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Manuscripts in Myeloma 2016

BY RAVI VIJ, MD, MBA

2015 saw the approval of four new drugs by the FDA for the treatment of patients with multiple myeloma. However, myelomatologists remain a productive lot and 2016 provided another bumper harvest of manuscripts in multiple myeloma. It is perhaps worth inking a few lines to highlight their major contributions.

Relapsed/Refractory Disease

Monoclonal Antibodies

The incorporation of monoclonal antibodies in our therapeutic armamentarium was perhaps the highlight of the year. Several of the trials that formed the basis of this revolution in myeloma therapy were published in manuscript form this year.

Lonial, et al., published results on an open label randomized phase II trial of daratumumab monotherapy in patients with treatment refractory multiple myeloma

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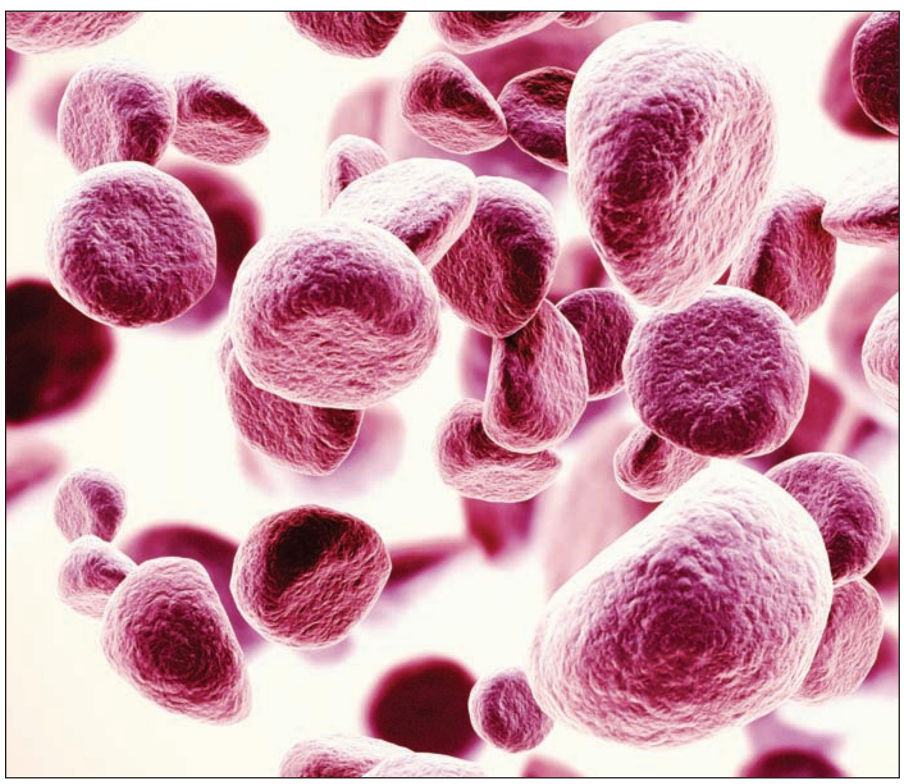

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Benefits of Automation in Radiation Oncology

BY VALERIE LABERTA

CME Article

Automation, at maturity, could be the conduit to higher quality, safer treatments, all harnessed to a more rapid and accurate delivery system of radiation oncology. The potential exists for technology to inform and execute treatment plans with minimum human intervention and its attendant errors. Automation could also provide physicians with an escape from time-consuming, repetitious tasks, while providing them with more time to do what they do best—interact with patients.

While the gallop toward the automation of increasingly more processes is moving at a thoroughbred's pace, the field is really only "semi-automated" at this point, remarked Meral Reyhan, PhD, Assistant Professor, Division of Medical Physics, Thomas Jefferson University, Philadelphia. "I say 'semi-automated' because even though many processes are 'automated' they still require a human to check that the process has been carried out correctly. For example, even when using the best

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Cellular Immunotherapies for Leukemia Patients

BY DAVID G. MALONEY, MD, PHD

High dose therapy and allogeneic hematopoietic stem cell transplantation (HCT) began at Seattle's Fred Hutchinson Cancer Research Center in the 1960s, led by Nobel Prize–winning E. Donnall Thomas, MD, and represented one of the first curative treatments for relapsed leukemia.

Using reduced intensity conditioning, Rainer Storb, MD, and colleagues were among the first to show that donor immune T cells play a major role in successful allogeneic HCT through graft-versus-leukemia effects (GVL). Further proof of the immune system's leukemia-eliminating potential comes from the activity of donor lymphocyte infusions (DLI) in some patients who relapse with leukemia after HCT.

Unfortunately, allogeneic HCT and DLI can also cause graft-versus-host disease (GVHD), in which the donor immune system attacks the patient's normal tissues. Depletion of all donor T cells from the graft reduces GVHD, but also limits GVL and increases the incidence of serious infections and disease relapse.

Engineering Improved HCT Outcomes

One approach to potentially improve HCT outcomes is to selectively remove the cells that cause GVHD, sparing GVL. Preclinical studies by Marie Bleakley, MD, PhD, MMsc, and Stanley Riddell, MD, showed that $CD45RA^+$ "naïve" T cells (T_N) are enriched for the capacity to cause GVHD while donor grafts depleted of $CD45RA^+T_N$ can

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PERIODICALS

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image registration algorithm, a physician still must go through all of the images and make sure the registrations are correct."

With that clarification in mind, however, Reyhan said automation is making an impact in a multitude of areas, such as contouring, treatment planning, image registration, transferring of treatment fields from the treatment planning system to the treatment delivery system, recording and verifying radiation delivered, aggregating data for analysis of radiation treatment, and many of the quality assurance measurements for the treatment machines.

Yan Yu, PhD, MBA, FAAPM, FASTRO, Professor and Vice Chair Director of Jefferson's Division of Medical Physics, Department of Radiation Oncology, emphasized, "Dosimetric treatment planning occupies a central stage in every radiation therapy treatment course. This is a highly skilled and time-consuming step, during which patients wait anxiously for their first day of treatment, often with tumor still growing in the body."

Understandably, any reliable shortcuts would benefit both clinicians and patients.

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be better able to identify the impact of automation on radiation oncology.

Contouring

"In its present state, automation in radiation oncology is helpful in the contouring of imaging," offered Bruce Minsky, MD, FASTRO, Professor of Radiation Oncology at MD Anderson Cancer Center, Houston, and Immediate Past Chair of the American Society for Radiation Oncology's (ASTRO) Board of Directors.

"When we design radiation fields, we need to contour many organs in the radiation field to make sure that we treat the tumor and spare the normal tissues," he continued. "This is tedious and time-consuming. Now we have contouring programs that will automatically contour normal structures—making this step much more rapid."

Keeping caution in mind, Reyhan remarked that while several companies have come out with software using sophisticated computer vision algorithms/machine learning to automate the contouring process, "most of these programs work excellently the majority of the time, but no one is ready to trust patient care to something that works excellently the 'majority' of the time. It needs to work perfectly 100 percent of the time before it is truly 'automated' in radiation oncology."

Treatment Planning

The entirety of treatment planning indeed will see significant changes as a result of automation, added Todd Pawlicki, PhD, FAAPM, FASTRO, Professor of Radiation Oncology at the University of California, San Diego, and a member of ASTRO's Board of Directors.

"Currently, treatment planning is done by a trial-and-error process and the 'optimal' treatment plan is largely dependent on the knowledge and experience of the person creating the treatment plan," Pawlicki explained, adding that there are a number of publications in peer-reviewed literature showing there is variability in treatment plan quality not only across centers, but even in the same center where there are several different treatment planners.

"Knowledge-based treatment planning is an automation technique that can ensure that treatment plan quality is optimal, independent of the treatment planner," he added. "Furthermore, it is much more efficient to create treatment using knowledge-based treatment planning—taking the process of treatment planning from hours to minutes. This is a rapidly evolving area and the full benefits are still to be experienced."

Such knowledge-based treatment planning may eventually be accessed automatically through growing databases of patients and their treatment plans, said Minsky. "For example, let's say we have 400 patients being treated for the rectal cancer field all stored in a database. When we see a new patient with rectal cancer, we would be able to scan them and run their disease and body characteristics through those plans and—almost like facial recognition—be able to pull out a plan from somebody who has been treated with the same type of anatomy and stage of cancer. We would rapidly see if there is a plan that has already been developed with a similar type of patient that might be useable as a template to reduce the amount of time that it takes for our treatment plan to be perfected."

Yu commented that the vision of autonomous treatment planning has been around for some 20 years, and noted that scientists at Thomas Jefferson were the first to identify two critical challenges to autonomous treatment planning: representation of multiple planning objective tradeoff strategies, and inverse planning optimization—the process for the computer to find the best plan after human treatment planners tell it what is considered "best."

"It was recognized at that time that inverse planning optimization could be readily achievable in the near future with increases in computing power, and that the multi-objective tradeoff strategy problem required much closer attention," Yu noted. "We continued to pursue this line of scientific inquiry with automated treatment planning for stereotactic radiosurgery and intraoperative brachytherapy, both of which required rapid planning under pressure as the patient might be in distress or under anesthesia."

Yu went on to credit other groups that have since broadened these approaches to clinical decision support "… involving assessment of physicians'—and remarkably (and potentially) patients'—preferences in how they would prefer to trade off between tumor control and toxicities; or knowledge-based treatment planning; or indeed more brute-force exploration of all possible tradeoffs. At the same time, and just like we anticipated 20 years ago, inverse planning is now ubiquitous. The field of radiation oncology was changed forever when inverse planning entered center stage in treatment planning, catalyzing the era of intensity modulated radiation therapy and volumetric modulated arc therapy."

Flexibility & Speed

Automatic-contouring is still rapidly evolving as is automatic treatment planning, and with each come high hopes for improved care that is more flexible in real time, Reyhan added. "Once we can fully automate contouring and treatment planning, then we can easily adapt treatment on-the-fly," he said. "For example, when a tumor shrinks or a patient loses a lot of weight, such changes affect the radiation dose to the tumor. Implementing adaptive therapy would bring us one step closer to more personalized patient care."

Minsky, too, weighed in on the important potential for faster treatment plan readjustments. "We, as a profession, are now in the process of developing MRI-guided radiation therapy. This is accomplished with machines that combine both an MRI with a radiation therapy delivery system," he explained. "In this setting, we will be able to track the tumor in real time. For example, when a patient breathes there is movement in the lungs, liver, and other organs. Historically, we had designed the radiation fields large enough so that we would cover the tumor despite the movement, but we couldn't help but include nor-

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AUTOMATION

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mal tissue in the margins. Now the radiation field can be tracked such that the radiation field will follow the tumor in much the same way a missile is tracked. We will be able to spare more normal tissue from unnecessary treatment."

Minsky also pointed out that in contrast to one treatment plan for the duration of a patient's treatments that could span multiple weeks, MRI-guided radiation therapy may open the door to the need for daily updated radiation plans. "To be able to use this adaptive radiation requires a great degree of automation to allow rapid turnover of our planning processes. With automation we could redo the treatment design every day," he claimed. "As image-guided machines become more widely available, the need to have more rapid daily planning will only be achieved by automation of the processes."

> Automation, at maturity, could be the conduit to higher quality, safer treatments, all harnessed to a more rapid and accurate delivery system of radiation oncology.

Speed of treatment delivery is another noteworthy area in which automation is making a change for the better, according to Minsky. "When the technique called intensity-modulated radiation therapy was developed over 20 years ago, we could only treat two patients per hour because of all the many fields of radiation that needed to be delivered in one setting. Now with the advent of multileaf collimators, we can treat one patient every 8-10 minutes. It makes a significant difference."

These individual "leaves" are used on linear accelerators to move independently in and out of the path of a particle beam to block it and provide shaping of radiotherapy treatment beams.

Better Implementation

Pawlicki pointed to yet another area that benefits from automation: the acceptance and commissioning for radiation therapy equipment. "Radiation therapy equipment, e.g., linear accelerators, are expensive large devices and bringing them into clinical service requires several weeks of coordinated work between the vendor and medical physicists to characterize the mechanical and radiation properties of the device," he noted. "Quality assurance programs need to be set up and the radiation delivery device must be modeled in a treatment planning system. How well the device is prepared for clinical use depends on the knowledge and expertise of the medical physicists and there are several instances in the public domain that document the effect on patients when this has been done improperly."

By way of example, Pawlicki pointed to a Feb. 24, 2010, *New York Times* report (www.nytimes.com/2010/02/25/us/25radiation.html) on a hospital in Missouri that over-radiated 76 patients, most of whom had brain cancer, by about 50 percent, due to miscalibration of new equipment.

"Of course, the best possible education and training is important," said Pawlicki, "but, this type of error can also be mitigated by automating the process, i.e., removing, or at least reducing, the role of the human in the process. Automation can take this process from weeks to days for new devices, and at the same time, ensure that the acceptance is consistent across all devices and institutions and of the highest quality. Some vendors have already taken steps to automate acceptance and commissioning of new equipment."

Adam Dicker, MD, PhD, FASTRO, Senior Vice President, Enterprise Radiation Oncology, Professor and Chair, Department of Radiation

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Oncology, Thomas Jefferson University, agrees that quality and safety is an area that can be significantly impacted by such technology and analytic approaches.

The ASTRO-AAPM effort, RO-ILS (www.astro.org/RO-ILS.aspx), the only radiation oncology society-based patient safety organization, is preparing for machine learning approaches to data mine reports submitted by institutions. Dicker, a member of the advisory committee for RO-ILS, noted, "We have spent 3 years creating a better taxonomy of defining the severity of incidents and near misses. The goal was always to create a more automated process. The success of the program and the sheer number of reports makes conventional methods too slow and cumbersome. Our goal is to contribute back to the radiation oncology, medical physics, and therapy community information that will improve the quality and safety for the entire field."

Automation carries a high degree of potential in radiation oncology—some of which is already realized, and some which is being perfected for the near future. Minsky added that automation could be perceived as a threat to services now provided by humans, or as an opportunity. "I fall in the latter camp," he said. "Automation will increase our accuracy and throughput, and give us more time to be with our patients. Automation cannot relate to patients and it will never be a substitute for clinical judgment—but it sure can add and subtract very quickly," he added with a chuckle.

Yu also stands firmly in the "opportunity" camp. "The next frontiers are rapidly upon us. Automation can mimic human reasoning in quality assurance of treatment plans, e.g., to catch gross errors that may be missed by a human expert (due to time pressure, fatigue, or simply being human), examine a treatment strategy against all available clinical evidence, standard of care and innovative trials, or be just an autonomous robot that performs repetitive but precision-dominated manual tasks.

"Will automation in radiation oncology liberate the highly skilled workforce to pursue ever more challenges, of which there are many? The answer is a resounding yes." OT

Valerie Laberta is a contributing writer.