

Noteworthy Grand Rounds

of the

**Michael & Marian Ilitch
Department of Surgery**

Wayne State University
School of Medicine

Detroit, Michigan, USA

Issue 1. May 2021

The Changing Face of Oncology: Modern Skill Sets for the Cancer Surgeon and Changing Scientific Paradigms

by Donald W. Weaver, MD

May 2021

Dr. Weaver is chair of the Department of Surgery at Wayne State University School of Medicine and chief of surgery for the Detroit Medical Center. He one of the longest serving faculty members still active in clinical care. He received his MD degree from Loma Linda University. Dr. Weaver has over 100 publications in peer reviewed journals, as well as book chapters. He has had funding from the National Cancer Institute and from pharmaceutical companies and device companies. He has reviewed for many journals, and has many honors.

Objectives

This is a fairly broad presentation that hopefully will have interest to a variety of people—not only surgeons. My overall objective is to show how and why surgery and especially surgical oncology is changing. We will take a look at where surgery is going and (since I've been around for a while) where it's been. I hope to provoke thinking about the changing scientific paradigms in surgery and oncology in general.

Background

The 1960s through the 1980s was the era of what I would call super-radical surgery. ICU care had been improving. The mechanical ventilation of patients became a much more scientific endeavor. So did blood banking, anaesthetic techniques, understanding the pathophysiology of shock and resuscitation, and more. All of this made an opportunity for "big surgery." There were not, then, as many highly effective cytotoxic therapies as there are today, and radiation was much more primitive. Surgery was still the mainstay in the treatment of many cancer patients.

But in the 1990s the pendulum began to swing back. Surgery began to adopt more minimally invasive techniques. At the 1989 American College of Surgeons meeting I watched Dr. Edie

Redick, a private practicing surgeon, present the notion of removing the gall bladder with laparoscopy. This was a seminal event and I remember people crowding around the televisions in the booths showing the technique.

Now, we're in an era where less is more and surgery, though still important, is no longer the main player as perhaps it once was. Better radiotherapy and better chemotherapy have changed surgery in ways that are difficult to comprehend, and technology is the engine of that change.

Super-radical Surgery

In the era of super-radical surgery there was really only one question: Can you do the procedure? And this was often answered: "Yes, but without regard to the quality of life or the function of the patient." We would take flaps from the chest and move them into the throat, take things off the forehead and put them into inside the mouth, perform major radical surgery of the breast, and so forth, but nobody really thought too much about the quality of life, about the fact that the patient couldn't swallow their own saliva or couldn't eat or their arm would end up the size of a fence post because of the radical nature of the lymphadenectomy. People thought more about whether or not this thing could be done.

In the late 1900s Jerome Urban popularized and extended radical excision of breast cancer where you would take the ribs out along the medial aspect of the rib cage adjacent to the sternum and take out all the internal mammary lymph nodes. There were other extended nodal dissections for stomach cancer. Fortner at Sloan Kettering popularized, or at least tried to popularize, the portal vein excision for pancreatic cancer. In the colon and rectum there was a lot of thought about proceeding with internal iliac lymph node dissection and periaortic lymph node dissection.

Organ Preservation

Again, the whole notion was that more was better. But we're now in an era of organ preservation, and we ask ourselves: "What is going to be the functional position of the patient once we're finished with our surgery? And are we compromising cures by trying to do some organ preservation?"

The Sloan-Kettering website illustrates this, saying: "Our surgeons are at the forefront of developing surgical procedures, reconstructive breast, colon, tongue and mouth and rectum following cancer surgery and new techniques to spare organs and preserve function."¹ This is the mantra of surgical oncology today—that is, the sparing of function.

Taking the breast as an example of the road to organ preservation, you can see a progressive stage from the extended radical mastectomy of Urban, through the radical mastectomy of Halstead which take the pectoralis major and pectoralis minor but left patients with (almost certain) severe and almost disabling lymphedema, the modified radical mastectomy which then provided the opportunity for the patient to keep their pectoralis major and

pectoralis minor through simple mastectomy/quadrantectomy.

And now there's even a movement afoot asking: "Can ablative procedures be used as a way of preserving organs in patients who have breast cancer?" This may be one of the best examples, both with the limited resection of the primary and also with nodes varying procedures associated with sentinel lymph node dissection. And of course radiotherapy and chemotherapy are major players in the desire to preserve organs.

Methods of Organ Preservation

So what are the factors which can be brought to bear to help in the preservation of organs? Certainly the better neoadjuvant treatment we have today has revolutionized the opportunity for organ preservation. As well, we have ablation techniques, minimally invasive surgery, node sampling using sentinel devices, and better imaging—something that is perhaps not recognized as much as it needs to be as an aide to the surgeon in the preservation of organs. And of course, early detection is always one of the best methods of organ preservation: If you detect something early, you have the opportunity of doing something little.

One of the interesting areas where organ prevention has been most effective is in rectal cancer. It's now estimated that about 75% of patients who, two decades ago, would have had an abdominal perianal [??] resection with a permanent colostomy for the treatment of the rectal cancer, now can be treated with some kind of rectal-sparing procedure.

Better neoadjuvant treatment has really impacted the breast cancer, rectal cancer, head and neck cancer, esophageal malignancies, and others that are I think on the docket for continued improvement in terms of organ preservation. As neoadjuvant therapy improves, things will also

¹ Memorial Sloan-Kettering has since edited the "About" pages of its website. This quote was taken from <https://www.mskcc.org/mskcc/html/13706.cfm>, of which the author has a screen print.

improve in terms of organ function for a number of other organ sites as well.

Node sampling just needs to be mentioned in passing because we don't do (particularly in breast cancer and even in melanoma) the kinds of radical lymphadenectomies that once were quite popular. Still, there are opportunities. There are studies going on in a variety of other disease sites including colon, rectum, gastric, head and neck, thyroid, GYN malignancies, and neurologic malignancies that may, in the future, allow lymphadenectomy to become something that is of historical interest only.

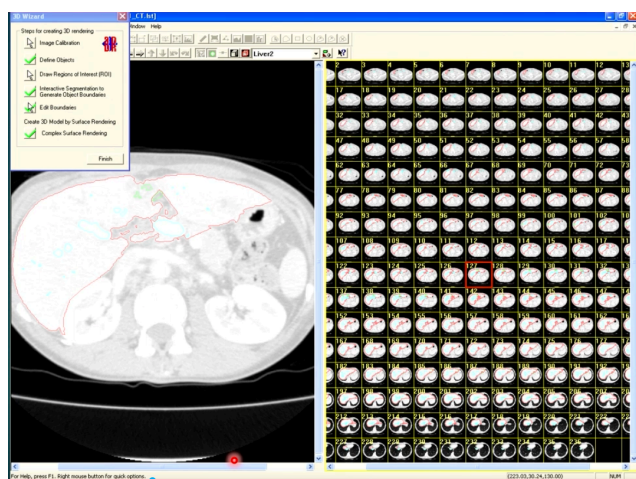


Figure 1. 3-D model of the liver

Imaging

One of the areas where organ preservation I think can be benefited is in the area of imaging. One of the things that we've been doing in our department is working on some segmentation of cross sectional imaging to try to develop three dimensional organ images, particularly the pancreas and the and the liver. These organs are not easily segmented automatically because of the motion that takes place during the technique to get the pictures, but we've been working (as have others) on trying to reconstruct for better organ preservation 3-D images like those below.

The somewhat primitive image at Figure 2 shows the inflow to the liver, the portal vein, and the superior mesenteric vein. The yellow parts are tumors—this helps in the segmentation of the of the liver. You can see the hepatic artery and the inferior vena cava. This is the [on fossa ???] view.

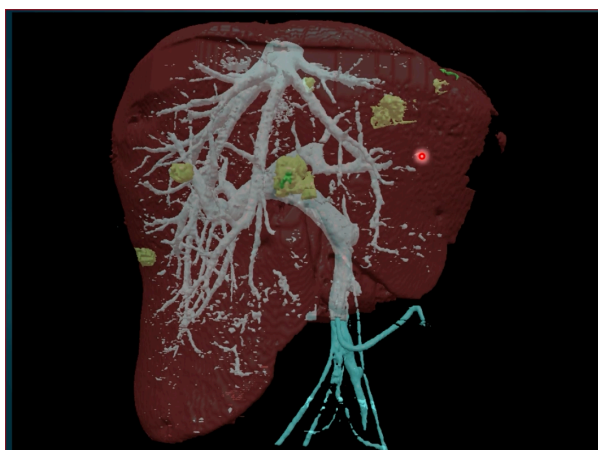


Figure 2. Inflows to the liver

Figure 3 below shows the sagittal view with the inferior vena cava and the hepatic and left and the right branches of the portal vein. This would be very helpful in planning the the treatment for such a such a patient.

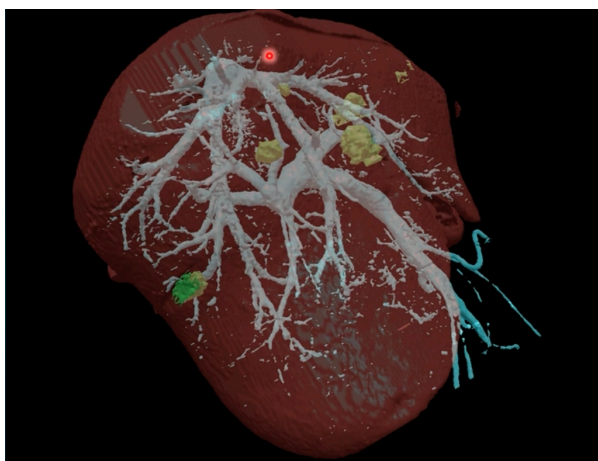


Figure 3. Sagittal view

Figure 4 shows the posterior view, with the hepatic vein, the inferior vena cava, and the portal inflow.

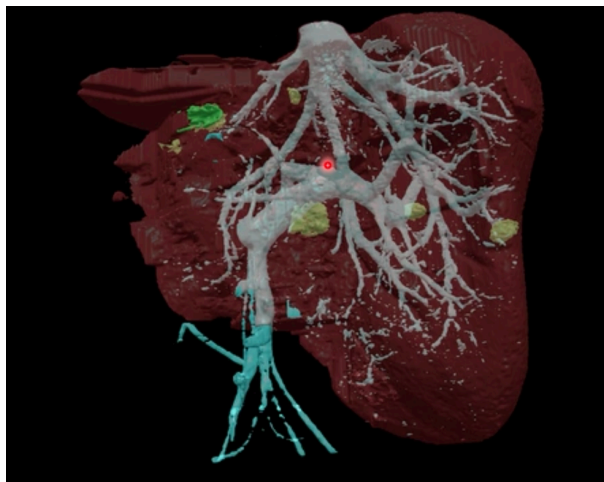


Figure 4. Posterior view

I foresee a day in the not too distant future when the surgeon will sit at a workstation with such a three dimensional reconstruction, consider how best to approach the lesion, looking at things such as what kind of incision would provide the best route to the organ, what would be the way in which you can do the most efficient surgery with least blood loss, and so on. I think this will be here within a few years.

The use—also intraoperatively—of high resolution ultrasonography is something I think we will see more and more of. Even now, surgeons in various specialties, including surgical oncology, are using intraoperative ultrasound and in some centers now the CT machine has been moved back into the operating room.

Image guided surgery and cross sectional imaging within the surgical field is both necessary and will be beneficial to patients. As well, virtual imaging and the ability to put virtual images on top of the patient themselves and

help guide the surgeons hands is being done experimentally and again, I think, is not far from reality.

Minimally Invasive Surgery and Organ Preservation

Nearly three decades of modern laparoscopy have confirmed the value of minimally invasive surgery and benign disease. A generation of surgeons has incorporated the skill set into their practice. But the question still remains: Is the minimally invasive surgery something which is good in the care of cancer patients?—Are the margins adequate? Do we do get enough lymph nodes? Is ligation high enough? Are there any issues with portside recurrence or seeding of the of the tumor? These are questions some people still ask; although, to be very frank, most people now just plow ahead using minimally invasive surgery without pondering them.

The first question is always appropriate: Can it, in the end, be done, and can it be as effective as open surgery? The answer to "Can it be done?" is yes. Every abdominal procedure and essentially every thoracic procedure that has been done with an open technique has now been done with minimally invasive technique, including complex pancreatic surgery and complex hepatobiliary surgery. Even liver resections are being done by minimally invasive technique.

Perhaps the best randomized study to show the effectiveness of minimally invasive surgery for cancer was the COLOR trial, published in *Lancet* in 2005. It compared minimally invasive surgery for colon cancer with that of open surgery, and determined that the minimally invasive procedure took slightly longer and resulted in a slightly shorter length of stay, but there was no difference in terms of lymph node recovery, local recurrence, margins, and complications.

Surgical Ablation

The Karmanos Cancer Center probably has the world's most replete experience in the use of

ablation techniques for the treatment of malignancy, based on work that Dr. Littrup did early on and Drs. Aoun and Critchfield are continuing. Indeed, Wayne State University Medical School and the Karmanos Cancer Center are recognized as world leaders in ablation technology.

Obviously, ablation techniques can use a variety of heat sources and heat sinks. Whether you heat or freeze the tissue or use some kind of electroporation is not as important as the fact that you have an opportunity to very directly influence the destruction of the tumor through the ablative techniques. Essentially all organ sites have been subject to ablation techniques. Some are easier than others, some are more accessible than others. Some have more application others. But but I think one of the major advantages of ablation techniques is that you can preserve organ function.

Perhaps something that we've not thought enough about is the use of ablation techniques as an adjunct to resection to enhance margins. This might be seen, for example, in breast cancer cases, where sometimes it's difficult to get a clean peripheral margin. We've used ablation techniques on a number of occasions in order to get better margins at the wall of the pelvis. I've done six patients with pancreatic tumors to ablate the margin along the superior mesenteric vein and the superior mesenteric artery. This is an area where positive margins are most likely to occur. I think we have the opportunity to think even more about how to use ablation technology in the management of these patients.

Ablation also has a role to play in organ preservation in order to enhance function. Hepatocellular carcinoma puts the entire liver at risk, and recurrence and secondaries within the liver are very common. In addition, these patients almost always have compromised liver function. So the ability to target the lesions and ablate them, and preserve as much of the liver

as possible, is certainly very beneficial to the patient. It may be that as time goes by we'll see more and more use of this in prostate, to preserve a function; and also patients with compromised lung function.

Skill Sets for the Modern Surgeon

Clearly, surgical oncology is only one player on a multi-modal team. But the skill sets for the modern surgeon continue to evolve. First of all, a skill set must include minimally invasive surgical techniques, including not only standard and minimally invasive laparoscopy but also NOTES therapy, trans endoscopic microsurgery, image guided surgery, and robotic surgery. As well, high resolution ultrasonography within the operating room is increasingly required and is a skill set that the surgeon needs. This will be even more the case when the CT scanner gets back into the operating room as well.

This changing skill set is a very great challenge for those who are in the business of training surgeons. This is the first generation of surgeons who will complete their training without the skill set needed to finish their career. My father was a surgeon. When he finished his surgical residency, in 1958, he had the skill set to completely finish his career. But nowadays, it's very clear that we leave the surgical trainee with only a base foundation of what they're going to actually need. The real question is: How are we going to continue to upgrade the training that's going to be required as technology continues to change? And how can we judge emerging technologies in the future? How about their costs and their usefulness? And how do we incorporate these technologies into practice and training?

There is a basement underneath the operating rooms at Harper University Hospital housing hundreds of instruments, some of which cost millions of dollars, which were used two or three times and then never used again. Somebody came back from a meeting or an encounter with a salesman who said: "This is the latest and

greatest thing and you just have to have it!" Somebody convinced somebody in administration to put it in the budget and buy it. They used it three or four times and it ended up in the basement. How to judge emerging technologies is something we really need to think much more about and figure out what is cost effective, what is useful, and what can be reasonably expected to remain part of the future.

And then: How to incorporate these technologies into practice? When I was in the middle of my practice, laparoscopic surgery became something everybody wanted to learn. In truth, most surgeons learned it from vendor representatives, who would bring the equipment and tell you how to set things up and do things. I think, in retrospect, it was an ineffective and inappropriate way to introduce new technologies, and we need to think more about it.

In addition, procedural medicine such as cardiology, gastroenterology, pulmonology, and even procedural radiology such as interventional radiology is becoming more and more invasive at the same time as surgery is becoming less and less invasive. And we're reaching a convergence point, driven by technology, where the surgeon and the interventionalist are going to end up standing shoulder to shoulder.

New specialties and training programs will of necessity emerge. But how? There's no forum, there's no way we can say that a surgeon should spend time in the radiology suite learning ultrasonography or the placement of tubes and probes and wires and so forth. This remains a very great challenge, but I think that when fee for service has gone (if ever!) then talk will begin. Right now, we're in a series of turf wars. Everybody wants to chip off a little piece of somebody else's business. This is another great challenge for us in training.

The Future

So this is the question: How do we introduce new ideas, new therapies, new technologies in a

time when the conventional scientific means of assessment—the large randomized trial—cannot keep up with the explosion of knowledge and technology? In the 1970s, '80s, and '90s, and even to some extent now, there's phase three trials, where we're coming to form what we now call level one evidence (SWOG trials, ECOG trials, GITSG trials, trials where there's 300 patients in each arm, each one getting a slightly different therapy, but not very much)—all well regulated, with IRB oversight and so forth. This is what we came to believe was the best way of moving forward in oncology.

But now, many trials are begun asking questions which are rendered obsolete by changes in the therapy over the life of the trial. So while you are trying to accrue patients for a trial, some new technology, some new drug therapy, comes along and renders your trial obsolete. One of the best examples I remember is from the time when we were looking at the treatment of liver resection patients and whether or not there was some kind of postoperative adjuvant therapy that would help to prevent recurrence in patients who have had liver resection for colorectal metastasis.

Margaret Kemeny put together a trial using 5-FU and then 5-FUdR as an infusional therapy. She published in the *New England Journal of Medicine* in 1999. The study found that infusing 5-FUdR gave a slight advantage in terms of overall recurrence and survival in patients undergoing hepatic resection for liver metastasis. But in 1999, ocelea platim was approved for therapy, and the difference in terms of response to therapy between 5FU/5FUdR and ocelea platim was like lightyears. So Kemeny's seminal study, which had taken many years to complete, was rendered obsolete almost overnight.

Modern technology, informatics, and therapeutic interventions are changing too rapidly to sit still waiting for a clinical trial to conclude. Technology and minimally invasive surgery make many randomized trials even impossible. You'd never

have a trial, for example, of percutaneous angioplasty for heart versus coronary artery bypass. You'd never get anybody to approve that. Closer to home, think of the local excision and the management with neoadjuvant therapy of patients with rectal cancer versus a standard abdominal perinatal resection.

So we have challenges, because the technology and the therapeutic intervention innovations are occurring more rapidly than can be assessed by conventional means, by which I mean the large phase three trial. As well, the intuitive embrace of technology by the general population—our patients—makes evidence based medicine difficult. For example, no study has ever shown that the treatment of prostate cancer using the robot is superior in terms of oncologic outcome but patients believe it is so they demand robotic surgery. As a result, hospitals scurry to buy the \$2 million machine, which costs about \$2,000 per case.

An Ethical Tipping Point?

So the question is this: How do we introduce and use innovation while respecting and protecting the rights and well being of our patients? Can we be both cautious and forward thinking at the same time? Can we be both scientific and nonlinear at the same time? In asking these questions—as I have at various forums—I've been accused of being unscientific, anti-intellectual, and even—once—dangerous. I submit that the era of the large prospective randomized study is coming to a close. My Karmanos colleague Dr. Vorovit told me 30 years ago that there was never a major breakthrough in oncology that came from a clinical trial. I don't know if that remains true today but I do think that the large, multi-institutional, 3-400 patients-per-arm trial are coming to a close because we are at the beginning—indeed, were more than just at the beginning—of so called personalized medicine, or genomic medicine.

If you don't believe this, all you have to do is to listen to the advertisement on television for the

Josephine Ford Cancer Center. It goes something like this: "You're very special. You are unique. Your cancer is also very special, and it is unique. And we have unique personalized care for you if you come and get your cancer care from us." This is the great challenge we face. What should we do?

Well, we could delay innovation and new technology until we've done all the vetting and gathered all of the level one evidence that the technology can be properly employed. Or we can think about it more and develop new paradigms for vetting progress. We must use technology itself to overcome the obstacles created by technology.

I think it is appropriate here to put in a plug for surgery. Surgical procedures have always carried with them an element of innovation. This raises what is really the heart of the issue: It seems to me just as unethical to consign a patient to treatment which is obsolete as to assign a patient to treatment which is promising but unproven. You can argue with that, but it is my feeling. Certainly, it is a great challenge for those of us taking care of patients in an era of such rapidly expanding technology. We know that the tried and true is not very good, and we know that there is very promising therapy but it's unproven. How do we get around that ethical dilemma?

The Way Forward

First of all, I think we need better data registries to keep track of what we do, including outcomes. Electronic medical records which are accessible to data mining and informatics I think are really essential. But also, I don't think we've given the multidisciplinary conferences and multidisciplinary tumor boards either enough credit or enough responsibility to help to provide the ethical hedges needed in such cases. The multiple participants and the various specialties that make up these multidisciplinary groups must become the champion for the patient.

I had an experience recently in a GI tumor board which impressed me greatly. There was presented the case of a homeless young man with a very advanced rectal cancer. He was drug and alcohol dependent. A very thoughtful discussion occurred concerning several things: Number one, what was the optimum therapy for a patient like this with this kind of tumor? But then the conversation turned to what was optimum therapy for this particular patient? What was he likely to accept? What was he likely to follow through on? And so forth. I felt heartened by this warm discussion about how to treat this patient in the most compassionate and most effective way. I think that the multidisciplinary tumor groups can be and must be an ethical hedge to keep us on the right track for our individual patients, both for and against what is new and what is innovative.

I also think AI-based computer modeling and planning and simulation will inform our actions and protect our patients. We need to think more about inviting the information technology folks and the computer geniuses into our clinical realm to help us to harness the opportunities. Around the turn of the century, Dr. David Eddy's "Archimedes" was touted as "a mathematical model of human physiology and disease intervention and healthcare systems. Highly detailed and rigorously validated against more than 50 clinical trials, the model is used to understand the likely costs and health outcomes of a wide range of interventions."

Archimedes has been superseded (such is the pace of change) by better computer modeling involving artificial intelligence, machine learning, and deep learning, that I think have to be brought into the clinical realm and exploited. Customized personal therapy is not on the way—it is here already. Molecular and genetic markers in the tumors and the host and the variety of *in vivo* and *in vitro* assays will allow us to target therapy on an individualized, unique, and special basis for our individual patients.

We must ask ourselves, because we're in these most exciting of times, how we will evaluate the risks and the benefits and the outcomes for the individual patient with the same scientific rigor with which we have venerated the prospective randomized trial and the population statistics that go with it. How do we calculate the risks and benefits for an individual patient with the same scientific rigor that we've done for the cohort studies?

The new paradigm for the future is going to be based on individual uniqueness and customization, on personalized medicine. It's going to be based on computer modeling and predictive simulation. And it's going to be based on solid, well developed ethical principles. Our scientific understandings and the opportunities we have in science and in the care of our patients far exceed the thoughtfulness we've placed on the ethical principles that are designed to help control them.

Fundamental to the discussion is this: Can non-empirical scientific constructions lead to genuine knowledge in science? Can thought experiments (what some people have called a rationalist view) or computer modeling have the same scientific end in themselves, or are they only to be justified as stages on the way to genuine empirical discovery? This, I think, is really the crux of our questions.

Conclusions

So the trends in surgical oncology? Less is more. This is seen in minimally invasive surgery, in selective nodal sampling, in ablation technologies, better images and image guided surgery, in organ preservation in general, and new technology. Intuitive embracing of these concepts by our patients really does represent a great challenge, I think, for those of us who are interested in the science of medicine, and it tends to circumvent the evidence-based kind of practice. We live in a time when new ideas will occur at a rate more rapid than they can be systematically tested. That is, we're just

leapfrogging with technology and with opportunities for care. It is not ethically superior, in my opinion, to withhold potential innovations, any more than it is to recklessly implement them.

Population statistics are going to have less importance as customized personalized therapies and computer modeling are developed. We must rethink and re-study and redefine the ethical principles and boundaries which guide our use of new ideas. And technology must be used to overcome the obstacles caused by technology—by that I mean computer modeling and artificial intelligence and so forth. Surgeons, I would argue, are in a good position to wrestle with these issues since the operation—that is, what we do in the in the operating room—has

always had the elements of customization, use of innovative ideas, and the need for ethical decisions.

Science as it is presently defined must be broadened to include carefully constructed non-empirical constructions; particularly those with ethical boundaries. Some will call this thinking reckless, unscientific, and dangerous, but I believe that failure to do this will result in fewer innovations and stall opportunities for true breakthroughs.

Alvin Toffler, the author of *Future Shock*, said the illiterate of the 21st century will not be those who cannot read and write but those who cannot learn and unlearn, and then relearn.

* * *

This paper is edited from the transcript of the author's Grand Rounds presentation to the Karmanos Cancer Institute in Detroit, Michigan on **XXXXX** May, 2021