Folks, welcome to Yale Cancer Center, Grand Rounds. I’m Kevin Billingsley, and I have the pleasure of welcoming our visiting speaker today. Doctor Charles Balch is, no exaggeration, a giant of multidisciplinary cancer care and surgical oncology. We’re thrilled to have him here today. Doctor Balch is a professor of Surgical Oncology in the past chair of the Department of Surgical Oncology at the UTMD Anderson Cancer Center.
He has had an extensive and distinguished career as both a clinical and academic surgical oncologist, and he's one of the leading authorities in both Melanoma and Breast Cancer Care. Over the course of his career, Doctor Balsh has made significant contributions to laboratory research in tumor tumor immunology and human T lymphocyte differentiation. He started his medical career in Med school at Columbia, where he and then he went on to surgical training at both Duke and the University of Alabama, followed by additional laboratory
00:01:09.912 --> 00:01:12.161 experience with an immunology

00:01:12.161 --> 00:01:13.946 fellowship at the Scripps Clinic,

00:01:13.946 --> 00:01:16.876 which clearly laid the groundwork

00:01:16.880 --> 00:01:19.508 for his Seminole contributions

00:01:19.508 --> 00:01:22.793 in tumor immunology and Melanoma.

00:01:22.800 --> 00:01:25.188 He’s the founding Editor in Chief

00:01:25.188 --> 00:01:27.263 of the Analysis Surgical Oncology

00:01:27.263 --> 00:01:29.735 and Editor in Chief for the

00:01:29.735 --> 00:01:31.520 Patient Resource Cancer Guides,

00:01:31.520 --> 00:01:34.385 which are distributed to over

00:01:34.385 --> 00:01:38.280 1,000,000 patients every year.

00:01:38.280 --> 00:01:40.716 Doctor Balch has had an extensive

00:01:40.720 --> 00:01:43.304 history of prominent leadership roles

00:01:43.304 --> 00:01:46.280 in multiple centers across the country.

00:01:46.280 --> 00:01:48.430 He served as the Executive
Vice President and CEO of ASCO. He’s also served as the President and CEO of the City of Hope National Medical Center, as well as the Chair of Surgery at MD Anderson. Over the course of his career, he’s accumulated over 700 publications across a variety of areas in research and clinical practice. And one of the things that in my conversations with him, he and I have truly connected on are the importance of leadership and community building around multidisciplinary cancer care and care coordination.
So one of the things that I think I have taken away from my conversations have taken away from my conversations with him that I’m sure he will be sharing today is the importance and our ability as oncologists to serve our patients and our communities and a variety of ways. And he’s really shown how all of us can do this over the course of our careers, both through our direct clinical care, both through clinical translational and basic science, and through research, through mentorship, and through education.
through leadership and patient advocacy.

So today, he will be speaking on the role of surgery after neoadjuvant systemic therapy.

And it is a real pleasure to have you here, Doctor Balch.

Well, thank you, Kevin, Bill and Sleep for a wonderful introduction and I'm honored to be here with all of you today.

So there are many themes we could talk about because we are now in a revolution of oncology care.

Profound changes are occurring now and I thought what would be
important today is a theme to talk about how the field of surgery and surgical oncology is going to have to change and adopt to the new advances in molecular profile diagnosis in systemic therapies, in immunotherapy and the changes we are going to have to adopt to. So for some of you might say that’s not what I’m doing in my practice today, but I can almost guarantee you within the next 5 to 10 years, everybody in this room who is a surgeon is going to be impacted by the things that we’re showing today.
And so as I go over some of these themes, I'd like you to think about the strategies that work in one tumor area, but understand that these are common to our understanding about the management of other cancers as well. That's particularly true in the immunotherapy field. So I've presented examples that I think are larger strategies that apply to our cancer care delivery system that is now being almost exclusively multidisciplinary. There are very few circumstances now where one modality in solid tumors will treat the patient anymore.
So let me go over this. This is flying above the trees. Think about the strategies, not the details on the slides. And there are many things I can’t cover in the time allowed that we can take for questions later on if necessary. So we’re should I use this? Yeah, you can advance with the keyboard if you want. OK. All right. Well, let me start out with just the key messages of what I’m going to present as examples over time, so that you can focus on the strategies. The first thing because of the theme.
00:05:58.744 --> 00:06:01.703 of this talk is that surgery will
NOTE Confidence: 0.884209504210526
00:06:01.703 --> 00:06:05.224 not be the first treatment for most
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00:06:05.224 --> 00:06:08.160 cancers except for stage 1 cancers.
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00:06:08.160 --> 00:06:09.996 That's a revolutionary change.
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00:06:09.996 --> 00:06:12.291 Where is heretofore the patients
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00:06:12.291 --> 00:06:14.913 usually went to the surgeon first who
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00:06:14.913 --> 00:06:16.960 then kind of coordinated the care.
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00:06:16.960 --> 00:06:21.010 But now because of these advances
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00:06:21.010 --> 00:06:23.035 in systemic therapy,
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00:06:23.040 --> 00:06:26.672 that surgery will not be the first and we
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00:06:26.672 --> 00:06:29.584 need to be part of a multidisciplinary
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00:06:29.584 --> 00:06:33.642 team and we must emphasize that be
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00:06:33.642 --> 00:06:36.070 involved in multidisciplinary treatment
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00:06:36.160 --> 00:06:39.253 plans because each of us bring to the
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00:06:39.253 --> 00:06:41.636 decision making a different perspective
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00:06:41.636 --> 00:06:44.965 based upon our training and so forth.
And it’s the collective wisdom of the different oncology specialists that is really what’s best for the patient. So all of us treating cancer in a specific disease need to be together and collectively decide on the best treatment plan for a patient, what’s the right combination and sequence that involves all of our modalities. And that as I’ll show you that the standard of care, what we called neoadjuvant surgery, think our medical colleagues are beginning to talk about neoadjuvant surgery, that the primary treatment is systemic now,
but it doesn’t make a difference in the term.

But what we call neoadjuvant therapy is now becoming the standard of care for many, if not most cancers. And this is an area based upon clinical trials that is showing value in almost every cancer where it’s tested. There’s sure there’s a few that are resisted, but if you think about the future and the advances we’re making, this will be a common element of our treatment that the first treatment will not be surgery, it will be a systemic treatment. And I’ll go over with you about the value of that to the patient in.
their management.
The other part of this is that immunotherapy now is the established 4th modality of cancer. But I want to emphasize as I get to the slide, this is a totally different treatment and the standard chemotherapy, targeted therapy, endocrine therapy that directly treats the cancer immunotherapy, these checkpoint inhibitors do not treat cancer and that has to be the first part of the logic because we can’t use the rules of chemotherapy.
00:08:33.225 --> 00:08:35.520 when we applied to immunotherapy.
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00:08:35.520 --> 00:08:38.340 It’s a different process and we’re
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00:08:38.340 --> 00:08:40.720 treating a dysfunctional immune system
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00:08:40.720 --> 00:08:45.436 that is common to most cancers.
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00:08:45.440 --> 00:08:47.288 So the other emphasis on this
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00:08:47.288 --> 00:08:48.885 because there’s some emphasis, well,
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00:08:48.885 --> 00:08:51.075 maybe we don’t need surgery anymore,
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00:08:51.080 --> 00:08:53.040 but I would argue that surgery is
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00:08:53.040 --> 00:08:55.997 going to be incredibly important for staging,
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00:08:56.000 --> 00:08:59.008 as I’ll show you as a reliable means
NOTE Confidence: 0.884209504210526
00:08:59.008 --> 00:09:01.792 of staging the tumor response and
NOTE Confidence: 0.884209504210526
00:09:01.792 --> 00:09:04.764 giving to the pathologists not only
NOTE Confidence: 0.884209504210526
00:09:04.764 --> 00:09:07.074 whether there’s a complete response,
NOTE Confidence: 0.884209504210526
00:09:07.080 --> 00:09:10.097 but the residual tumor burden is now
NOTE Confidence: 0.884209504210526
00:09:10.097 --> 00:09:12.829 an important prognostic factor that is
NOTE Confidence: 0.884209504210526
00:09:12.829 --> 00:09:15.559 going to dictate our subsequent treatment.
And then because of these advances in systemic therapy that surgeons will no longer be performing the radical operations that we did in the past because that was all that was available for many cancers. And so we’ll be doing de-escalation much more conservative tissue sparing, organs sparing operations and even if, as I’ll show you in three different cancers in our future watch and wait that we will not do surgery, we’ll follow the patients. And then there’s going to be a whole new lexicon that will need to do much more conservative tissue sparing.
more research on salvage surgery.

Which patients can we select not to do surgery?

How often do we follow them, What operation do we do when they relapse?

And can we do this without compromising their survival by not doing an operation at the outset.

And I'll show you three different examples.

And then for those of you who are in training that in all of us who are in practice, the field is moving fast in both the continuing education through organizations like ASCO.

And in our training we need to have surgeons who are trained in oncology.
And as Kevin Billingsley and I’ve talked about, I really present myself because the way I think is I’m an oncologist who operates because oncology deals with the chronic condition of cancer, whereas surgery deals with the episode of the perioperative period. But once the patient’s wounds have healed, they’re still an obligation for us as surgical oncologist to continue being involved in the long term management of the patient. So that’s the summary of what I’m going to talk about.
I do want to just take a moment to say I predicted this 30 years ago in my presidential address in at the SSO, and I wanted to point out what I said, 'cause this was about surgical oncology in the 21st century. And I said that in the 21st century, only a minority of patients with cancer will have surgery alone as a single modality. And it’s more likely that chemotherapy and even radiation therapy will be the initial treatment for many patients, while surgical treatment for some types of cancer will be relegated to a secondary or tertiary level. That was 30 years ago.
And that prediction now is really valid for most types of solid tumors.

So why is that? Because we’re now in a new pathology with molecular diagnostics in this slide, which is just a cartoon, showed the old way with these general diagnosis of solid tumors, we gave our therapy and hope that 10% of the patients might respond and we declared that as a victory. But now with genomic analysis, we select patients based upon their specific mutational events and other factors. And now as you’ll see,
instead of getting 10% response rates,

we’re talking about 50 to 70%

pathological complete responses based

upon the selection of the patients and

these new agents that are so much more effective. So as I mentioned,

one of the things that is revolutionary is the advent of various immunotherapies because we now have discovered which

different than all of our strategies beforehand where we assumed the immune system was deficient and we gave various forms

of immune stimulants which didn’t work.

So now we are discovered that in most human

cancers that have survived in our patients,

they’ve done that by releasing low doses
NOTE Confidence: 0.925574668095238
00:13:10.517 --> 00:13:13.105 of their tumor antigen and inducing
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00:13:13.105 --> 00:13:16.087 tolerance so that no matter how much
NOTE Confidence: 0.925574668095238
00:13:16.164 --> 00:13:19.076 you try to stimulate the immune system,
NOTE Confidence: 0.925574668095238
00:13:19.080 --> 00:13:21.055 it can’t respond because it’s
NOTE Confidence: 0.925574668095238
NOTE Confidence: 0.925574668095238
00:13:22.640 --> 00:13:24.453 This is no different than if you
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00:13:24.453 --> 00:13:26.307 were allergic to grass and you go
NOTE Confidence: 0.925574668095238
00:13:26.307 --> 00:13:28.456 to the allergist, what do they do?
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00:13:28.456 --> 00:13:31.180 They inject low doses of grass so that
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00:13:31.180 --> 00:13:33.160 regardless of your exposure to grass,
NOTE Confidence: 0.925574668095238
00:13:33.160 --> 00:13:35.512 your immune system does not recognize
NOTE Confidence: 0.925574668095238
00:13:35.512 --> 00:13:39.678 it as not self and does not react to it.
NOTE Confidence: 0.925574668095238
00:13:39.680 --> 00:13:41.976 And so I think we’ve learned now
NOTE Confidence: 0.925574668095238
00:13:41.976 --> 00:13:44.500 that for many human tumors and we’re
NOTE Confidence: 0.925574668095238
00:13:44.500 --> 00:13:46.040 still sorting through this,
but it is revolutionary as a discovery

that the main reason that tumors have survived in patients we see clinically is because they have blindfolded the immune system into a tolerant state.

So if we can unblindfold the immune system, we then have a personalized treatment that reacts against the specific array of tumor antigens in each individual patients.

So if tolerance is broken now, then the immune system can reject the foreign invaders.

And of course, there's a price for that when we're doing something profound by breaking tolerance that the spillover is
breaking tolerance to self antigens. And so if you look at the array of complications we have with immunotherapy, you can explain them all as a form of autoimmunity. The good news is that we could treat autoimmune diseases with Prednisone and taper. Those over time reverse the toxicity. And interestingly, in contrast to chemotherapy, you can go back to the same immunotherapy in these patients and surprisingly they don’t enter into toxicity the way they did the first time around.
So there’s a lot we have to learn about this. And when I wanted to point out if course as you know that Jim Allison and to Soko Hanjo received the Nobel Prize for this. But I think another person who profoundly influenced the field that I wanted to give a shout out is here at Yale. And that’s my friend who I worked with, Li Ping Chen, when he was at Hopkins and we were working on Melanoma immunotherapy. We wanted to give credit to Leipeng, which I think is under appreciated by the rest of the world. He was the first to specifically state that a monoclonal antibody against
B7H1 would break tolerance in a mouse and therefore be an effective therapeutic strategy for cancers. And Leipeng worked with a group of us. This is Li Ping and Suzanne Tipalian, who I helped recruit to the surgery department at Hopkins, and her husband, Drew Pardo, who is the chair of immunology. So this is an example of translational research in the collaboration. So Li Ping’s research directly stimulated Drew and Suzanne to take out a seed culture they had.
frozen to do a phase one study.

They grew up this monoclonal antibody.

Mike Carducci at Hopkins, the phase one director gave it to a young person as an assistant professor named Julie Bramer, who is a pulmonary oncologist. And our recommendations was that you use renal cell and Melanoma to test this new drug because everybody knows that's the only diseases that work.

But Julie came in one day at our Friday meeting said you won't believe this, but my lung cancer patients are responding to this new drug.
So BMS swooped in, bought the biotech company that had done the seed culture and that became the volume up. But it’s a great example of collaboration between clinical and laboratory scientists that led directly to a major advance in cancer treatment. This is an unusual example, but it shows the power of the immune system.

This is a grapefruit sized Melanoma that was treated with a single dose of nivolumab and epilumab with a complete destruction of that tumor.
That’s APCR after one treatment. And I use that only as an example to show you the power of the immune system when you take the blindfolds off, when you break tolerance. And that’s unusual to have this, but as I’ll show you, it’s not uncommon either. So now there are 9 powerful checkpoint inhibitors with different mechanisms of action. And as we know with drugs that when we combined drugs with different mechanisms action, we can get an additive effect. So now we’re showing that the
combinations of anti CTLA 4 which works in the central lymphoid section and either anti PD one or PDL one combination is better than either alone. 
And this slide just shows you briefly in a cartoon that they’re now with different trade names but the same types of drugs working in this signaling pathway between PDL ONE and PD ONE and a separate mechanism of the first drug which was Ibilimed, which works in the central lymphoid tissue with a different mechanism of action. And now even after only 11 years.
when the 1st paper was presented,

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I'll show you a slide in a minute.

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You can see where the FDA has approved as

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an indication the use of immunotherapy,

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the same drug,

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the same drug course.

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We're not treating cancer.

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We're treating a common deficit in

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most cancers that come alongside our

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traditional treatments to treat the

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patients with a variety of cancers.

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And every month there's new indications

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that are approved based upon what

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is now over 1000 clinical trials

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going over various drug doses and

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indications for immunotherapy.
So that those powerful drugs that were started out with advanced disease have now moved into the neoadjuvant space. And I want to show you the reason why that is valuable in neoadjuvant therapy. So from this wonderful paper from my colleagues at MD Anderson that the advantages are one that downstages tumors and increases the ease of surgical resection, including importantly the conversion of inoperable or borderline operable tumors into operable ones. Importantly, as I’ll show you,
the pathological response is a surrogate endpoint for long term benefit.

So we can find out if drugs work within six weeks instead of giving them after surgery and following the patient for five years and then going back and seeing how many survived. So doing this up front gives us a better indication early on based upon the pathological response.

And what you'll see is the residual tumor burden is important now in a cancer management. It allows us to test novel combination strategies and investigational drugs because we can take out the tumor.
after the exposure to these drugs and determine the new molecular profile of the cells that are refractory.

And I’ll show you a classic clinical trial that she demonstrates that. And then the other reason is the improved responses are better than in patients with advanced burned metastatic disease where their previous chemotherapy itself is immunosuppressive and their volume of cancer itself provides an antigen excess which is immunosuppressive itself.

So if we’re doing this up front, when there’s a smaller tumor burden,
you get a better immune response and then we have some molecular markers, the CPS score and and other markers, but we really need better and more precise markers to help select our patients. So these are just a partial example of successful neoadjuvant trials that have led to approved indication by the FDA. And my point is this is a range of cancers, this is a common abnormality to human cancers. And as we’re learning how to use these checkpoint inhibitors and various combinations and sequences, they’re adding to the advances of our cancer management not
as a substitute necessarily, but alongside is what I call the 4th modality of cancer treatment. So here’s another hypothesis that has been proposed that I’ll show you the results that led to a clinical trial. And as you could see in the upper cartoon that if the surgeon takes out the bulk of the tumor and leaves microscopic tumor left behind and gives immunotherapy, there’s not many cancer cells to stimulate the immune system. But on the other hand, if you give the immunotherapy up front, when there is a larger and more
representative tumor burden

and tumor antigen exposure,

you will get a more robust and

consistent immune response.

And this is demonstrated amazingly

in this randomized clinical trial

which proves this hypothesis.

In fact, I'm astonished at the results.

So this randomized trial gave

everybody with metastatic Melanoma

18 courses of a single drug.

Drug in this case was pembro Elizabeth.

And they were randomized

to receive 18 courses,

but half the group got three

courses up front and everybody
else got 18 courses afterwards.

So that was the only difference with this monotherapy.

We don’t use monotherapy anymore like this, but look at the difference between those patients who had three courses of single agent immunotherapy up front and those who didn’t, which demonstrates what I just showed you in that hypothesis is the value in survival rates by giving checkpoint inhibitors before they’re to the bulk of their tumor is removed and this gives the rationale for neoadjuvant immunotherapy.
Another example that I want to show you from my colleague Merrick Ross. This is a Melanoma patient who presented with borderline operable bulky nodal metastasis in the groin and the pelvis. And this patient would have ordinarily had a radical dissection of the groin after immunotherapy, you can see that there is a down staging and the tumor size has decreased, so facilitating an operation. But it wouldn’t surprise you that when all the tumor was removed there was nothing left.
00:24:48.544 --> 00:24:50.736 inflammation and scar tissue in
00:24:50.736 --> 00:24:52.400 a classic rejection response,
00:24:52.400 --> 00:24:55.600 the same as what you’d see with a
00:24:55.600 --> 00:24:57.996 transplanted organ or a viral infection.
00:24:57.996 --> 00:25:00.390 That the mass that we’re seeing
00:25:00.466 --> 00:25:02.800 on X-ray was not tumor anymore,
00:25:02.800 --> 00:25:06.838 it was scar and inflammatory tissue.
00:25:06.840 --> 00:25:10.320 So the key point here is we can’t
00:25:10.320 --> 00:25:13.240 gauge responses by X-ray verification.
00:25:13.240 --> 00:25:15.354 The surgeon needs to take it out,
00:25:17.873 --> 00:25:22.800 new molecular profile to look at the
00:25:22.800 --> 00:25:27.078 molecular profile of the refractory cells.
00:25:27.080 --> 00:25:30.056 So this was the first immunotherapy
00:25:30.056 --> 00:25:32.970 trial presented in the world 2010.
NOTE Confidence: 0.909291
00:25:32.970 --> 00:25:35.840 So this is a very new field.
NOTE Confidence: 0.909291
00:25:35.840 --> 00:25:38.096 This was using the maximum tolerated
NOTE Confidence: 0.909291
00:25:38.096 --> 00:25:40.925 dose of a single agent EPI LUMA Med
NOTE Confidence: 0.909291
00:25:40.925 --> 00:25:43.148 and of course the problem with this
NOTE Confidence: 0.909291
00:25:43.148 --> 00:25:45.154 although this became a standard of
NOTE Confidence: 0.909291
00:25:45.154 --> 00:25:47.320 treatment until we found out that
NOTE Confidence: 0.909291
00:25:47.320 --> 00:25:50.539 at that MTD that 50% of patients
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00:25:50.539 --> 00:25:53.570 had grade three grade 4 toxicity and
NOTE Confidence: 0.909291
00:25:53.659 --> 00:25:56.165 some patients died because of that.
NOTE Confidence: 0.909291
00:25:56.165 --> 00:25:59.000 It was also shown that as a single
NOTE Confidence: 0.909291
00:25:59.000 --> 00:26:01.478 agents it’s inferior to anti
NOTE Confidence: 0.909291
00:26:01.480 --> 00:26:02.794 PD1 checkpoint inhibitor.
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00:26:02.794 --> 00:26:06.406 So in large part this drug was not
NOTE Confidence: 0.909291
00:26:06.406 --> 00:26:09.160 used anymore because of the toxicity.
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00:26:09.160 -- 00:26:09.627 However,
the teaching point here is you can’t treat immunotherapy agents like drugs and in fact a dose now of 1 to 3 milligrams which is not very toxic when added to another checkpoint inhibitor has an added benefit.

So we have to get away from testing these some of these agents by their maximum tolerated doses when actually lower doses work just as well if not better and a more tolerable.

So we’ll go over the details of this randomized study that looked at different dose schedules and doses of combining hippilumamid at 3kg and 1
milligrams with combinations of nivo.

And this Arm B,

just to accelerate the talk,

turned out to be the most
efficacious in the least

toxic. But here’s the teaching point I

This is the radiological response to patients

being treated in this randomized study

with metastatic Melanoma, mainly stage 3.

And you can see there’s a complete

response radiologically in 10% of patients,
a partial response in 50%.

However, when the patients had surgery

and the pathologist could examine it,
you see the difference,
57% of those patients had APCR and 7% had a near PCR. So compare the difference between the radiologic response and what the pathologist found. You cannot look at these masses on X-rays and know what’s inside them because these tumors in many cases are replaced by inflammation and scar tissue. So the surgeon has to take them out and give the specimen to the pathologist. And as I’ll show you in tumor after tumor, the determination of PCR near PCR versus more residual tumor burden is now an important part of our cancer management.
But in my early days, giving interleukin interferons tumor cell vaccines, if we had a 5% PCR rate, that was a victory.

If we had a 15% partial response, that was a victory.

And as I told one person earlier, we tortured people with alpha interferon over many dose schedules in years because that’s all we had and we improved survival rates by 2%.

So now in this new era of Melanoma management with the advent of immunotherapy because we still don’t have good chemotherapy, we have some targeted therapy.
Look at the pathological responses now that range in this study between 65 and 80% and pathological complete response in dose schedule BPCR in 57% of patients. Never in the history of treating cancer have we seen these kind of dramatic responses. So this also shows you just in one other cartoon the value of combining two different checkpoint inhibitors which have different mechanisms of action. And if you look on the two pies charts, you can see that with an anti PD one you get a 20% PCR but if you add low doses of ipilumab you double that to 43%.
So again showing as we use with combination chemotherapy with different mechanisms of action, the new standard is using these combined checkpoint inhibitors. But the important point is the lower doses and shorter schedules work just as well as high doses given over a long time because what we're doing is like turning on and off switch, we're breaking tolerance. And I predict that we will not be giving a year of immunotherapy before we'll have to do the clinical studies to show that it's equally good of giving shorter courses.
So this is one of my first key points about the impact on surgery. So this is a study Prada study going on now which is a randomized study but for which we have some of the early results. These are patients who present with stage 3B and 3C disease. They have clinically and radiologically detected nodal metastasis and index node has a marker placed in the largest lymph node. Then the patients gets only two cycles of combination of immunotherapy, only two cycles and then that index node that’s all that is removed. And you can see the strategy those patients
who had APCR or near PCR less than 10%

viable cells had no therapeutic lymph node dissection and no adjuvant therapy.

Where’s those that had APCR did get a therapeutic, no dissection and follow up and those that did not get a response had both a therapeutic lymph node dissection and adjuvant immunotherapy.

But the point is that’s already been reported is that in the patients entered into this trial that 60% of them never needed a therapeutic lymph node dissection, which was their standard treatment before because they achieved APCR or near PCR.

And I’ll show you more examples of
this and other diseases as well.

So let me move on to breast cancer and neoadjuvant therapy.

So there’s another principle here that if we don’t get a pathological complete response, you could predict that the residual tumors are going to be refractory to the drugs that you gave up front. So why continue them afterwards when these refractory tumors probably have a different molecular profile in the strategy here which is a classic in that I think applies to other tumors as well was this Catherine study which took her two positive patients.
who got neoadjuvant treatment.

They all had residual invasive disease after getting their standard,

her two therapy either single or dual therapy targeted therapy and then we're randomized to switch their treatment if they had residual disease into a different drug TDM one or continued the same drug that they were on before.

And this study of course showed that by switching therapies intuitively this makes sense.

You get an improved survival rate in those patients who we stopped after six weeks and switched to another therapy to treat the refractory
tumors and that in turn increased survival rate in these patients. And this is going on in all the other subtypes of breast cancer. And my point here is you look at the residual tumor burden, which shown in the different colors the differences in survival rates over 8 years based upon the subtypes of breast cancer and how those patients who have APCR or new PCR do very well over 8 years. But in contrast, those patients who have more residual tumor burden obviously are going to
need a different therapy and have a worse prognosis if we continue to give the same treatment and don’t switch. And so now there are a number of clinical trials, I’m just showing one examples. It was showing that post neoadjuvant treatment options a different treatment than what was given up front but directed by the residual tumor burden cause can improve survival rates. So the teaching point here is now we have enough agents we can go to second line therapy early based upon the residual tumor burden after the surgeon.
00:34:15.187 --> 00:34:17.477 takes the area out where the tumor
00:34:17.477 --> 00:34:20.039 was and gives it to the pathologist.
00:34:20.040 --> 00:34:23.851 So here’s another important strategy is
00:34:23.851 --> 00:34:26.536 if we’re combining chemotherapy with
00:34:26.536 --> 00:34:28.894 immunotherapy that the chemotherapy that
00:34:28.894 --> 00:34:32.187 works directly on the tumor is going to
00:34:32.187 --> 00:34:34.515 break down the tumor into apoptosis.
00:34:34.520 --> 00:34:36.840 It will release tumor antigen
00:34:36.840 --> 00:34:39.199 and in so doing becomes a boost,
00:34:39.200 --> 00:34:41.444 an immunological boost or an internal
00:34:41.444 --> 00:34:44.190 vaccine if you will for the immune
00:34:44.190 --> 00:34:46.160 system where tolerance is broken.
00:34:46.160 --> 00:34:48.463 So it wouldn’t surprise you if you
00:34:48.463 --> 00:34:50.200 use these combinations you will
00:34:50.200 --> 00:34:51.238 get better responses.
And in these non randomized studies in the right you can see the PCR rates was 60% or more PCR by using a combination of neoadjuvant therapy in a series of trials, I'll just go over them quickly, the KEYNOTE 522 and the impassioned O31 using different checkpoint inhibitors combined with the same classic chemotherapy up front for 12 weeks and then randomizing the patients between checkpoint inhibitors or placebo. You can see in both of these trials that the PCR rate was higher in both trials by adding immunotherapy to chemotherapy is neoadjuvant therapy.
So now for and this is only for right now been used in triple negative breast cancer. Although the recent studies to show the addition of immunotherapy in selected patients with ER positive tumors also are have an additive effect. But now with these advances in this shift that neoadjuvant therapy is preferred in almost all breast cancer patients except for maybe stage 1A and 1B. And that is a profound change in how we treat breast cancer And that APCR is associated with markedly improved outcomes.
are going to do in contrast to our classic studies doing surgery 1st and then giving adjuvant therapy and then trying to measure 5 year survival rates 8 to 10 years later. So this is a very important advance. It allows us to keep moving on with new strategies and cancer management. The highest pathological response rates, around 63%, is used with the combination of pembrolizumab and a classic chemotherapy Carbotaxol followed by ACEC and the Pembro not only improves the PCR rates, but also results in smaller residual cancers across the entire spectrum of disease,
and that means it facilitates more conservative operations. It switches patients who needed a mastectomy for medical reasons into having the options of having lumpectomies because their tumors are smaller. So we also have learned that patients with residual disease have a poor prognosis and need additional or different treatment and allows us based upon the response to individualize their therapy. So this is our future, not only in breast cancer but in other tumors as well.
So this is another part of our advance which I'll show you in other diseases as well. I showed you in Melanoma how we're now eliminating the therapeutic no dissections in those patients who have APCR.

This is from my colleague Henry Cure at MD Anderson who's presenting this information for the first time next month in Miami and he kindly loaned me the slides to show to you today. They have a prospective trial of eliminating breast surgery in selected patients who are exceptional responders for neoadjuvant systemic therapy. And the reason that they do this after their neoadjuvant therapy and
they these are generally used with chemotherapy that they use a vacuum assisted core biopsy to in the area where the tumor is guided by ultrasound. And if there's no residual disease they have no further breast surgery but if they have residual disease they get standard treatment. So Henry is presenting for the first time they're multi institutional study, 50 patients who had no breast surgery whose average size at the beginning was 2.3 centimeters and after a brief exposure to systemic chemotherapy was less than a centimeter.
They had to do 15 vacuum assisted biopsies in these patients.

But here are the results so far, 62% had APCR among the triple negative breast cancer patients who had a checkpoint inhibitors plus chemotherapy was 71 percent, 55% in the her two positive.

And what he’s going to present so far after 4.1 years of treatment, not a single patient has relapsed so far in the breast.

And I could go over and show you other studies where we’re now looking at eliminating radiation therapy.
in these patients who have APCR. It’s changing how we treat patients based upon their responses to neoadjuvant treatment and they’re now doing a study not yet reported in patients getting systemic therapy standard lumpectomy and being randomized to getting no radiation therapy to the breast if they had APCR including in their lymph nodes. So let me as another example so go over lung cancer. This is another example where the molecular profile profoundly effects our targeted treatment even in subsets.
00:40:13.251 --> 00:40:15.914 of patients now of three to 7%.
NOTE Confidence: 0.844040274545454
00:40:15.914 --> 00:40:18.112 And in these small subsets we not
NOTE Confidence: 0.844040274545454
00:40:18.112 --> 00:40:20.079 only have first line therapy,
NOTE Confidence: 0.844040274545454
00:40:20.080 --> 00:40:21.499 second line therapy,
NOTE Confidence: 0.844040274545454
00:40:21.499 --> 00:40:25.104 even third line therapy for these small
NOTE Confidence: 0.844040274545454
00:40:25.104 --> 00:40:27.834 subsets defined by molecular markers.
NOTE Confidence: 0.844040274545454
00:40:27.840 --> 00:40:29.240 And as we do more of this,
NOTE Confidence: 0.844040274545454
00:40:29.240 --> 00:40:31.193 this is going to be the standard
NOTE Confidence: 0.844040274545454
00:40:31.193 --> 00:40:33.519 of care for all cancers as our
NOTE Confidence: 0.844040274545454
00:40:33.519 --> 00:40:35.294 molecular profile allows us to
NOTE Confidence: 0.844040274545454
00:40:35.294 --> 00:40:37.498 select patients who are responsive
NOTE Confidence: 0.844040274545454
00:40:37.498 --> 00:40:39.274 to certain systemic therapy,
NOTE Confidence: 0.844040274545454
00:40:39.280 --> 00:40:40.584 but not for others.
NOTE Confidence: 0.844040274545454
00:40:40.584 --> 00:40:43.504 But I wanted to show you in terms
NOTE Confidence: 0.844040274545454
00:40:43.504 --> 00:40:44.836 of the immunotherapy,
NOTE Confidence: 0.844040274545454
00:40:44.840 --> 00:40:47.354 how these first studies of using
NOTE Confidence: 0.844040274545454
00:40:47.354 --> 00:40:49.651 neoadjuvant therapy had a major
NOTE Confidence: 0.844040274545454
00:40:49.651 --> 00:40:52.300 pathological response in 45% of patients.
NOTE Confidence: 0.844040274545454
00:40:52.300 --> 00:40:54.680 But the reason I wanted to show
NOTE Confidence: 0.844040274545454
00:40:54.751 --> 00:40:57.159 these slides is this is an example
NOTE Confidence: 0.90974770375
00:40:57.160 --> 00:40:59.365 published in the New England Journal of
NOTE Confidence: 0.90974770375
00:40:59.365 --> 00:41:01.440 Medicine of the pre treatment imaging.
NOTE Confidence: 0.90974770375
00:41:01.440 --> 00:41:02.760 And after four weeks
NOTE Confidence: 0.90974770375
00:41:02.760 --> 00:41:04.080 there was residual tumor.
NOTE Confidence: 0.90974770375
00:41:04.080 --> 00:41:06.796 This was judged as a partial response,
NOTE Confidence: 0.90974770375
00:41:06.800 --> 00:41:09.240 but when the surgeon took out that mass,
NOTE Confidence: 0.90974770375
00:41:09.240 --> 00:41:11.676 there was no viable tumor left.
NOTE Confidence: 0.90974770375
00:41:11.680 --> 00:41:13.655 And this is again illustrating
NOTE Confidence: 0.90974770375
00:41:13.655 --> 00:41:15.235 and yet another disease,
NOTE Confidence: 0.90974770375
00:41:15.240 --> 00:41:17.320 the importance of the surgeon
NOTE Confidence: 0.90974770375
00:41:17.320 --> 00:41:19.200 doing the staging and giving
NOTE Confidence: 0.90974770375
63
the tumor to the pathologist.

Here's another example from the same article,

fairly large tumor that didn’t move at all.

This was judged as a non response,

but nevertheless the surgeons took

it out and that mass that you’re

seeing on X-ray was replaced

completely by scar and inflammation,

it was APCR.

So now they’re randomized studies

of neoadjuvant therapy.

I’ll just go over this quickly in

the interest of time using either

nivolumab plus chemotherapy,

platinum doublets or pembrolizumib

with essentially the same results
And you could see in this one study Checkpoint 8.6 that adding the PD1 nivolumab plus chemotherapy was better than chemotherapy alone. And in this study now moving from stage 3 to stage two lung cancer also demonstrated it with pembrolizumab that you get an additive effect with the hazard ratio of .58 in a highly significant difference in event free survival and later on with follow up in overall survival. So these two studies are just two examples demonstrating the additive
value of checkpoint inhibitors

And the teaching point here is

if you look at the responders in

the outcome in the green lines,

most of these patients will survive

for a long time without relapsing.

In fact,

at MD Anderson and her Melanoma group,

my colleagues tell me that it is

less than 5% of patients who have

APCR after neoadjuvant therapy have

failed so far in their experience

that now goes past five years.

So let me show the last example

on colorectal surgery,
which is also another area where neoadjuvant therapy here using chemotherapy and radiation therapy. And I don’t have time to go over the details other than to show you in randomized trials which I’ll just briefly show the results. Different combinations and sequences of chemotherapy and radiation therapy up front has caused a pathological or near pathological response in almost 50% of patients. So again just to show you the value of clinical trials in advancing our standards of care.
these are two randomized studies showing different combinations and sequences of radiation therapy, both short term and long term therapy, and then whether the chemotherapy was given sequentially or simultaneously. But the bottom line is the patients who got longer exposures to standard chemotherapy as neoadjuvant therapy did, those did better than those who got shorter courses and this was shown in the repeater study. The this is a failure rate. Those patients who got longer courses of chemotherapy did better than those who had standard treatment.
And in this protege study now with seven years follow up that the patients who got radiation therapy first followed by long term course of more intensive chemotherapy with Fulurinex did better than those who had the standard short term chemotherapy and in the experience at MD Anderson, this is from our Chair of Colorectal department, George Chang.
You could see those patients again that achieved APCR did better with long term follow up.

These were 18% of the patients but no local recurrences in a very low risk of distant metastasis based upon the responses to the neoadjuvant therapy, again showing this in yet another disease as a strategy.

And then finally this Oprah study which again randomized patients with different combinations of neoadjuvant chemotherapy, long term radiation therapy and chemotherapy and then we’re randomized to receive either watch and wait.
00:45:49.620 --> 00:45:52.350 if clinically and by X-ray they had a clinical complete response.

00:45:52.443 --> 00:45:55.278 They went into a watch and wait program and the results of this we’re pretty striking.

00:45:55.280 --> 00:45:57.660 You can see that the patients who had the more intensive neoadjuvant therapy did better with long long course radiation therapy followed by FOLFOX.

00:45:59.600 --> 00:46:00.560 And the important point is that the three-year failure of the event free survival in patients who had no surgery was 53%.

00:46:00.560 --> 00:46:03.008 And if regrowth of the tumor
then all of these patients were salvage with a TME operation.

But in those who had shorter courses of chemotherapy did not do as well.

But overall, as in this slide, nearly half the patients who received neoadjuvant therapy, especially with the longer courses of chemotherapy and longer courses of radiation therapy. You can see that half of the patients avoided surgery even after six years of follow up. And those who recurred and had salvage surgery had essentially...
the same survival rates based upon the time of diagnosis as those patients who had surgery up front.

So I wanted to finish with what I think is an example of our future when we have the biomarkers that can give us an exact prediction of response with checkpoint inhibitors. So in standard pathology report usually shows the immunohistochemistry results with either microsatellite instability high or mixed instability high or mixed responses in mismatch repair deficiency. Sorry. And the point here is this is
for the first time that the FDA approved a drug with checkpoint inhibitors based solely on the molecular profile. So regardless of which tumor type it is, colorectal, gastric, pediatric breasts, sarcomas which are very infrequent. The most common is in colorectal cancer which is 10 to 15% of patients have these biomarkers which is a surrogate for a poorly differentiated tumor. So think about it, the immune response is looking for foreigners, not self. The more foreign the object is in our body, the more robust the immune system is. So it shouldn’t surprise you that
the more poorly differentiated tumor, higher tumor mutation burden or have these biomarkers are going to be the most responsive to immunotherapy. But this is dramatic. When the first studies were done, you can see there was a pathological response, major response in every patients who were treated with a checkpoint inhibitor and look at these results. A single dose of ipilumab and only two doses of nivolumab led to 100% pathological response in these patients who were MMR deficient and
even in 27% of those who did not have that mutation with this short term dual agent and his larger series have been presented like this. At ASCO you could see that 95% of patients have expressing this biomarker in this case in colon cancer had a major pathological response at 67% had APCR with short term dual immunotherapy based upon this tumor marker. And here’s the other point is larger series have been reported again using one dose of IPI and at a low dose only 1 milligram per kilogram. Remember we started out at 10 milligrams, which was too toxic in that in 99% of
patients they had a pathological response. So this is pretty dramatic. Now for the surgeons. This was published in the New England Journal of Medicine only on 12 patients who expressed this biomarker and who got a checkpoint inhibitor and based upon that response had no radiation therapy and no surgery and had been followed up now for more than four to five years. And these aren’t small tumors. You could see in this example published in the New England Journal Medicine, these were large tumors that over
00:50:42.618 --> 00:50:45.600 time with this checkpoint inhibitor
NOTE Confidence: 0.704941
00:50:45.600 --> 00:50:47.490 disappeared and in these patients
NOTE Confidence: 0.704941
00:50:47.490 --> 00:50:50.320 with the follow up with no radiation,
NOTE Confidence: 0.704941
00:50:50.320 --> 00:50:51.044 no surgery,
NOTE Confidence: 0.704941
00:50:51.044 --> 00:50:52.854 there were no recurrences based
NOTE Confidence: 0.704941
00:50:52.854 --> 00:50:54.440 upon this tumor marker.
NOTE Confidence: 0.704941
00:50:54.440 --> 00:50:57.191 So this also applies in the lower
NOTE Confidence: 0.704941
00:50:57.191 --> 00:51:01.664 frequency of patients with GI tumors.
NOTE Confidence: 0.704941
00:51:01.664 --> 00:51:05.969 Gastrointestinal and esophageal cancers,
NOTE Confidence: 0.704941
00:51:05.969 --> 00:51:09.476 which you could see in these studies used
NOTE Confidence: 0.704941
00:51:09.480 --> 00:51:13.266 in a combination of pembrolizumab and Folfox,
NOTE Confidence: 0.704941
00:51:13.266 --> 00:51:15.159 achieved 23 of 26 patients were
NOTE Confidence: 0.704941
00:51:15.160 --> 00:51:18.205 free of disease.
NOTE Confidence: 0.704941
00:51:18.205 --> 00:51:21.088 And the overall survival in these patients
NOTE Confidence: 0.704941
00:51:21.088 --> 00:51:24.800 who presented with advanced disease,
NOTE Confidence: 0.704941
00:51:24.800 --> 00:51:27.560 treated with preoperative disease
and that 65% of those patients based upon the tumor marker, it’s a small percentage of patients had APCR with gastric and esophageal cancers. And now they’re going on in this series of trials, the first one in Cohort 1, they found APCR in 60% of patients with this MMR deficiency. The major response was 80%. And now the next phase of this trial is those patients who have a complete or near complete response radiologically and endoscopically get no surgery and follow up for GI.
00:52:05.450 --> 00:52:08.475 for gastric and gastroesophageal malignancy.
NOTE Confidence: 0.855290297777778
00:52:08.480 --> 00:52:10.160 So I’ve shown you in Melanoma,
NOTE Confidence: 0.855290297777778
00:52:10.160 --> 00:52:12.272 in lung cancer and breast cancer
NOTE Confidence: 0.855290297777778
00:52:12.272 --> 00:52:14.623 and now in colorectal cancer based
NOTE Confidence: 0.855290297777778
00:52:14.623 --> 00:52:17.245 upon tumor markers and usually based
NOTE Confidence: 0.855290297777778
00:52:17.245 --> 00:52:19.061 upon combinations of checkpoint
NOTE Confidence: 0.855290297777778
00:52:19.061 --> 00:52:20.809 inhibitors plus chemotherapy that
NOTE Confidence: 0.855290297777778
00:52:20.809 --> 00:52:23.374 we’re now moving in selected patients
NOTE Confidence: 0.855290297777778
00:52:23.374 --> 00:52:26.223 to not doing surgery and watch and
NOTE Confidence: 0.855290297777778
00:52:26.223 --> 00:52:28.808 wait and then follow up with the
NOTE Confidence: 0.855290297777778
00:52:28.808 --> 00:52:30.999 patients and in those that fail,
NOTE Confidence: 0.855290297777778
00:52:31.000 --> 00:52:33.460 which is still the minority of
NOTE Confidence: 0.855290297777778
00:52:33.460 --> 00:52:35.800 patients to do salvage surgery.
NOTE Confidence: 0.855290297777778
00:52:35.800 --> 00:52:37.480 So these are my summary slides.
NOTE Confidence: 0.855290297777778
00:52:37.480 --> 00:52:39.184 There are changes now,
NOTE Confidence: 0.855290297777778
00:52:39.184 --> 00:52:41.740 but these strategies I’ve told you

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are increasingly going to be applied for all solid tumors that will impact all of us in oncology fields. That new adjuvant therapies selected by tumor molecular profiles is now and will increasingly become the standard of care for most cancers, for all but the earliest stage 1 cancers. And that surgery is vitally important for staging and local regional Disease Control. I’ve showed you data that there may be a place for watch and wait, but that’s in a selected group of patients and then everybody else. There’s still an important role for
surgery in staging these patients.

And interestingly now as we're doing less surgery for early disease,

we're going to be doing more surgery for stage 4 and borderline resectable Stage 3 disease because we can downstage the patients.

And those of us treating even Stage 4 disease need to know whether the masses we're seeing on X-ray is inflammation or viable tumor,

So we need to better refine the role of watch and wait.

This is a new thing.
I'm not proposing it except in clinical trials and the intensity of follow-up in the appropriate type of salvage surgery on relapse is going to be a new area for which we are going to need a lot of prospective data. And I think as I've shown you, we're changing the standards of care based upon these prospective clinical trials that are neoadjuvant clinical trials that involve surgery as part of the clinical trial. So surgeons must engage their patients in the clinical trials where appropriate and design surgical
trials to document the results

of DE escalation strategies,

new sequences of treatment and

and the results of salvage therapy.

And I think for those of us training

residents and fellows that surgical

training must include more exposure

to contemporary cancer management.

And as many of you know at least

in the public to have surgeons who

are also trained in oncology to be

part of the multidisciplinary team.
order to keep up with the rapidly moving field based upon one or two

diseases are increasingly going to have to focus their treatment to one or two organ sites in order to stay current with the rapid advances.

So here are my key messages for the surgeons to be prepared and informed to make major changes in the surgical management of your cancer practice, including deferring surgery until after a trial of neoadjuvant therapy. Because of the benefit I've shown you now in multiple tumor types, to consider surgical excision for
borderline or inoperable tumors that are downstage with systemic therapy and consider more conservative surgical procedures with the downstaging. And then we as surgeons have to adopt a mindset of being an oncologist who operates cancer management is dealing with now a chronic disease. Surgery is kind of a vertical specialty that focuses on the operation and the perioperative period. But our job is not done once the wounds have healed. There is another phase for which we need to be involved in giving systemic therapy up front and how
we do what we do afterwards. And we also need to be at the arena when treatment plans are made to bring the surgeons perspective to multidisciplinary treatment. And without being critical, I know that your medical oncology training and radiation oncology training does not include surgery as part of your training and in fact you’re biased because you see our failures. I’ll give you one example. My daughter who’s APA in GI medical oncology at MD Anderson sees a few of these salvage surgery patients that
Say our patients come in with these huge inoperable, miserable tumors. I don’t see why we’re doing salvage surgery. So I immediately called my son Glenn, who’s doing all the colorectal surgery and said, you know that happens but only in 5% of our patients. But my daughter thinks that we should be doing this because she sees the failures, the ones that do well don’t go to those medical oncology clinics. So I think it’s bringing the surgeon’s perspective to those that are different in medical and radiation oncology. And it’s the collective wisdom we
all bring that is better for patient care decision making.

And then this last thing I don’t have a solution for, but I want to give you an example. My son Glenn, who’s head of the division of colorectal surgery at Emory had a conversation with his chair. So John Sweeney said Glenn, I noticed your RVUs are down, what’s going on and Glenn responded. Well, half of my rectal cancer patients are getting a clinical complete response and going into watch and weight status and now I’m...
flooded with these patients doing flexible sigmoidoscopy exams every three months and there is little RVU. And so my point is in this new era of oncology management, how are we going to gain gauge the clinical performance that here to is based upon volume of care. When oncology advances in all of our fields are driving us to perform less intensive therapy, surgeons are doing more conservative operation, less frequent lymphadenectomies. more watch and wait.
Radiation oncologists are going from six weeks standard courses to three weeks to weekly to no radiation oncology. So they’ll be less income if you’re doing shorter courses of radiation. And of course we’re a medical oncology colleagues. I think we’re going to be giving shorter courses of adjuvant therapy especially immunotherapy instead of one to two years of expensive drugs. And then what are we going to do with these patients who are in watch and wait and are well patients that just need to be follow up.
the oncology specialist can’t see the new patients in those interactive treatment if they’re seeing well patients for follow up. So we have to delegate that follow up to mid level providers or even non oncology trained physicians who will follow these patients and send them back in those few that relapse and that’s a change in how we manage our patients. It’s a different team effect but with the like Glenn said if half of his patients are getting a clinical complete response, he can’t follow all of those
patients for a lifetime,

somebody else has to do that and

then send back those that relapse.

So that’s the end of my talk.

I hope that this has been helpful

in telling you about our.

Present and future strategies and

how that will impact on the surgical

management of our cancer patients and

the value of clinical trials in make

in changing our standards of care.

So thank you all for the opportunity of

coming and I hope this was helpful to you.

Thank you for a talk that

was uplifting, exciting
and also provocative.

I know that I was getting late.

There may be some time

for one question from

the audience for Hoocha.

So thank you, Charles, for presenting,

really just giving us food for

talking about where

I want to come back to your last point,

which is interdisciplinary collaborations.

And for the trainees in the room,

I thought it’d be helpful to share a lens of,

you know I was in Hopkins during that period

and many of those first offers were felons.

Patrick Ford, the lung trial you showed and
was a fellow sitting in a conference and we were talking about this with surgeons, medical oncologists and radiation oncologists and the colorectal trials.

My very good friend Louise Diaz and I remember sitting with Louise running our colon tumor board and an observation that was made on a small trial that on our phase one trial one of the patients was mismatched repair efficient, it was one patient and it was an observation made and wrote Suzanne Topallion, he’s a surgeon as you mentioned. He wrote that in the clinical Cancer Research it was an advance smaller.
than this that led to this entire field of opening up in multiple tumor types from that very small observation. So my question to you is that how do we encourage that as we're becoming bigger that event happenstance that's how research is done, that's how great clinical initiatives happen. How do we foster that as leaders we're sitting in this room that that's a luxury that we barely have. So I wondered what's your thoughts about, I think the answer is we're if we're looking for advances in care see opportunities and we can base a clinical trial prospectively on a hypothesis.
or even retrospective data that leads to the design of the trial that we need to be thinking about.

We have to practice evidence based care. And if we don’t have this in this rapidly developing field, we’re going to go back to empirical medicine based upon marketing of drug companies and instrument companies.

So I think you know to add to what Nita has said that it’s so important for us to insist on our patients wherever possible being in clinical trials where they’re eligible so that we can advance the field based upon
evidence and not based upon marketing strategies but it.

But we all need to have an open mind and I’m enthusiastic about the results, there are a lot of patients who failed with our current treatment. So there’s still a lot to do and I think that’s going to be based upon the team working together, each bringing different perspectives. I love the story with Lei Ping Chen who said this works in the mouse, who said this works in the mouse, maybe it works in the patient and he brought that hypothesis to what
became a major immunotherapy advance. So the collaboration and between the clinical teams and between the research teams and the clinical teams is I think the what’s important and championing the collective wisdom that we all bring with our different perspectives in bringing that together in our decision. Thank you very much. I think Doctor Balch will be here for a little bit longer.
I know you’ll be spending some time with the surgical residents, it’s been wonderful. Thank you all for the honor of coming here today. No. And I get this. He get this luggage.