPHL) is:
   a. less aggressive.
   b. more aggressive.
   c. more common.
   d. less sensitive to chemotherapy.

5. Typically, the first symptom of HL that a patient notices is:
   a. difficulty swallowing.
   b. persistent coughing.
   c. an enlarged gland in the neck.
   d. continuous stomach ache.

6. A ________ should be part of a diagnostic workup for HL.
   a. staging laparotomy
   b. needle aspiration biopsy
   c. fasting glucose test
   d. contrast-enhanced diagnostic CT of the chest, abdomen and pelvis

7. The National Comprehensive Cancer Network (NCCN) lists ________ among unfavorable indicators for HL stage I and II.
   a. presence of local symptoms
   b. presence of systemic symptoms
   c. cancer in any lymph node
   d. a mass anywhere in the body > 3 cm
8. Which of the following statements are true about treatment effects for patients with HL?
   1. Heart disease is a potential adverse effect.
   2. Long-term survival is rare.
   3. By 10 to 15 years following diagnosis, deaths from treatment toxicities outnumber deaths from the disease.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2 and 3

9. According to this Directed Reading, the most detrimental effects of the MOPP protocol are ________ and ________.
   a. leukemia, sterility
   b. infections, vomiting
   c. lung cancer, breast cancer
   d. heart disease, ovarian cancer

10. ________ is the current gold standard in chemotherapy treatment for every stage of HL.
    a. Time-escalated BEACOPP
    b. COPP
    c. ABVD
    d. Stanford V

11. Patients with advanced HL and an international prognostic score (IPS) of 4 or more commonly are treated with:
    a. MOPP
    b. Stanford V
    c. radiation therapy only.
    d. BEACOPP.

12. Radiation dose for the Stanford V protocol in bulky disease is:
    a. 30 Gy IFRT + 10 Gy EFRT.
    b. 40 Gy.
    c. 30 Gy EFRT + 10 Gy IFRT.
    d. 36 Gy.

13. Subtotal nodal (or lymphoid) irradiation includes which regions?
    a. lymphoid regions above the diaphragm only
    b. abdominal lymphoid regions
    c. the liver and spleen
    d. all areas at risk, including the spleen

14. Radiation treatment for HL involves a (an):
    a. 18 mV photon beam for areas above the diaphragm and 6 mV photons for areas below the diaphragm.
    b. 6 mV photon beam for areas above the diaphragm and 18 mV photons for areas below the diaphragm.
    c. 12 mV photon beam for areas above the diaphragm and 18 mV photons for areas below the diaphragm.
    d. 6 mV photon beam for areas above the diaphragm and 12 mV photons for areas below the diaphragm.

15. The NCCN has created guidelines for radiation therapy as:
    a. a stand-alone treatment for all stages of HL.
    b. a stand-alone treatment for high-risk patients in advanced stages of the disease.
    c. part of a combined-modality treatment in CHL.
    d. no part in HL treatment; chemotherapy alone is used.

16. According to the NCCN treatment algorithms, restaging with PET-CT for CHL should occur:
    a. after completion of initial chemotherapy cycles, before consolidation radiation therapy.
    b. after 1 chemotherapy cycle.
    c. after consolidation radiation therapy.
    d. before any treatment occurs.

17. Refractory or relapsed disease is best treated with a protocol that involves:
    a. ICE.
    b. dexa-BEAM.
    c. high-dose chemotherapy followed by autologous peripheral blood stem cell transplant.
    d. BEACOPP and radiation.

18. Generally, ________ is used to treat early-stage LPHL.
    a. radiation only
    b. the same protocol as is used for CHL
    c. chemotherapy only
    d. cryotherapy
19. FDG-PET has not proven helpful in determining whether treatment should be modified for patients with HL.
   a. true
   b. false

20. How much time should elapse before performing a PET scan after radiation treatments for HL?
   a. 3 weeks
   b. 8 weeks
   c. 4 days
   d. 4 months

21. According to this Directed Reading, FDG cannot be given to people with:
   a. high blood glucose levels (more than 200 mg/dL).
   b. low blood glucose (less than 70 mg/dL).
   c. prediabetes (fasting blood glucose 100 to 125 mg/dL).
   d. controlled diabetes.

22. At the completion of treatment, a CT scan shows a hepatic lesion 2 cm in diameter, with an uptake equal to that of the liver. This lesion is negative for lymphoma.
   a. true
   b. false

23. Which of the following statements are true concerning pregnancy and HL?
   1. Pregnancy alters the course of the disease.
   2. Pregnancy does not alter survival rates.
   3. Patients who are pregnant present special diagnostic and treatment challenges.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2 and 3

24. Elderly patients with HL who have lung problems should not be treated with __________, a drug that is toxic to the lungs.
   a. bleomycin
   b. doxorubicin
   c. gemcitabine
   d. mechlorethamine

25. A young, female HL survivor who received radiation therapy 8 years ago should take the following steps:
   a. annual mammography and breast MR imaging plus monthly breast self-exams.
   b. annual chest x-rays and biannual CT exams.
   c. annual PET-CT and MR imaging.
   d. monthly breast self-exams and mammography on an age-based screening schedule.

26. According to this Directed Reading, __________ is a long-term adverse effect of neck irradiation.
   a. hoarseness
   b. hyperthyroidism
   c. hypothyroidism
   d. permanently sore throat
Radiation-induced Spinal Cord Injuries

Kevin S Collins, MSEd, R.T.(R)(T), CMD; Eric Matthews, PhD, R.T.(R)(CV)(MR); Richard C McKinnies, MSEd, R.T.(R)(T)

Cancer can affect anyone at any age; however, it is diagnosed most commonly in people older than 55 years.¹ For 2008, the American Cancer Society predicted 1,437,180 new cases of cancer would be diagnosed. Skin cancer is estimated to account for more than an additional 1 million new cancer patients in 2008.² The American Cancer Society also forecasted approximately 565,650 deaths associated with cancer in 2008.

With this common and often deadly disease, there are 3 main treatment options for patients to consider: radiation therapy, chemotherapy and surgery. These treatment options can be delivered individually or in combination. Each treatment option has its own side effects to consider; this article discusses only the radiation effects on the spinal cord. Not all radiation treatments cause damage to the spinal cord, but risks must be considered when the cord is included in the treatment field. The 2 most common areas treated with radiation that involve spinal cord irradiation are cancers of the lung, head and neck.² Total incidence for these sites for 2008 was estimated to be 267,580 and approximately one-third of these patients will have radiation therapy as part of their cancer treatment.¹,² When irradiating a patient for lung cancer treatment, the thoracic spine is the primary area receiving radiation. When irradiating the head and neck area, the cervical spine and the cervicothoracic junction are the primary areas in the treatment fields.²

Anatomy

The spinal column is divided into 33 segments, commonly defined by their location. Beginning at the base of the skull and moving toward the legs, there are 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, 5 sacral vertebrae and 3 vertebrae within the coccyx. The sacral and coccygeal vertebrae commonly fuse and are counted as 1 vertebral section each. The spinal cord extends from the medulla oblongata, within the brain, to the conus medullaris at approximately the level of the second lumbar vertebra, or L2.³ Like the brain, the spinal cord is a combination of white and gray matter; within the spinal cord, the white matter generally is anterior to the gray matter as it transits the spinal column within the vertebral foramen. The white matter transmits impulses to and from the brain via axonal elements of neurons. The cytoplasmic extensions of glial cells form a myelin sheath for the axons of the cord. The gray matter houses cell bodies of sensory, motor and autonomic neurons. The primary function of the spinal cord is the transmission of sensory and motor nerves between the body and the brain.

Discussion

Radiation myelitis, also known as chronic progressive radiation myelopathy, is among the most serious side effects of radiation therapy.⁴ In defining radiation myelitis, textbooks identify 4 levels of the syndrome (see Box). Radiation myelitis, regardless of the specific type, typically first appears 9 to 15 months following irradiation, but the initial signs and symptoms have been reported to appear as long as 3 years after the conclusion of radiation therapy.⁵,⁶ There are many reasons that caregivers see a wide range for initial onset and severity of radiation myelitis. The factors that affect the radiation tolerance of the spinal cord are the volume (length) of...
The cord included in the therapeutic field, dose per fraction and total cumulative dose received (see Table).

The primary mechanism that causes damage to the cord is demyelination, or slowly progressing atrophy. The atrophy results from the slow turnover of oligodendrocytes as a result of the killing of glial progenitor cells.\(^7\) This white matter necrosis is dependent on the volume of cord irradiated; a secondary mechanism of spinal cord degeneration, vascular injury, is less dependent on the volume of irradiated tissue.\(^7,8\) The vascular injury may accelerate, precipitate or initiate these white matter changes.\(^7\) The white matter consists mainly of myelinated nerve fibers but also has some unmyelinated nerve fibers.\(^7\) Radiation interacts with these fibers and causes damage to the supporting glia. In response to this damage, the patient loses spinal cord function and develops paralysis.\(^8\) The side effects experienced depend on the vertebral level of the radiation-induced damage.

### Effects of Spinal Injury

<table>
<thead>
<tr>
<th>Level of Injury</th>
<th>Effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between C1 and C5</td>
<td>Paralysis of some or all muscles used for breathing and all arm and leg muscles. Typically fatal unless a ventilator is used.</td>
</tr>
<tr>
<td>Between C5 and C6</td>
<td>Paralysis of the legs, trunk, hand and wrist. Weakness of the muscles that move the shoulder and elbow.</td>
</tr>
<tr>
<td>Between C6 and C7</td>
<td>Paralysis of the legs, trunk and part of the wrists and hands. Normal movement of the shoulders and elbows.</td>
</tr>
<tr>
<td>Between C7 and C8</td>
<td>Paralysis of the legs, trunk and hands.</td>
</tr>
<tr>
<td>C8 to T1</td>
<td>Paralysis of the legs and trunk. Weakness of the muscles that move fingers and hands. Horner syndrome (drooping eyelid, a constricted pupil and reduced sweating on one side of the face). Possibly normal movement of the shoulders and elbows.</td>
</tr>
<tr>
<td>T2 to T4</td>
<td>Paralysis of the legs and trunk. Loss of sensation below the nipples. Normal movement of the shoulders and elbows.</td>
</tr>
<tr>
<td>T5 to T8</td>
<td>Paralysis of the legs and lower trunk. Loss of sensation below the rib cage.</td>
</tr>
<tr>
<td>T9 to T11</td>
<td>Paralysis of the legs. Loss of sensation below the navel.</td>
</tr>
<tr>
<td>T11 to L1</td>
<td>Paralysis of and loss of sensation in the hips and legs.</td>
</tr>
<tr>
<td>L2 to S2</td>
<td>Various patterns of leg weakness and numbness, depending on the precise level of injury.</td>
</tr>
<tr>
<td>S3 to S5</td>
<td>Numbness in the perineum.</td>
</tr>
</tbody>
</table>

*At any level of the spinal cord, severe injury can cause loss of bladder and bowel control.

**Figure 1.** Effects of spinal injury by level. Adapted with permission from Porter RS, ed. The Merck Manual of Medical Information - Second Home Edition. Whitehouse Station, NJ: Merck & Co Inc; 2006.
Acute transient myelitis often has the quickest initial onset of any of the varieties of radiation myelitis, appearing 2 to 4 months after the completion of treatment. With this form of myelitis the patient typically experiences tingling and electric shock-like sensations in his or her extremities with flexion or extension of the spine, which is called Lhermitte sign or Lhermitte syndrome. This phenomenon appears to be the result of transient demyelination of the ascending sensory neurons. No treatment typically is required; Lhermitte syndrome typically resolves without treatment 2 to 40 weeks after irradiation.

The remaining 3 levels of radiation myelopathy are much more severe and their appearance can be delayed. These include acutely developing paraplegia or quadriplegia, lower motor neuron disease in the extremities and chronic progressive radiation myelopathy. Typically, the first signs of these side effects appear 20 to 30 months postiradiation treatment. The spinal cord impairment and its particular side effects depend on the vertebral level at which the damage occurs. These side effects are considered irreversible and typically have a high fatality rate.

Radiation injuries that occur between C1 and C7 could cause quadriplegia, which manifests as paralysis of the arms, legs and trunk below the level of the injury. If the injury is above C5, the patient also might experience cardiovascular and respiratory problems. Damage in this region is the most severe and carries the worst prognosis. Injuries at T1 and below can induce paraplegia, which involves sensory or motor loss in the lower limbs and trunk. See Figure 1 for side effects of injuries at various levels.

The tolerance dose 5/5 (TD5/5) is used to determine the risk of certain side effects related to radiation doses. The TD5/5 indicates a 5% risk of a given complication within 5 years. The TD50/5 indicates a 50% risk of the complication within 5 years. The standard TD5/5 for the spinal cord, with myelitis/necrosis as the side effect, is 47 Gy when a total spinal cord length of 20 cm is irradiated. Dose tolerance increases when the irradiated spinal cord volume is less. For example, the TD5/5 for 10 cm of irradiated spinal cord is 50 Gy, increasing to 60 Gy for 5 cm of dose field.

Dose fractionation is the administration of total dose in smaller parts, and it directly influences the susceptibility of the spinal cord to radiation damage. As the dose per fraction increases, the dose tolerance decreases. This concept is important to consider because many different dose fraction schemes are available to the radiation oncology team. On the conservative side, the rule of thumb in the clinical setting is not to exceed 45 Gy for the spinal cord dose. If it is necessary for successful treatment, a small volume of cord is allowed to receive a higher dose.

Substantiating the rule of thumb, 1 study noted that approximately 1% of patients experienced radiation myelopathy 2 years after radiation when 50 to 55 Gy was received; 5% of the studied patients experienced myelopathy after 55 to 60 Gy. Radiation doses exceeding 60 Gy caused the incidence of spinal cord injury to increase steeply. When using any total dose, the risk of damage also increased when the daily doses were greater than 2 Gy per fraction. This increase in side effects partially is due to the slow repair of sublethal damage in the spinal cord.

A second study reviewed 1 1 12 patients treated in the head and neck region. Only 2 patients experienced myelopathy when their total dose was less than 50 Gy. A third study indicated that radiation myelopathy in primates has a 50% rate of occurrence when the total dose to the cord is in the 68 to 73 Gy range.

Conclusion

With radiation therapy being 1 of the 3 main treatments for cancer, radiation-induced spinal cord
injuries are a major concern. Each staff member must be aware of the tolerance dose and factors that affect the likelihood of a spinal cord injury (see Table). The side effects of cord irradiation can be minimal to severe, depending on the dose received and the location in the vertebral column. To decrease a patient’s chances of developing radiation myelitis, it is imperative to consider the total dose the patient will receive and the fractionation of the total dose.

References

The textbook-style Spine Radiosurgery is the “first book dedicated to spine radiosurgery.” It contains contributions by pioneers of the field of radiosurgery, including introductions by Drs Lunsford and Mehta that provide a brief history of radiosurgery and the emergence of extracranial radiosurgery. The chapters are divided into 3 sections: Radiobiology, Physics and Techniques and Clinical Application of Spine Radiosurgery.

The introduction to radiosurgery begins with a detailed discussion of the radiobiology of radiosurgery, including single dose vs multiple fractionation; cell survival and the various molecular, cellular and histopathologic complications; and treatment volume, cord tolerance and retreatment tolerance for both conventional and stereotactic radiation delivery.

The role of patient immobilization, patient movement and the accuracy of dose delivery with different radiosurgery systems is detailed. Authors also describe the use of different imaging modalities for treatment planning, localization, assessment and analysis. Treatment delivery options are demonstrated through the clinical experience from the University of Pittsburgh Medical Center and Memorial Sloan-Kettering Cancer Center. In addition, features for the linear accelerator with cone-beam computed tomography and other systems are compared. The quality assurance chapter reviews the origins of spine radiosurgery systems, the methods used for continuous patient position monitoring and dosimetric considerations.

The authors discuss target delineation and radiation dose based on the “physical and biological characteristics of radiosurgery,” as well as consideration of tumor and host factors and normal tissue constraints. The authors present their findings on spinal radiosurgery dose for pain, tumor control, recurrent tumors and primary tumors. Separate discussions address spinal metastatic treatment, spinal cord compression, treatment failures and complications, benign extramedullary spinal tumors and primary spine tumors.

Spine Radiosurgery is an incorporation of knowledge about and collaborative experience with spinal radiosurgery. While outlining the complexity of a multidisciplinary treatment approach, it provides a basic understanding of the process and resulting patient outcome. Throughout the book, the authors emphasize patient response and outcome with discussions on quality assurance, patient immobilization, dose delivery, clinical outcomes and quality of life. Each chapter lists numerous references for additional information. This book could be helpful for physicians and radiation therapists seeking historical perspective, current practices and future applications of radiosurgery.

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Ureteral Carcinoma
Kristen Houtman, BS, R.T.(T)

Tumors of the upper urinary system (ureter and renal pelvis) are unusual, with fewer than 3000 patients diagnosed annually in the United States. Primary tumors of the ureter occur only half as frequently as do tumors of the renal pelvis, but ureteral tumors have been increasing in incidence over the past 23 years. Upper tract tumors develop in men 2 to 3 times more than in women, with a peak age of development of these tumors in the seventh and eighth decades of life.

Although ureteral carcinoma is not often seen or treated in radiation oncology, it is important to understand the disease and how it is treated. This article discusses anatomy, symptoms, diagnostic tests, treatment options, side effects and prognosis.

Ureteral Anatomy
The anatomy of the ureters and surrounding structures is important in understanding ureteral tumors. The ureters are muscular tubes that carry urine from the kidneys to the urinary bladder, passing anterior to the psoas major (see Figure 1).

Although the position of the ureteropelvic junction varies, it serves as a “landmark” that separates the renal pelvis and the ureter. The ureters propel urine along by the motions of peristalsis and by gravity. In an adult, the ureters are usually 25 to 30 cm long and 3 mm wide. The ureters enter the bladder posteriorly, running within the wall of the bladder for a few centimeters. There are no valves in the ureters, and backflow is prevented by pressure from the filling of the bladder and the tone of the muscle in the bladder wall. The ureter opens into the trigone of the bladder; the opening is called the ureteral orifice.

The ureter is composed of the following layers: epithelium, subepithelial connective tissue and muscularis, which is continuous with a connective tissue adventitial layer. The major blood supply and lymphatics are found in the outer layer. Pelvic fat surrounds the ureter.

The mucosal lining of the ureter is similar to that of the urinary bladder, being composed of transitional cell epithelium. Thus, most renal pelvic and ureteral cancers are transitional cell carcinomas. Squamous carcinomas only account for approximately 10% of renal pelvic cancers and are much rarer in the ureter. Adenocarcinomas and mesodermal tumors are also very rare. Benign tumors include fibroepithelial polyps, leiomyomas and angiomas. The ureter and renal pelvis can be invaded by cancers of contiguous structures, such as primary renal, ovarian or cervical carcinomas. However, true metastasis to the ureter is rare. Commonly, tumors of the upper urinary tract are multifocal, but they also can occur singly.

There are 2 spiral layers of smooth muscle in the ureter wall: an inner loose spiral and an outer tight spiral (see Figure 2). The inner loose spiral sometimes is described as longitudinal, and the outer spiral as circular. The distal third of the ureter contains another layer of outer longitudinal muscle.

Symptoms and Diagnostic Tools
The typical presenting signs and symptoms of ureteral carcinoma are hematuria and flank pain. Other, less common presenting symptoms are weight loss, anorexia and lethargy, which are more common indicators of metastatic disease. Between 10% and 15% of patients are asymptomatic.

The etiology of ureteral carcinoma is unknown, but studies have implicated environmental carcinogens and stresses as risk factors for this type of cancer. Workers in chemical, petrochemical and plastic industries, aniline dye workers, and those exposed to coal, coke, tar and asphalt are at an increased risk for renal pelvis and ureteral carcinomas. Cigarette smoking is also a major risk factor for upper-tract carcinomas.

The initial work-up for a patient suspected of ureteral carcinoma is a history and physical examination. A patient’s personal, family and...
social histories are taken. The physical exam includes listening to the lungs and palpating the cervical lymph nodes, the area of pain and the abdomen. Urinalysis might be performed to check for hematuria and blood tests might be performed to see if there are other abnormalities.2

The first imaging examination typically performed is intravenous urography.2 Iodinated contrast media is introduced intravenously and a series of radiographs are taken at timed intervals as the contrast material proceeds through the kidneys, ureters and into the bladder. This examination often is reported as abnormal in patients with upper urinary tract cancers. Further examinations must then be conducted because the tumors must be differentiated from nonopaque calculi, blood clots, papillary necrosis and inflammatory lesions such as ureteritis cystica, fungal infections or tuberculosis.2

The next examination to be performed is typically retrograde pyelography, which allows more in-depth examination of the collecting system.3 Retrograde pyelography is the major diagnostic tool for ureteral neoplasms.4 Contrast material is injected into the ureteral orifice with a bulbacorn tip catheter. Intraluminal filling defects can then be identified in the ureter or renal pelvis.7 The tumor can appear as a pedunculated mass, a fixed filling defect, a focal irregularity of the ureteral wall or even a smooth stricture.4 The “goblet sign” is common and is considered pathognomonic for ureteral tumor. The goblet appearance is created by the dilation of the ureter distal to the lesion.2

Sonography, computed tomography (CT) and magnetic resonance (MR) imaging can identify soft-tissue abnormalities of the renal pelvis, but may fail to identify ureteral filling defects directly.2 All 3 imaging techniques can differentiate blood clot and tumor from nonopaque calculi. MR and CT can be used to examine the rest of the body for signs of regional lymph node metastasis or more distant metastasis.2

In ureteropyeloscopy, a rigid but flexible ureteropyeloscope is passed transurethrally through the ureteral orifice and allows direct visualization of upper urinary tract abnormalities.2 Through this instrument, a biopsy sample can be taken to confirm the presence of a ureteral tumor.2

Staging
Pathologic staging of ureteral carcinoma depends on histologic determination of the extent of invasion by the primary tumor. Appropriate regional nodes may be sampled to determine the extent of the disease.1 The staging system is the same for renal pelvis and ureter carcinomas.1 It is very difficult for urologists to get to the tumors and therefore difficult to stage them.

Treatment
Adjuvant treatments for ureteral tumors include surgery, radiation therapy and chemotherapy. There are different types of surgery,5 and surgery is the best option for patients with an upper-tract cancer. A radical nephroureterectomy is the removal of the entire kidney along with its perinephric fat, Gerota fascia and ureter with 1 cm of normal bladder mucosa surrounding the ureteral orifice. This surgery is for patients with normal contralateral kidney function.6 Typically, a regional lymphadenectomy then is performed.5

Distal ureterectomy is recommended for grade 2 to 3 or invasive tumors of the distal ureter, provided the proximal upper tract is free of disease.5 This can be used because recurrence proximal to the original
lesion is rare.5 Tumors in the middle or upper third of the ureter generally are best treated by nephroureterectomy.1 Radiation therapy remains an unproven adjunct for the control of residual tumor, unresectable disease or local recurrence.1 One study suggested the use of postoperative radiotherapy with 60 Gy to tumors in stage II, III or IV.1 The difficulty in establishing an accurate diagnosis, much less accurate staging of the ureteral tumor, is a major deterrent to preoperative radiation therapy.1 In addition, the potential for abdominal complications when treating with curative intent is high.1

Urothelial cancers tend to respond to cisplatin-based chemotherapy, especially combination chemotherapy regimens.1 Few data exist on the treatment of ureteral tumors, but in the experience of some physicians, ureteral tumors tend to be more responsive than transitional cell carcinomas arising in the bladder.1 The role of adjuvant chemotherapy in ureteral tumors remains unproven.1

Critical structures limit how much radiation can be delivered safely. The critical structures when palliatively treating a ureteral tumor that is located in the middle of the ureter are the opposing kidney and the spinal cord (see Figure 3).8 If this tumor were being treated for curative intent, there would be more critical structures because the radiation dose would be significantly higher. A dose-limiting structure for curative intent might include the intestines. A TD5/5 is the amount of radiation that causes 5% of patients to have complications within 5 years, and the TD95/5 is the amount of radiation that causes complications in 95% of patients within 5 years.8 Table 1 lists the TD5/5 and the TD95/5 for the critical structures.

**Survival Rates and Potential for Metastasis**

In order of decreasing frequency, the most common metastatic sites for ureteral carcinoma include regional lymph nodes, lung, bone and liver.2 Rare sites of metastasis include the spermatic cord and the penis.7 Lymphatic spread for renal pelvis and proximal ureteral tumors is initially to the regional hilar, paraaortic and paracaval nodes; distal ureteral tumors typically invade the pelvic nodes.7 The probability of developing upper-tract tumors in patients with bladder cancer is only 2% to 4%, compared with a risk of 1% to 3% for developing bladder cancer subsequent to an upper-tract tumor.3 Metastasis to the ureter most commonly occurs with carcinoma of the cervix or colon, or retroperitoneal lymphoma.1

The rate of survival for ureteral carcinoma is influenced by both the grade and the stage of the tumor.1 The overall survival rate is approximately 40%, with a 5-year survival of 56% for a well-differentiated cancer, as opposed to 16% for poorly differentiated lesions.1 Any spread to regional lymph nodes suggests a poor prognosis.1 Table 2 presents 5-year survival rates for ureteral tumors of various grades.

**Conclusion**

Ureteral carcinoma is a rare form of cancer. However, knowing the basics, such as presenting symptoms, epidemiology, diagnostic tests, anatomy, staging, treatment options, alternative treatments, critical structures, dietary needs, side effects, routes of spread and prognosis, is important to the radiation therapist’s ability to assist effectively in treatment.

**References**


**Table 1**

<table>
<thead>
<tr>
<th>TD5/5</th>
<th>TD95/5</th>
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<tr>
<td>Spinal Cord (20 cm³)</td>
<td>47 Gy</td>
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<tr>
<td>Kidneys</td>
<td>23 Gy</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>40 Gy</td>
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<tr>
<td>Colon</td>
<td>45 Gy</td>
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**Table 2**

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>5-Year Survival (%)</th>
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<tr>
<td>G1</td>
<td>&gt; 80</td>
</tr>
<tr>
<td>G2</td>
<td>30 to 90</td>
</tr>
<tr>
<td>G3 to G4</td>
<td>&lt; 25</td>
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Box
Locally Advanced Ureteral Carcinoma: A Case Study

The patient was an 84-year-old white man who presented with blood in his urine and left flank pain. His medical history included hypertension, gout and depression. The patient had undergone a cholecystectomy, a right eye lens implant and a colostomy in the right upper quadrant of the abdomen secondary to a locally advanced ureteral tumor near the splenic flexure region. He also had a stable lesion on the posterior aspect of the upper pole of the right kidney, which was suspected to be an oncocyto-ma. The patient had an uncle with a history of throat cancer, was married, did not drink and quit smoking in 1966. He did, however, smoke up to 3 packs per day for 23 years. He was a retired tool and die worker and was in the Navy.

The patient in this case underwent typical diagnostic imaging procedures for physicians to diagnose his tumor, including CT scans of the abdomen and pelvis, a retrograde pyelogram, ureteroscopy and a biopsy. The CT scans revealed a ureteral mass, and retrograde pyelogram findings included a long irregular narrowing of the proximal left ureter with some hydronephrosis proximal to the narrowing. The biopsy report indicated that the tissue was positive for malignant cells; favorable for urothelial carcinoma. The patient also underwent many radiographic chest examinations, bone scans and additional CT scans to determine whether there was any metastatic disease.

This patient’s ureteral tumor was in the middle of his left ureter (see Figures 3-6). However, ureteral tumors are seen more commonly in the lower third of the ureter. This patient’s records did not reference his staging, lymph node involvement or grade.

Continued on next page
The only statement was that his tumor was locally advanced. This may be because of the extreme difficulty in staging ureteral carcinomas. According to the radiation oncologist who treated this patient, the patient was stage IV because the disease had spread to the pelvic sidewall.

The patient underwent surgery at the time of diagnosis, but the nephroureterectomy was aborted because the tumor was locally advanced. Four courses of paclitaxel and carboplatin chemotherapy were given over a 5-month period.

Approximately 1 year later, the patient complained of unremitting flank pain in the area of the tumor, which he rated as 6 on a scale of 1 to 10. He was referred for radiation therapy for symptomatic management. The radiation treatment was palliative, with the goal of controlling pain. The prescription was 35 Gy in 14 fractionations for a daily dose of 2.5 Gy with a machine energy of 15 mV and no boost or brachytherapy procedure planned.

The patient was set up in the supine position using a wing board with headrest B and arms overhead. He also had a cradle for his leg position. He had 4 tattoos for positioning: 1 central axis tattoo in the left hypochondriac region, a straightening tattoo directly underneath in the left lumbar region and 2 side tattoos for leveling.

The treatment fields used were an anterior field and a posterior field. Neither of these fields had wedges. The anatomy being treated was the tumor on the left ureter, and the field size was 12.8 cm by 12 cm. The gross tumor volume was calculated at 483.679 cm$^3$ and received a mean value of 35.291 Gy. The anatomy shielded was the right kidney and the spinal canal. The volume of the right kidney was 229.145 cm$^3$ and received a mean value of .374 Gy. The volume of the spinal canal was 48.0773 cm$^3$ and received a mean value of 1.340 Gy. The anterior field received 49% of the dose and the posterior field received 51% of the dose (see Figure 3).

The patient experienced pain, nausea and loss of appetite. Many of his symptoms were present before his radiation treatment, with the exception of the nausea. He was prescribed an antinausea medication that relieved his symptoms.

The patient described in this case was incurable, and his prognosis was a few months to 1 year. This prognosis was based on the extent of the disease and the patient’s inoperable status.
Preparing entry-level professionals for practice in an ever-changing healthcare environment presents a tremendous challenge to educators. Although programs provide students with solid technical foundations for practice and templates for handling routine clinical problems, educational programs cannot possibly prepare graduates for all of the situations that they will encounter during their professional careers. For this reason, it is imperative that radiation therapists and other health care professionals prepare to be critical thinkers. Reflection as the basis for reflective practice has generated interest in the nursing, occupational therapy and medical education literature as a means for empowering students to learn from and build upon their clinical experiences while developing a skill that will aid them in the lifelong learning demands of a changing health care world. This article presents the concept of reflective practice and discusses its applicability to radiation therapy education.

Defining Reflective Practice

Reflection involves purposefully thinking about an experience with the goal of gaining new insights, ideas and understanding.1 Reflective practitioners routinely use these insights, ideas and understanding to recognize similarities between their experiences and the new or unique problems they encounter and to inform their actions in new situations. According to Westberg and Jason, if students in the health professions are to develop into reflective practitioners, they need to be reflective during and after their clinical education experiences.2 Schön referred to these 2 occasions of reflection as reflection-in-action and reflection-on-action.1

In our profession, reflection-in-action might be thought of as “thinking like a radiation therapist,” a type of artistry that goes beyond simply applying theory and technical knowledge in a given clinical situation. Just like riding a bicycle and making adjustments based upon speed, balance and bumps encountered, therapists must constantly redesign what they do as they are doing it. This “thinking on one’s feet” may take the form of adapting a patient’s treatment position to alleviate discomfort, modifying instructions and explanations given to a patient to accommodate his or her level of understanding or concerns, or double-checking a patient setup when something doesn’t look right. Schön described reflection-in-action as the ability to “reshape what we are doing while we are doing it.”

We often are not aware of our reflection-in-action. Like a person riding a bicycle, radiation therapists have a feel for what they do and might find it difficult to explain to students why and how they make adjustments in their everyday work. It is often not until the unexpected occurs or something goes wrong (eg, a fall off the bicycle or an error during patient treatment) that we truly reflect on what we were thinking about or feeling during the experience.

The second type of reflection, reflection-on-action, is essentially a cognitive postmortem that occurs after an experience, when we stop and ponder what actually happened, the role we played, what we were feeling at the time and what we might learn from it. Like reflection-in-action, reflection-on-action frequently is prompted by a critical incident involving an error, a difficult situation or an unexpected result.3 Reflection-on-action allows health care professionals to revisit their experiences to explore and learn from them.

Schön argued that the use of both forms of reflection enables students and professionals to learn continually from their experiences.1 He further pointed out that reflecting on reflection-in-action indirectly shapes future actions because doing so begins an internal dialogue of thinking and doing from which one learns to become more skillful.

Killion and Todnem extended Schön’s concepts to include a third type of reflection, reflection-for-action.4 They described...
reflection-for-action as the process through which novice and expert radiation therapists can begin to anticipate situations and plan through mental preparation before being faced with clinical problems. They posited that it is not sufficient to reflect-in-action and reflect-on-action but that reflection-for-action also is crucial to professional development and quality care.

Reflection in Radiation Therapy Education

Traditionally, education in the health professions has neglected reflective knowledge in favor of technical, scientific knowledge. Although the ability to reflect and build on one’s repertoire of knowledge and experience clearly is essential for competence as a health care professional, it often is not addressed in the educational curriculum. The importance of reflection as part of the learning process has been emphasized by many investigators in nursing, social work, occupational therapy and medical education and is becoming an important feature of professional training programs in many disciplines.

In educational programs in fields such as radiation therapy, where learning takes place in the classroom and the clinic, reflection has been cited as a means of integrating learning that occurs in the 2 settings. Reflection enables learners to identify what knowledge they have gained through reading or lectures that they can bring to a particular clinical problem or situation. To encourage reflection, a clinical instructor might ask a student who is being introduced to a particular treatment setup, “Tell me what you’ve learned in your anatomy class about the lymphatics in this part of the body,” or “What do you know about how this type of cancer tends to spread?” This encourages the student to reflect on what already has been learned and tie that knowledge to a particular clinical problem.

Good professional judgment refers to an ability to transfer knowledge to recognize the familiar in the unique. Reflection can be used to develop this ability by encouraging learners to consider what they have learned from their experiences, generalize from particular experiences and then apply the knowledge to solving new problems. Reflective journals and group discussions focusing on critical or significant incidents are associated with improved clinical reasoning and decision-making skills and increased use of knowledge in action. Asking students to write about or discuss something that happened in the clinic that stood out as a particularly positive or negative experience, how they felt at the time, what they did and what they might have done differently is one means to encourage reflection that promotes learning from experience.

Reflection as part of the educational experience can enhance learner self-confidence and self-direction. Encouraging learners to think about and identify what they might already know or have experienced that is related to a new situation can bolster self-confidence by helping students recognize that they know more than they initially realized. Reflection also can provide a means by which learners identify deficits in their knowledge and errors in their thinking, evaluate their own performance, acknowledge their strengths and ask for help. This self-direction ultimately gives learners a perspective on themselves as central to the learning process, which can serve as a foundation for lifelong learning. Furthermore, insights gained through reflection can be the basis for meaningful discussions between learners and preceptors.

Strategies for Fostering Reflective Practice

In addition to the suggestions mentioned above, other strategies can be used to promote reflection. Journaling is one such strategy. According to Westberg and Duffin, journaling gives “writers the opportunity to become participant/observers of their own learning, to describe a significant experience and to then reflect on that experience to see what they can learn from having had it.” Keeping a journal provides an opportunity for students to revisit clinical experiences in an attempt to develop new perspectives that can be used to guide future actions. Writing about experiences also can help students to discover and clarify the knowledge underpinning their actions. A more private activity than debriefing or discussion, journaling helps learners to make explicit those feelings, ideas and impressions that they may not be prepared to share with others.

Private reflection is an individually centered activity; some authors have suggested that it is less effective than reflection through collegial interaction and dialogue. Clinical debriefing sessions can be used to provide the interaction and exchange of ideas that individual reflection lacks. Used as the basis for discussion, critical incidents and cases about mistakes, ethical dilemmas and difficult situations can be discussed in small groups to raise awareness of common situations and reactions to them. Because it is not possible to expose all students to every type of clinical problem they might encounter in practice, group reflection can add to the diversity of situations to which students are exposed. Sharing experiences with others presents the opportunity for students to become aware of strategies that may be useful in similar situations they might encounter in the future.

Talking with students for a short time during a clinical day can prompt reflection, allowing them the time they need to gather their thoughts and feelings and to consider their actions or the actions of others in a meaningful way. These informal encounters might benefit both individuals, the clinical instructor has an opportunity to develop a stronger rapport and relationship with the student and, consequently, gain
a deeper understanding of the student’s experience both as a student and as a person. It also can be a time for the student to consider, with the help of an instructor, particular aspects of practice in depth. If these brief discussions are to encourage reflection, instructors should be cautioned that this is not the time for questioning students about facts or technical parameters. Rather, these encounters are most valuable when students and clinical instructors look back together at an experience with the intent of increasing awareness and understanding of the situation.

Whichever strategies are employed, opportunities that permit students to reflect on and acknowledge their feelings in a nonthreatening environment can lead to a reduction in the anxiety that often accompanies the clinical education experience. Reflective experiences also can help create an atmosphere of cooperation as students and instructors share their experiences, achievements and disappointments. Reflection helps students to find meaning in clinical situations and to begin accepting responsibility for identifying learning needs and actively seeking information and resources to meet those needs.6

Beyond Education

The benefits of reflective practice are not limited to the educational setting, but also hold great value for practicing radiation therapists. Schön argued that professionals are less likely to solve problems using “academic knowledge” and are more likely to rely on their own “theories in use”1 Because these implicit theories are derived from experience and are frequently individual and unacknowledged, reflection is useful for enabling practitioners to articulate and to learn from their theories in use.

Reflective practice can enhance personal and professional learning8 and assist in the development of professional knowledge by generating practice-related research questions. Instead of adhering unquestioningly to the routines and rituals particular to the clinical area, reflective practice can enable radiation therapists to question their practices and to articulate, learn from and value the knowledge and skills derived from their everyday work. It is in doing this that radiation therapists can build a body of practice-centered knowledge that will form the foundation of our profession.10

Furthermore, reflective practice promotes lifelong learning. The concept of the reflective practitioner has been embraced widely by other health professions for the role it can play in the development of professional competence and its emphasis on the individual’s responsibility to maintain and increase level of competence by integrating learning into everyday practice. Reflection also provides data for self-examination and self-evaluation and increases learning from experience.

Finally, reflective practice can enhance self-esteem through learning. The ability to examine one’s own actions, thoughts and feelings is regarded by many as a hallmark of professional excellence. By incorporating reflection into radiation therapy education and work, we can explore our professional practice and come to understand the nature and boundaries of our own role and that of other health care professionals.9

References

Preparing entry-level professionals for practice in an ever-changing health care environment presents a tremendous challenge to educators. Although programs provide students with solid technical foundations for practice and templates for handling routine clinical problems, educational programs cannot possibly prepare graduates for all of the situations that they will encounter during their professional careers. For this reason, it is imperative that radiation therapists and other health care professionals prepare to be critical thinkers. Reflection as the basis for reflective practice has generated interest in the nursing, occupational therapy and medical education literature as a means for empowering students to learn from and build upon their clinical experiences while developing a skill that will aid them in the lifelong learning demands of a changing health care world. This article presents the concept of reflective practice and discusses its applicability to radiation therapy education.

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Being in the radiologic sciences since Jimmy Carter was president and many times feeling as if I am the oldest person sitting in the room, tidbits of information continue to astound me. At one time in my career, I felt quite confident in my skills, abilities and knowledge. However, as I get older and learn more about radiation oncology, it becomes apparent to me that what I know is not even the tip of the “radiation oncology iceberg of knowledge.” There is still so much to learn.

An interesting example is the concept of cancer cells and percentage. We all know that cancer cells are easier to kill than normal cells. From the seventh grade of our formal education, we also have understood the concept of percentage. For example, if 10 people are in a room and 50% of the people leave before dessert is served, how many people don’t eat dessert? Of course the correct answer is 5.

All radiation therapy students have to take radiobiology. It is in the ASRT Radiation Therapy Professional Curriculum; from the PhD and MD perspective, it may be the most important course in the curriculum. Therefore, we can assume that all certified radiation therapists have completed a formal radiobiology course, which should mean they are competent at least in radiobiology basics. However, there is a simple concept that I continuously find the majority of radiation therapists do not understand. This concept is about cancer cells and percentage.

Why is cancer so difficult to cure? The question is written about in the media constantly. As radiation therapists, when we are asked this question, how do we answer? The following scenario about cancer cells and percentage may help.

What kind of numbers are we dealing with when treating cells that compose a mass and how are these measured? Most radiation therapists understand from radiobiology class that a 1 cm tumor volume comprises 1 billion cells and that it takes a lot of radiation to make those cells go away.

It actually is very difficult mathematically to kill all of the cells and that is where most of us do not understand the simple concept previously mentioned. Many radiation therapists still tend to think in terms of percentages instead of logarithms. Maybe the following analogy will help.

Let’s say for example that you’re in a bowling alley facing 10 bowling pins. The bowling pins represent cancer cells and it’s your turn to bowl. If you knock over 90% of the bowling pins, how many pins did you knock down? I bet you answered 9. However, since the bowling pins represent cancer cells, you would be wrong. You actually just knocked over 1 bowling pin and 9 bowling pins remain. I guess at this point you are realizing that not everything you learned in seventh grade is true. Or you may be saying that I am wrong. But let me proceed.

If you roll your second bowling ball and, again, you knock over 90% of the bowling pins, how many did you knock over? Again, your answer is probably something like 8, or you may be gaining wisdom and figuring out that “Dr Adams, Father Time teacher” always has his points to make. But again you would be wrong if you answered something close to 8 bowling pins. The correct answer is again 1. And if you rolled a third ball? Again, the answer is 1.

Now we are seeing why radiobiology can be not only a difficult course, but also a course, from a teaching perspective, that takes a great deal of conceptualizing and educating. It is a course that really has meaning and adds value to what we know and do as radiation therapists. When we kill cancer cells, we measure with the concept of logarithms. These are based on the concept of “log-based 10,” which basically means that we are raising 10 to specific powers. For example, for the 1 billion cancer cells that make up 1 cm of tissue, the 10 is raised to a power of 9. If the 10 is raised to a power of 10, then there are 10 billion cells. Go ahead, pull out your calculator and try it.
So to go back to our analogy, let’s say you’re aiming your bowling ball at a tumor with 10 billion (10^10) cells and you take out 90% of them. Sounds pretty good, right? But you’ve only reduced the number of cells by 1 logarithm! There are still 1 billion (10^9) cells left. To completely eradicate the cancerous cells, you’ll have to do the same thing 9 more times, which is why curing cancer is a lot harder than bowling.

When you took radiobiology in school, this may be the most important concept you should have walked out of the classroom with at the end of the semester. That is, as radiation therapists, we kill cells in terms of logarithm units. Secondly, from a scientific perspective, as the number of bowling pins decreases, it actually becomes more difficult to take out, for example, the last 3 pins. That is why during the past 15 years, we are seeing more combination therapies. For example, when we treat prostate cancer with intensity-modulated radiation therapy, what we do is important and we kill many cancer cells, but in reality when we get to 72 Gy, we only have knocked over about 3 of the bowling pins. The hormonal treatment given after what we do actually serves to knock over the final 7 pins, and that can be quite difficult to achieve. The same example could apply to breast cancer surgery, hormonal treatment or chemotherapy for any number of cancers.

Therefore, the next time someone asks you why you can’t cure all of the cancers that come through the radiation therapy department, I hope you can answer from the analogy of the bowling pins. Everything we do is built continuously upon the science of radiobiology. It is very important that we understand its basic concepts. It makes us better at what we do. Finally, the majority of the truth we find in radiation oncology always is based in the science and mathematics, whether we want to believe it or not.
The Role of the Canadian Radiation Therapist

Rosanna Macri, BSc, M.R.T.(T); Amanda Bolderston, MSc, M.R.T.(T), FCAMRT

The roles of Canadian radiation therapists reflect the diversity of the country and its wide-ranging geography. The role of a clinical radiation therapist in a small rural center greatly varies from that of a research-focused practitioner in a larger urban department. The following article will draw a brief sketch of Canadian radiation therapy practice.

Canadian Practice Overview

All Canadian therapists work within the publicly funded cancer care system. Their employers are often the local host hospitals, cancer centers or provincial cancer agencies, such as in British Columbia (BC) and Alberta. Despite being publicly funded, resources (eg, access to equipment) vary from center to center; thus, techniques can be quite different provincially, let alone nationally. In addition, although the Canadian Association of Medical Radiation Technologists (CAMRT) sets national entry-to-practice examination criteria and standards, prelicensure education currently varies across the country.

Students in Ontario emerge from their educational program with a baccalaureate degree from the University of Toronto, Laurentian University in Sudbury or McMaster University in Hamilton. BC students graduate with an applied science degree from the British Columbia Institute of Technology. In Manitoba and most of the rest of Canada, students graduate from their program with a diploma.

Therapist Roles

Regardless of where they work, the radiation therapist is a member of an interprofessional team that includes the radiation oncologist, medical physicist and other health care professionals who work with and support patients and their families.

The General Practitioner

Most Canadian radiation therapists practice across a broad clinical spectrum, using skills that include the following areas:

Patient Treatment and Planning

All radiation therapists are required to have the working knowledge to perform all aspects of radiation planning, as prescribed by the radiation oncologist, and treatment processes in compliance with their center’s organizational policies. Therapists working in planning and simulation also must have an advanced working knowledge of computed tomography and, in many of the larger institutions, magnetic resonance imaging and positron emission tomography equipment. Knowledge of various software programs, as well as image fusion and contouring techniques, also are often needed.

Patient Assessment

The radiation therapist is responsible for continuously assessing the patient throughout the treatment process. Where problems arise, the therapist needs to decide upon the appropriate course of action or referral within the interprofessional team.

Education

Radiation therapists also are educators. They are an information resource for patients,
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their families, colleagues, students within the cancer center and the larger community. The radiation therapist is responsible for explaining treatment procedures and educating patients and their families about potential side effects and self-management strategies. Most radiation therapists routinely mentor prelicensure students in the clinical environment and provide formal and informal feedback to the students and the educational institution.

Quality Assurance

Daily responsibilities for the treatment radiation therapist include ensuring treatment unit quality and patient documentation accuracy. Furthermore, a radiation therapist is responsible for assembling the relevant information for treatment, such as blood test results, treatment accessories, plan distributions, calculations and much more. Therapists ensure that treatment plans and images are approved by the radiation oncologist, as well as analyze treatment verification images. More recently, they have begun to analyze the daily 3-D images that guide radiation treatment (i.e., image-guided radiation therapy) to ensure accurate setup and shielding. The role also requires the radiation therapist to check patient prescription instructions, measurements, calculations, signatures, documentation and all physicians’ orders.

Organization

In many departments, a radiation therapist will be in an organizational role on each treatment machine. In some departments, these therapists are labelled resource or reference therapists. Their primary responsibility is to organize the workflow for that particular unit. They are responsible for the orientation of new staff in the area and act as a liaison between their unit and other health team members including supervisors.

The Planner or Dosimetrist

Although planning is within every therapist’s initial skill set, some therapists remain in the planning department permanently or semipermanently and become planners or dosimetrists. Dosimetry, in this case, is defined as:

The knowledge base and expertise necessary to generate radiation dose distributions and calculations. This includes knowledge of the overall functionality and clinical relevance of radiation oncology treatment machines and equipment to enable the design and optimization of clinical radiation treatment plans.

The dosimetrist is responsible for producing the optimum treatment plan in accordance with the radiation oncologist’s prescription. These treatment plans can range in complexity from simple single electron calculations to intensity-modulated radiation therapy, tomotherapy and brachytherapy distributions. Although these therapists also teach radiation therapy students, they may take on the role of teaching radiation oncology residents and fellows the art of treatment planning.

The Educator

Education roles vary between departments. Many departments have prelicensure students. In these institutions, clinical staff provide them with mentoring and socialization into the role of the radiation therapist. Clinical coordinators (or clinical instructors) schedule and coordinate the radiation therapy student’s clinical education. They also evaluate the application of theoretical and practical education in the clinical setting and the clinical competence of students, providing a link between the educational institution and the clinical setting.

Similarly, the professional development of radiation therapists is the responsibility of the clinical educator. This education specialist is responsible for ensuring consistency in practice. He or she usually is responsible for planning, implementing, delivering and evaluating staff training and education programs, conducting ongoing needs assessments and staff orientation programs and other activities.

Other teaching roles may include clinical applications specialist-type roles. Software, techniques and technology change so quickly that some departments employ staff therapists to teach software applications, troubleshoot and update the software, as well as translate it for better functionality within the work environment. These therapists also might be responsible for updating and maintaining intranet Web pages for policies, procedures and education.

The Leader

In all departments, supervisors coordinate and evaluate patient care and staffing activities. The radiation therapy manager oversees the functions of the department, organizes workflow and coordinates processes and activities. In addition, the manager usually will prepare and manage budgets, assess resource requirements, evaluate performance, administer policy and develop program standards. Managers also typically resolve complaints and ensure that radiation therapists in their department practice in accordance with the standards of practice of the profession.

The Research Therapist

The definition of the profession is founded in part on its development and maintenance of a body of research. In the past decade, a growing number of therapists have been involved in research. In some clinics or departments, specific research radiation
therapy positions have been created to provide dedicated time to conduct research individually or in collaboration with other health care professionals. These research therapists also might be responsible for promoting research in the department, providing research mentorship and other related activities, such as facilitating a journal club or compiling research reports. Research therapists could have academic appointments with affiliated university departments and disseminate their research in the form of papers presented at meetings or journal publications.

**Expanded Roles**

Similar to other countries, radiation therapists in many Canadian departments have moved into “novel areas of clinical work as new technology forces innovative ways of working.” This forward momentum is driven by the need to improve patient care and has led to areas of expanded and enhanced practice. Although roles and definitions vary from center to center, typical enhanced or expanded roles include a move into areas not traditionally associated with radiation therapists that require increasing educational provision.

For example, at the Odette Cancer Centre in Toronto, the high demand for palliative care has guided the creation of the Rapid Response Radiotherapy Program (RRRP) and Bone Metastases Clinic (BMC). These groups include a team of diverse health care professionals, including the palliative radiation therapist. This specialty therapist participates in research and education with these 2 programs. Clinically, this therapist conducts patient assessments, education and counseling and coordinates patient treatment appointments with other appointments including consults and referrals. The therapist also is responsible for collecting data for the RRRP/BMC prospective database, coordinating research activities, screening patients for clinical trial suitability, accruing eligible patients and participating in the evaluation and analysis of RRRP studies.

Another urban Toronto center, Princess Margaret Hospital, has created a new model for radiation therapists called Advanced Integrated Practice (AIP), which is an initiative to “encourage and promote scholarship within radiation therapy.” AIP incorporates integrated clinical specialty roles designed to blend exemplary clinical practice with focused academic activities. This allows for a wide range of career development opportunities and a sharper focus on academic elements of practice, such as research and teaching. More than 40 AIP roles have been implemented at the center to date, including 11 integrated research positions. The AIP model also has increased the number of radiation therapy academic appointments to the affiliated University of Toronto Department of Radiation Oncology, substantially improving the output of abstracts, presentations and papers by radiation therapists.

**Advanced Roles**

Although there may be therapists in Canada working at an advanced level, to date the only official advanced practice initiative is within the province of Ontario. In 2004, the Ontario Radiation Therapy Advanced Practice group was formed to promote advanced practice roles for radiation therapists in Ontario. Under the auspices of Cancer Care Ontario, the group has obtained a series of funding grants from the Ministry of Health and Long Term Care to pilot a project to assess the usefulness of clinical specialist radiation therapist (CSRT) roles. Government priorities and proposed project outcomes include improved access to care, reduced wait times and ultimately healthier Ontarians. For radiation therapists, it is hoped the roles will lead to increased job satisfaction, career options and leadership opportunities, improved accountability, responsibility and opportunities to increase and use knowledge, skills and competencies. The research project currently is evaluating 10 roles across the province in 5 cancer centers, including an adaptive planning/tomotherapy CSRT, symptom management (breast) CSRT, target visualization and delineation CSRT and several specialized palliative roles.

**Conclusion**

Through this review of the role of the Canadian radiation therapist, it is evident that the profession is constantly evolving in line with many other countries. Scopes of practice are changing, and education is moving forward to keep pace with new competencies and skill sets in both the prelicensure and postlicensure arenas.

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STUDENTS SPEAK

Proton Therapy

Pamela Cartright, MAEd, R.T(R)(T); Swaty Singh; Kyle Coleman; Kiran Shrestha

Electrons are the negatively charged particles of an atom; they play a large role in traditional x-ray beam technology. Most radiation therapy modalities use accelerated electrons (photons) to treat cancer. However, proton therapy, which uses hydrogen atoms with their electrons removed, is one of the better treatments available for people with cancer. Protons are positively charged atomic particles that deposit energy differently than x-ray beams. Compared with an x-ray beam, a proton beam delivered with sufficient energy has a low entrance dose (ie, the dose in front of the tumor) and no exit dose beyond the tumor. X-ray beams, by contrast, can deposit most of their dose in tissues in front of the tumor. Because of proton characteristics, proton therapy is an excellent way to treat cancer patients.

Literature Review

Taheri-Kadkhoda et al investigated the potential advantages of intensity-modulated proton therapy (IMPT) and compared it with intensity-modulated radiation therapy (IMRT) in 8 nasopharyngeal carcinoma patients. For each patient, 9 coplanar fields using IMRT and 3 coplanar fields using IMPT plans were prepared. With IMRT, a step-and-shoot technique was used, a spot-scanned technique was used with IMPT. Both modalities were planned in 33 fractions to be delivered with a 3-D simultaneous integrated boost technique. All plans were prepared and optimized using the research version of the inverse treatment planning system. Averaged mean dose to target volumes was equal in both treatment techniques. Results showed that 3-field IMPT has greater potential than 9-field IMRT in covering the tumor volume and reducing the integral dose to nonspecific normal tissues and organs at risk, including the auditory apparatus, temporal lobes, larynx, esophagus and thyroid gland.

Auberger et al studied 6 patients with early-stage peripheral nonsmall cell lung carcinoma. Twenty-seven treatment plans were compared for conformal photon therapy, IMRT and normal proton therapy. A passive beam technique without intensity modulation was used for treatment planning of proton therapy. In all 27 treatment plans, dose volume histogram was calculated for clinical target volume, planned target volume; right, left and total lung; heart, spine and esophagus. The study concluded that there was no substantial difference between proton therapy and IMRT regarding tumor conformity, although the distribution in planned target volume and clinical target volume was slightly worse in treatment plans for 3-D conformal radiation therapy. However, proton therapy showed a significant benefit with regard to the dose distribution in the organs at risk.

Discussion

Historical Background

Physicist Robert Wilson proposed using protons as a radiation therapy option in 1946. The first hospital to use proton therapy in a clinical setting was Loma Linda University Medical Center in southern California, which opened its cancer center in October 1990. The hospital was designed to treat approximately 150 patients a day. Since opening, the Loma Linda University Medical Center has treated more than 10,000 patients. In the United States, universities in Pennsylvania, Texas, Florida, Massachusetts and many other states now are certified by the National Cancer Institute to treat patients with protons. In the past decade, use of proton therapy not only has accelerated in the United States, but also in the rest of the world. Switzerland, Germany, Japan, Russia, China, France, England and many other countries have opened centers that provide proton radiation therapy.

Advantages and Disadvantages

As Mark Gilbert, a physicist at Princeton Baptist Medical Center in Alabama, explained, one of the major disadvantages to proton
therapy is its cost. As the global economy has increased, so have the world’s income and expenditures. In time, the cost of these expensive accelerators should decrease (oral communication, November 2008). In the United States, these machines are not produced on a large scale. The cost to build and maintain a proton center is approximately $100 million. In addition to high expenses, there also is a government investment that has to take place to build and run the center. Another reason that there are so few proton therapy centers is the overwhelming need for a large staff to maintain and run the facilities.

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Blood Vessels Tied To Chemotherapy Outcomes

A recent study that appeared in the February issue of *Radiology* found that digital mammography can help determine the leakiness of tumor blood vessels, an important factor in predicting the success of chemotherapy.

Chemotherapy, which uses chemicals to destroy cancer cells, is ineffective in many patients. A means to predict chemotherapy’s effectiveness accurately could save thousands of individuals from the toxicity and side effects of the treatment.

Because chemotherapy’s effectiveness depends on the ability of anticancer drugs to escape from the bloodstream through the leaky blood vessels that often surround tumors, researchers reasoned measuring the leakiness of blood vessels might predict the treatment’s success or failure.

They developed a system based on nanometer-sized capsules containing a contrast agent that could only leak into tumors with blood vessels that were growing and therefore leaky. Digital mammography would help quantify the leakiness of the blood vessels.

In the study, researchers injected a long-circulating capsule filled with iodinated contrast agent into rats with breast cancer tumors. They performed digital mammography on the animals for the next 3 days and compared the preinjection and postinjection images to determine the rate of contrast agent accumulation in the tumors.

During the 3-day course, some tumors accumulated contrast agent, as evidenced by a rapid and significant increase in image brightness. Other tumors showed little increase in brightness.

After the researchers completed the imaging and quantified the leakiness of each individual cancer vessel, they injected the animals with liposomal doxorubicin, a chemotherapy drug. Contrast agent uptake by the tumors during the 3-day imaging sessions provided an accurate prognosis of the effect of the drug on tumor growth rate.

Cancer Survivors Face Lymphedema Risk

The medical community needs to pay more attention to lymphedema, a painful and debilitating condition that is one of the more serious side effects of surgery and radiation therapy in breast cancer patients, according to a panel of vascular experts.

Lymphedema is an incurable, often progressive condition that most commonly occurs because of surgery and radiation therapy for cancer treatment. It is characterized by progressive swelling of 1 or more limbs from the accumulation of excessive lymph fluid. Once established, the disease has an inexorable tendency to progress.

While lymphedema affects both men and women, it is a particular problem among breast cancer survivors, affecting between 15% and 30% of patients. It can strike patients many years after they had cancer treatment.

Lymphedema most commonly occurs in the upper limbs after breast cancer surgery and lymph node removal. The condition also may occur in the lower limbs or groin of colorectal, ovarian or uterine cancer patients who require removal of lymph nodes.

Despite the high numbers of people at risk for lymphedema, the medical community has paid only minimal attention to diagnosis and management, according to researchers who moderated a symposium on lymphedema awareness on February 11 at the Annual Meeting of the American Venous Forum in Phoenix, Arizona.

The vascular experts on the panel pointed out that physicians and medical staff who practice in fields where lymphedema is an infrequent occurrence may fail to diagnose the condition. In addition, many insurance companies do not recognize lymphedema as a serious condition that can become progressively worse without proper treatment. Ignorance about lymphedema could result in patients receiving suboptimal care, according to researchers.
Lymphedema often is diagnosed through a physical examination that reveals a region of persistent edema and painful thickened skin with a dimpled texture. Treatment includes exercise, skin care, compression and massage. Once the swelling is reduced, patients can manage the condition at home with the use of elastic compression garments, nonelastic directional flow garments and automated pneumatic compression pumps.

Patients who have undergone cancer treatment can reduce their chances of developing lymphedema by maintaining a healthy diet, exercising regularly and avoiding infections from cuts and insect bites. Women who have had double mastectomies should make sure that any needle procedures be performed in the leg rather than the arm, if possible.

Lymphedema affects 3 million to 5 million people in the United States and 170 million people worldwide, according to the World Health Organization. More than 3.3 million U.S. breast cancer survivors face a lifetime risk for the disease.

Breast Screening May Reduce Surgeries

An automated image screening process could help physicians quickly determine whether they have removed all the cancer from a patient during breast-conserving surgery, according to the preliminary findings of a recent study. The technique eventually could reduce unnecessary repeat surgeries.

During breast-conserving surgery, surgeons attempt to remove the tumor and a margin of healthy cells around it. Pathologists then can examine the removed tissue under a microscope to look for cancer cells in the outer margins. The process can take up to a week, and in 20% to 50% of cases, some disease remains, necessitating additional surgery.

A faster, accurate method would help reduce the costs and patient stress associated with repeat surgeries.

Researchers recently studied a technique called automated microscopy that can, with the help of specially designed computer software, look at cells on a microscope slide. A camera connected to the microscope takes photos of the slide, which then are analyzed for cancer.

For the study, researchers looked at normal breast tissue samples from 10 women and tumor samples from 24 women with cancer. The technique correctly identified invasive breast cancer cells in 83% of the tumor specimens, while a normal microscope identified cancer in only 65% of the cancer specimens.

The automated technique still needs improvement for use during breast surgery, according to researchers. Clinicians typically would examine 6 slides during breast-conserving surgery, and each slide requires about 2 hours for analysis. The research team would like to reduce the analysis time to as little as 5 minutes per slide, which would enable physicians to know whether the patient needs further surgery while she is still in the operating room.

The study appeared in the January 10 online issue of the Annals of Surgical Oncology.

Imaging Agent Detects Cancer Spread

A new fluorescent imaging agent highlights breast cancer cells that have spread to the lungs, according to a recent study on mice that appeared online in the December 7 issue of Nature Medicine.

Existing fluorescent imaging agents are limited by the fact they fluoresce even after they diffuse to new locations, making it difficult to distinguish tumor cells from normal tissue or dead or damaged tumor cells.

The new agent is a modified version of a small fluorescent compound known as boron-dipyrromethene (BODIPY) that binds to the HER2 protein found on the surface of some breast cancer cells. The BODIPY compound fluoresces when taken inside living cells, but stops fluorescing when it leaves the cell, as would happen when the cell dies or becomes damaged.

Researchers studied the compound’s cancer-detecting potential in a series of experiments on mice. They injected either the BODIPY compound or a control that always fluoresces into the tail of mice that had HER2-positive breast cancer tumors that had spread to their lungs. Only a day later, the investigators found fluorescence from the BODIPY compound only in lung tumors, while the control produced fluorescence in both the tumors and normal tissue.

The researchers also conducted experiments to confirm that the BODIPY compound detects only living cells. After they killed tumor tissues with alcohol, they found that the fluorescence of the BODIPY compound significantly decreased in tumor tissue, while the fluorescence of the control compound showed little change.

Researchers said that scientists could engineer the new compound to target specific types of cancer cells.

Device Improves Proton Therapy

A new device improves proton therapy by delivering more precise doses of radiation to cancerous tumors with minimal damage to surrounding healthy tissue, according to the developers. The technology could help increase the availability of proton therapy for cancer patients worldwide.

Proton therapy is an alternative to radiation therapy with x-rays for cancer treatment.

In x-ray therapy, the x-ray beams deposit their energy as they travel through tissue, with most of the dose deposited near the surface of the body. This results in collateral damage to healthy tissues that limits the dose physicians can use to destroy the tumor.

Proton beams deposit most of their energy where the beam stops. The proton therapy synchronon
deliver their radiation doses to tumors from different angles, allowing for more precise targeting of tumors with higher doses of radiation.

However, relatively few hospitals have proton accelerators, as they are costly to build and difficult to maintain.

A new accelerator design from the U.S. Department of Energy’s Brookhaven National Laboratory in Upton, New York, offers performance improvements, convenience and cost savings, according to the developers.

The novel design uses rapid cycling, a process in which proton beams are injected and extracted from the synchrotron in just 1 turn around the particle accelerator. Earlier machines required multiple turns. Rapid cycling eliminates the need for sensitive feedback systems to control the beam currents.

The accelerator also features strong focusing, which enables shaping and focusing of the proton beam to dimensions as narrow as 1 mm. This capability reduces collateral damage to healthy tissue and allows physicians to be more flexible in the doses they use.

“Our new design has improvements in beam-focusing technology to make the smallest possible beam size — that is, the sharpest possible ‘knife,’” said Stephen Peggs, PhD, from the Brookhaven laboratory.

The increased precision of the new accelerator could shorten the duration of treatment, according to Dr Peggs.

The accelerator’s compact beam size offers other benefits, including smaller components, such as beam pipes and magnets. The smaller size reduces costs by eliminating the need for water-cooling of most magnets.

“It’s more of a turn-key operation,” said Dr Peggs. “Turn it on and it consistently starts up like a transformer, rather than booting up like a PC.”

Dr Peggs and 3 other Brookhaven physicists have received a U.S. patent for the medical synchrotron. They are looking for industrial partners to license and commercialize the technology.

**Inherited Genes Play Role in Breast Cancer Metastasis**

Genes that contribute to the ability of breast cancer to metastasize can be inherited, according to a recent study on mice.

The genetic basis for breast cancer’s metastatic ability is the subject of much debate, with some researchers believing that somatic, or noninherited, gene mutations in tumor tissue are the primary determinant.

In the recent study, researchers performed a series of experiments in a mouse model of metastatic breast cancer. They identified a gene expression signature that enabled them to distinguish between the tumors of mice with a high or a low inherited susceptibility to tumor spread. They then converted the mouse gene signature to the corresponding human gene signature and analyzed 5 sets of human breast tumors.

The researchers used advances in microarray technology to identify gene signatures quickly within vast amounts of genetic information.

The genetic signature successfully predicted either relapse or disease-free survival in 4 of the 5 sets of human breast tumors.

As part of the experiment, the researchers also put highly metastatic tumor cells into the mammary fat pads of mice with high or low susceptibility to tumor metastasis. Previous studies have suggested that gene expression patterns in the nearby tissue, or stroma, are altered in tumors prone to metastasis.

The results suggested that metastatic differences between individual mice were due to genes in the epithelium, or outer layer of tissue that surrounds the tumor, rather than in the stroma.

The researchers concluded that, most likely, both the tumor epithelium and the stroma contribute to the development of the prognostic gene profiles.

“Our study provides additional evidence of the role of inherited genes in human breast cancer progression,” said Kent W Hunter, PhD, from the National Cancer Institute’s Laboratory of Cancer Biology and Genetics in Bethesda, Maryland. “Therefore our next step is to improve our current understanding of the role of the epithelium and stroma in tumor progression and develop more effective therapeutic strategies based on our new knowledge.”

The recent study supports previous findings by the same research team.

“Our earlier studies clearly established that inherited factors also play an important role in metastatic progression and can help distinguish which tumors have a propensity to metastasize,” said Dr Hunter. “Hopefully in the future we will be able to determine which women are more likely to have a tumor that would metastasize, and we could then tailor therapy specifically for them, avoiding the use of harsh treatments for those with a low probability of metastasis.”

The study appeared in the January 1 issue of *Cancer Research*.

**Hybrid Imaging Improves Thyroid Cancer Staging**

Hybrid imaging with single photon emission computed tomography and computed tomography (SPECT-CT) helps determine the spread of thyroid cancer to nearby lymph nodes, according to a recent study. Researchers said that SPECT-CT could enable earlier, more individualized treatment of the disease.

Differentiated thyroid carcinoma (DTC) is the most common form of thyroid cancer. Physicians treat it with radiiodine therapy, which exploits the
fact that 1 of the functions of the thyroid gland is to absorb iodine from the blood. The addition of radioactive iodine to the blood kills any remaining cancerous thyroid cells left over after surgical removal of the thyroid gland. The radioactive iodine also emits photons suitable for imaging.

In the study, 57 patients underwent SPECT-CT after radioiodine therapy. SPECT imaging locates malignant cell activity, while CT provides the exact anatomical location of the malignancies.

The SPECT-CT information led to a change of the original diagnosis in 35% of the study participants. Researchers reclassified 6 of the 11 images that had been classified as lymph node metastases as benign, and 11 of 15 lesions that had been considered indeterminate.

“Our data suggest that SPECT-CT should be used as a routine procedure in DTC patients at the first radioiodine treatment,” said Torsten Kuwert, MD, from the University of Erlangen-Nürnberg in Erlangen, Germany. “By upstaging or downstaging disease, this hybrid imaging tool may alter the management of more than one-third of patients with the disease.”

The researchers noted that spread to regional lymph nodes is a crucial factor in treatment planning because patients with lymph node metastases are at high risk for disease recurrence.

“Incorporated at first treatment, SPECT-CT allows us to better stratify patients into treatment groups,” added Dr Kuwert. The study appeared in the January issue of the Journal of Nuclear Medicine.

There will be approximately 37,540 new cases of thyroid cancer diagnosed in the United States in 2009, according to the American Cancer Society. About 28,410 of the new cases will occur in women, compared with 8,930 in men.

Worldwide Cancer Incidence Rises

Cancer is set to surpass heart disease as the world’s leading cause of death, according to a recent report from the World Health Organization (WHO). In response to the report, leading cancer organizations in the United States announced an initiative to combat the disease worldwide through vaccinations, smoking cessation programs and other measures.

The WHO report found that the burden of cancer doubled globally between 1975 and 2000 and will become the leading cause of death worldwide in the year 2020. Researchers estimated that cancer incidence will almost triple by 2030, with 20 million to 26 million new cancer diagnoses and 13 million to 17 million deaths.

The report found a growth in cancer incidence of approximately 1% per year, with larger increases in China, Russia and India. Researchers pointed to the adoption of Western habits in less developed countries, such as tobacco use and higher-fat diets, as 1 of the reasons for the growing burden. Demographic changes, including a projected population increase of 38% in less developed countries between 2008 and 2030, also will play an important role.

Along with increases in cancer incidence and death rates, the WHO report found deficiencies in cancer care. For instance, pain management and palliative care are limited in several African countries because of laws prohibiting any narcotics use.

“The rapid increase in the global cancer burden represents a real challenge for health systems worldwide,” said Peter Boyle, PhD, from the International Agency for Research on Cancer (IARC). “However, there is a clear message of hope: although cancer is a devastating disease, it is largely preventable.”

The IARC joined other U.S. organizations, including the American Cancer Society, the Lance Armstrong Foundation and Susan G. Komen for the Cure, in issuing a call to action to reduce cancer incidence worldwide. Among the recommended steps was an increase in the availability of a vaccine that protects against cervical cancer. The organizations also called for intensified efforts to reduce tobacco use, including having the U.S. Congress grant the U.S. Food and Drug Administration authority to regulate tobacco.

“We know that preventive measures such as tobacco control, reduction of alcohol consumption, increased physical activity, vaccinations for hepatitis B and human HPV, and screening and awareness could have a great impact on reducing the global cancer burden,” said Dr Boyle.

“It is my hope that by bringing proven interventions to places in the world impacted most by this disease, we can diminish needless suffering and save many lives,” added John R. Seffrin, PhD, chief executive officer of the American Cancer Society.

The organizations recommended investment in cancer research and expanded access to prevention and early detection measures in the United States, with a focus on increasing federal funding of medical research.
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CE Answers Section

USE A BLUE OR BLACK INK PEN. Do not use felt tip markers or pencil. Completely fill in the circles.

Correct Mark: ● Incorrect Mark: X ✔

Note: For true/false questions, A=true, B=false.

1 2 3 4 5 6 7 8 9 10

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P.O. Box 51870
Albuquerque, NM 87181-1870
Directed Reading Evaluation
Hodgkin Lymphoma

Thank you for taking the time to complete this survey. Your opinion helps us serve you better. Your comments will remain confidential and will not affect the scoring of your Directed Reading (DR) test. **Choose only ONE response for each question.**

Use a blue or black ink pen. Do not use felt tip markers. Completely fill in the circles.

1. What is your primary area of practice?
   - Administration/Management
   - Bone Densitometry
   - Cardiovascular-Interventional
   - Computed Tomography
   - Education
   - Magnetic Resonance
   - Mammography
   - Nuclear Medicine
   - O Quality Management
   - O Radiation Therapy
   - O Sonography
   - O Research
   - O Other

2. Which of the following best describes the highest educational level you have attained?
   - O Student who has not yet taken Registry exam
   - O Certificate
   - O Associate degree
   - O Bachelor's degree
   - O Master's degree
   - O Needed CE credits immediately
   - O Doctoral degree (e.g., Ph.D. or Ed.D.)

3. Why did you choose to complete this DR?
   - O Interested in the topic
   - O DR had the right number of CE credits
   - O Topic pertained to my area of practice
   - O Needed CE credits immediately
   - O Other

4. How relevant is this DR to your practice?
   - O Extremely relevant
   - O Very relevant
   - O Relevant
   - O Somewhat relevant
   - O Not relevant

5. How beneficial is this DR to your professional or personal development?
   - O Extremely beneficial
   - O Very beneficial
   - O Beneficial
   - O Somewhat beneficial
   - O Not beneficial

6. How would you rate the level of difficulty of this DR?
   - O Too difficult
   - O Somewhat difficult
   - O Just the right level
   - O Somewhat easy
   - O Too easy

7. How would you rate the length of this DR?
   - O Too long
   - O Somewhat long
   - O Just the right length
   - O Somewhat short
   - O Too short

8. Did this DR meet your expectations?
   - O Yes
   - O No
   - O Partially

9. How does this DR compare to non-ASRT CE products you've used?
   - O Significantly better
   - O About the same
   - O Better
   - O Slightly worse
   - O Never used other CE products

10. Would you recommend this DR to a colleague?
    - O Yes
    - O No

11. Overall, how valuable are the Directed Readings to you?
    - O Very valuable
    - O Considerably valuable
    - O Valuable
    - O Slightly valuable
    - O Not very valuable

If you have comments about this Directed Reading, please write them below or send them separately to Ellen Lipman, Director of Professional Development, ASRT, 15000 Central Ave SE, Albuquerque, NM 87123-3909 or elipman@asrt.org.
Some cancer patients develop a complication known as lymphedema. Lymph is an infection-fighting fluid that circulates throughout the body; “edema” simply means swelling. So lymphedema is a buildup of lymph in the body that causes swelling. This can happen as a result of surgery, radiation therapy, infection or because of the cancer itself — anything that disrupts the lymphatic system and the normal flow of lymph.

Patients with breast cancer are especially susceptible to lymphedema, which can cause swelling of the breast, underarm area or the arm on the side where the cancer was. Patients who had lymph nodes removed as part of their breast cancer treatment (also known as lymph node dissection) are more likely to develop lymphedema. Patients with pelvic cancers, such as prostate cancer, can develop lymphedema, too. In those cases, lymphedema causes swelling of the abdomen, genitals or 1 or both legs. Lymphedema also develops in patients who have lymphoma or melanoma.

In addition to swelling, patients with lymphedema may notice redness or heat in the affected area. Lymphedema can be uncomfortable or even painful. It can limit use of the swollen body part and sometimes causes infection. Lymphedema can develop days, weeks or even months after treatment.

It is important to get early care for lymphedema. According to the American Cancer Society, you should report the following signs to your physician as soon as possible:

- Fullness or heaviness in an arm or leg.
- Skin tightness in your arm or leg.
- Less movement in a hand, wrist or ankle.
- Tight fit in a sleeve or sock.
- Tight-fitting jewelry, such as a ring, watch or bracelet, when you haven’t gained weight.

Treatments for lymphedema include specialized massage, exercise, bandaging and compression garments. A physical therapist or other health care professional who is knowledgeable about lymphedema should provide this treatment.

You can help prevent or delay lymphedema by taking special care of the limb or limbs that are likely to be affected (that is, the arm on the side where there was breast cancer, or your legs if you have a cancer in the pelvic area). For example:

- Keep the limb that might develop lymphedema clean and watch it carefully for signs of infection, such as a rash, tenderness, heat or swelling.
- If you normally shave the area, use an electric razor to reduce the chances of a cut or nick.
- Protect the limb from sunburn by using a sunscreen labeled “SPF 15” or higher. Avoid anything that tends to chap or irritate the skin on that limb.
- Avoid saunas, hot tubs and excessively hot showers and baths. Test the water with an unaffected limb.
- Avoid tight clothing in the area.
- Use the limb normally, but do not overstrain or tire it. Do not lift heavy weights or participate in vigorous, repeated activity without checking with your physician first.
El linfedema

A

lgunos pacientes que padecen cáncer desarrollan una complicación que se conoce como linfedema. La linfa es un fluido que combate las infecciones y circula por todo el organismo, “edema” simplemente significa hinchazón. Entonces, el linfedema es una acumulación de linfa en el cuerpo que provoca hinchazón. Esto puede ser producto de una cirugía, de radioterapia, de una infección o puede deberse al cáncer propiamente dicho: algo que perturba el sistema linfático y la circulación normal de linfa.

Las pacientes con cáncer de mama son especialmente susceptibles al linfedema, que puede provocar hinchazón de los pechos, del área axilar o del brazo sobre el costado en que estaba el cáncer. Las pacientes a quienes se les extirparon nodos linfáticos como parte de su tratamiento para combatir el cáncer de mama (también conocido como disección de nodos linfáticos), tienen mayor tendencia a padecer linfedema. En esos casos, el linfedema provoca la hinchazón del abdomen, de los genitales o de una o ambas piernas. El linfedema también aparece en pacientes que tienen linfoma o melanoma.

Además de hinchazón, los pacientes que presentan linfedema pueden advertir enrojecimiento o calor en el área afectada. El linfedema puede resultar molesto e incluso doloroso. Puede llegar a limitar el uso de la parte del cuerpo que está hinchada y a veces provoca infección. El linfedema puede desarrollarse días, semanas e incluso meses después del tratamiento.

Es importante tratar el linfedema desde una etapa temprana. De acuerdo con la Sociedad Americana del Cáncer (American Cancer Society), debe informar inmediatamente a su médico los siguientes síntomas:

- Opresión o pesadez del brazo o la pierna.
- Tirantez de la piel en brazos o piernas.
- Menor movilidad de las manos, cintura o tobillos.
- Sensación de mangas o medias ajustadas.
- Sensación de que las alhajas le aprietan, como por ejemplo anillos, relojes o pulseras, aún sin haber aumentado de peso.

Los tratamientos para el linfedema incluyen masajes especiales, ejercicios individualizados, vendas y vendajes de compresión. Este tratamiento debe estar a cargo de un fisioterapeuta u otro profesional de la salud especializado en linfedema.

Puede prevenir o demorar la aparición del linfedema si presta especial atención al o a los miembros que pueden ser afectados (es decir, el brazo del lado donde estaba el cáncer de mama, o las piernas si tiene o tuvo cáncer en la zona pélvica). Por ejemplo:
- Mantenga el miembro que podría desarrollar linfedema limpio y controle cuidadosamente cualquier síntoma de infección, como por ejemplo sarpullido, dolor, calor o hinchazón.
- Si normalmente se afeita esa área, utilice una afeitadora eléctrica para reducir las posibilidades de sufrir cortaduras o rasguños.
- Proteja el miembro de la acción del sol, para lo cual tiene que usar una pantalla solar que en la etiqueta diga “SPF 15” o más. Evite todo lo que pueda agrietar o irritar la piel de ese miembro.
- Evite los saunas, el hidromasaje y las duchas y baños excesivamente calientes. Pruebe el agua con el miembro no afectado.
- Use el miembro normalmente, pero no lo someta a excesiva tensión ni esfuerzo. No levante pesos pesados ni realice actividad física fuerte y repetida sin consultar antes con su médico.
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