WEBVTT

00:00:00.000 --> 00:00:02.799 Good morning, everyone.

00:00:02.800 --> 00:00:05.293 It really gives you a great joy to introduce

00:00:05.293 --> 00:00:07.358 the speaker for Grand Mound today.

00:00:07.360 --> 00:00:09.838 Today's speaker is Doctor Fad Galley.

00:00:09.840 --> 00:00:11.132 He's our new recruit.

00:00:11.132 --> 00:00:12.747 He joined us in August

00:00:12.747 --> 00:00:14.520 last year from Fred Hutch.

00:00:14.520 --> 00:00:16.710 So he's a urological oncologist who

00:00:16.710 --> 00:00:19.036 specialized in taking care of patients

00:00:19.036 --> 00:00:21.430 with bladder and the urinary tract

00:00:21.499 --> 00:00:24.315 cancers and also test his cancer as well.

00:00:24.320 --> 00:00:26.198 He finished his medical school at

00:00:26.198 --> 00:00:28.199 Geyser School of Medicine at Dartmouth.

00:00:28.200 --> 00:00:29.436 He then wanted to, you know,

NOTE Confidence: 0.968948576666667

00:00:29.440 --> 00:00:31.732 UC San Diego for his surgical

NOTE Confidence: 0.968948576666667

00:00:31.732 --> 00:00:32.878 internship and residency.

NOTE Confidence: 0.968948576666667

00:00:32.880 --> 00:00:35.794 And then he went on to University of

NOTE Confidence: 0.968948576666667

00:00:35.794 --> 00:00:38.388 Washington in Seattle for his suicide

NOTE Confidence: 0.968948576666667

00:00:38.388 --> 00:00:40.236 of urology on College of Fellowship.

NOTE Confidence: 0.968948576666667

00:00:40.240 --> 00:00:43.152 And then he joined us as a

NOTE Confidence: 0.968948576666667

00:00:43.152 --> 00:00:44.400 faculty last August.

NOTE Confidence: 0.968948576666667

00:00:44.400 --> 00:00:46.180 His research interests include

NOTE Confidence: 0.968948576666667

00:00:46.180 --> 00:00:47.515 designing clinical trials,

NOTE Confidence: 0.968948576666667

00:00:47.520 --> 00:00:48.480 environmental development

NOTE Confidence: 0.968948576666667

00:00:48.480 --> 00:00:50.400 and urinary tract cancers,

NOTE Confidence: 0.968948576666667

00:00:50.400 --> 00:00:52.920 and he has received multiple

NOTE Confidence: 0.968948576666667

00:00:52.920 --> 00:00:55.440 awards and grants and publications.

NOTE Confidence: 0.968948576666667

00:00:55.440 --> 00:00:55.746 Dr.

NOTE Confidence: 0.968948576666667

00:00:55.746 --> 00:00:57.276 Gatti for those two years,

NOTE Confidence: 0.930761928571428

00:01:03.440 --> 00:01:04.756 great. Thank you all for being here.

NOTE Confidence: 0.930761928571428

00:01:04.760 --> 00:01:06.062 It's really an honor to get

NOTE Confidence: 0.930761928571428

00:01:06.062 --> 00:01:07.320 to speak with all of you.

NOTE Confidence: 0.930761928571428

00:01:07.320 --> 00:01:08.680 Like Doctor Kim has said,

NOTE Confidence: 0.930761928571428

00:01:08.680 --> 00:01:10.090 I started just about three

NOTE Confidence: 0.930761928571428

00:01:10.090 --> 00:01:12.032 months ago so this is early in

NOTE Confidence: 0.930761928571428

00:01:12.032 --> 00:01:13.677 my in my stay here at Yale.

NOTE Confidence: 0.930761928571428

00:01:13.680 --> 00:01:15.084 But it's it's it's really been

NOTE Confidence: 0.930761928571428

00:01:15.084 --> 00:01:16.722 such a pleasure to meet all of

NOTE Confidence: 0.930761928571428

00:01:16.722 --> 00:01:18.227 the other faculty and get to take

NOTE Confidence: 0.930761928571428

00:01:18.282 --> 00:01:19.716 care of patients with you all.

NOTE Confidence: 0.930761928571428

00:01:19.720 --> 00:01:21.240 So thanks for having me.

NOTE Confidence: 0.9016139925

00:01:23.640 --> 00:01:25.642 I'm going to speak today about biomarkers

NOTE Confidence: 0.9016139925

00:01:25.642 --> 00:01:27.597 within bladder cancer and this is sort of an,

NOTE Confidence: 0.9016139925

00:01:27.600 --> 00:01:29.400 it's a very, this is a broad title and

NOTE Confidence: 0.9016139925

3

00:01:29.400 --> 00:01:31.235 it's a bit of an ambitious maybe title.

NOTE Confidence: 0.9016139925

00:01:31.240 --> 00:01:33.768 So I think what's maybe more appropriate is

NOTE Confidence: 0.9016139925

00:01:33.768 --> 00:01:36.358 examples of biomarkers within bladder cancer.

NOTE Confidence: 0.9016139925

00:01:36.360 --> 00:01:38.128 And I'll sort of weave in a little

NOTE Confidence: 0.9016139925

00:01:38.128 --> 00:01:40.030 bit of overview of how we take

NOTE Confidence: 0.9016139925

00:01:40.030 --> 00:01:41.154 care of these patients,

NOTE Confidence: 0.9016139925

00:01:41.160 --> 00:01:43.056 talk about some of the work that we've

NOTE Confidence: 0.9016139925

00:01:43.056 --> 00:01:45.198 done and some of the work that's ongoing.

NOTE Confidence: 0.9016139925

00:01:45.200 --> 00:01:47.946 That's exciting disclosures,

NOTE Confidence: 0.9016139925

00:01:47.946 --> 00:01:50.928 none that are, none that are relevant

NOTE Confidence: 0.9016139925

00:01:50.928 --> 00:01:53.440 here and none that are ongoing.

NOTE Confidence: 0.9016139925

00:01:53.440 --> 00:01:54.200 And so like I say,

NOTE Confidence: 0.9016139925

00:01:54.200 --> 00:01:56.432 we'll sort of talk briefly about

NOTE Confidence: 0.9016139925

00:01:56.432 --> 00:01:57.920 an introduction to bladder

NOTE Confidence: 0.9016139925

00:01:57.984 --> 00:01:59.560 cancer patients and care,

NOTE Confidence: 0.9016139925

00:01:59.560 --> 00:02:01.516 we'll talk about non muscle invasive

4

NOTE Confidence: 0.9016139925

00:02:01.516 --> 00:02:03.924 bladder cancer which is sort of the early

NOTE Confidence: 0.9016139925

00:02:03.924 --> 00:02:06.199 part of the Natural History of the disease,

NOTE Confidence: 0.9016139925

00:02:06.200 --> 00:02:07.664 talk about advanced bladder cancer and

NOTE Confidence: 0.9016139925

00:02:07.664 --> 00:02:09.360 some of the ongoing clinical trials.

NOTE Confidence: 0.9016139925

00:02:09.360 --> 00:02:11.076 And then hopefully have some questions,

NOTE Confidence: 0.9016139925

00:02:11.080 --> 00:02:13.194 some time for questions at the conclusion.

NOTE Confidence: 0.90162625

00:02:15.320 --> 00:02:18.592 So to start, bladder cancer is a common

NOTE Confidence: 0.90162625

00:02:18.592 --> 00:02:20.559 and unfortunately lethal illness.

NOTE Confidence: 0.90162625

00:02:20.560 --> 00:02:23.000 It affects about 82,000 Americans

NOTE Confidence: 0.90162625

00:02:23.000 --> 00:02:25.266 per year and approximately 17,000

NOTE Confidence: 0.90162625

00:02:25.266 --> 00:02:26.796 Americans succumb to the disease.

NOTE Confidence: 0.90162625

00:02:26.800 --> 00:02:29.160 So 5th or 6th most common cause of

NOTE Confidence: 0.90162625

00:02:29.160 --> 00:02:31.174 cancer death depending on the gender

NOTE Confidence: 0.90162625

00:02:31.174 --> 00:02:34.775 of the patient and the prime the the

NOTE Confidence: 0.90162625

00:02:34.775 --> 00:02:37.780 majority of patients that they experience

NOTE Confidence: 0.90162625

00:02:37.780 --> 00:02:40.600 bladder cancer are in Medicare age,

NOTE Confidence: 0.90162625

00:02:40.600 --> 00:02:43.399 so sort of 65 years of age and older.

NOTE Confidence: 0.90162625

00:02:43.400 --> 00:02:45.992 So you can see here from from sincere

NOTE Confidence: 0.90162625

00:02:45.992 --> 00:02:47.948 data that approximately 80 to 85%

NOTE Confidence: 0.90162625

00:02:47.948 --> 00:02:49.583 of patients with bladder cancer

NOTE Confidence: 0.90162625

00:02:49.583 --> 00:02:51.701 are are elderly and those are the

NOTE Confidence: 0.90162625

00:02:51.701 --> 00:02:53.824 patients that bear the brunt of the

NOTE Confidence: 0.90162625

00:02:53.824 --> 00:02:55.636 mortality of bladder cancer as well.

NOTE Confidence: 0.90162625

00:02:55.640 --> 00:02:59.246 And so and so this is really a disease

NOTE Confidence: 0.90162625

00:02:59.246 --> 00:03:00.640 that affects primarily elderly,

NOTE Confidence: 0.90162625

00:03:00.640 --> 00:03:01.660 the elderly patients,

NOTE Confidence: 0.90162625

00:03:01.660 --> 00:03:03.360 although of course not exclusively

NOTE Confidence: 0.91091260125

00:03:05.440 --> 00:03:06.765 3/4 of patients that present

NOTE Confidence: 0.91091260125

00:03:06.765 --> 00:03:07.804 with bladder cancer, however,

NOTE Confidence: 0.91091260125

00:03:07.804 --> 00:03:09.756 do present in an early stage of the

NOTE Confidence: 0.91091260125

00:03:09.756 --> 00:03:11.598 disease what we call non muscle invasive.

NOTE Confidence: 0.91091260125

00:03:11.600 --> 00:03:12.960 And so you can see in the schematic,

NOTE Confidence: 0.91091260125

00:03:12.960 --> 00:03:15.235 which I am using here without permission,

NOTE Confidence: 0.91091260125

00:03:15.240 --> 00:03:15.746 without permission,

NOTE Confidence: 0.91091260125

00:03:15.746 --> 00:03:16.758 so hopefully that's OK.

NOTE Confidence: 0.91091260125

00:03:16.760 --> 00:03:19.336 But this is a schematic from the

NOTE Confidence: 0.91091260125

00:03:19.336 --> 00:03:21.598 Internet and shows you could see

NOTE Confidence: 0.91091260125

00:03:21.598 --> 00:03:24.156 that tumors in most patients present

NOTE Confidence: 0.91091260125

00:03:24.156 --> 00:03:26.910 in a fairly superficial stage of

NOTE Confidence: 0.91091260125

00:03:26.994 --> 00:03:29.320 the disease where either the mucosa

NOTE Confidence: 0.91091260125

00:03:29.320 --> 00:03:31.480 or the lamina propria are involved,

NOTE Confidence: 0.91091260125

00:03:31.480 --> 00:03:33.532 but not the deeper muscle layer

NOTE Confidence: 0.91091260125

00:03:33.532 --> 00:03:34.558 of the bladder.

NOTE Confidence: 0.91091260125

00:03:34.560 --> 00:03:36.612 And this is really a distinct

NOTE Confidence: 0.91091260125

00:03:36.612 --> 00:03:38.424 clinical entity because we can

NOTE Confidence: 0.91091260125

00:03:38.424 --> 00:03:40.384 often treat these patients with

NOTE Confidence: 0.91091260125

00:03:40.384 --> 00:03:41.560 bladder preserving modalities.

NOTE Confidence: 0.91091260125

00:03:41.560 --> 00:03:43.870 So these patients can be treated

NOTE Confidence: 0.91091260125

00:03:43.870 --> 00:03:45.760 with endoscopic resections of the

NOTE Confidence: 0.91091260125

00:03:45.760 --> 00:03:47.880 tumor and then intra vesicle therapy.

NOTE Confidence: 0.91091260125

00:03:47.880 --> 00:03:50.309 So we can actually instill a catheter

NOTE Confidence: 0.91091260125

00:03:50.309 --> 00:03:52.378 in the bladder and give either

NOTE Confidence: 0.91091260125

00:03:52.378 --> 00:03:55.304 immunotherapy in the form of BCG or

NOTE Confidence: 0.91091260125

00:03:55.304 --> 00:03:57.379 chemotherapies in the bladder and

NOTE Confidence: 0.91091260125

00:03:57.379 --> 00:03:59.204 and preserve preserve their bladder

NOTE Confidence: 0.91091260125

00:03:59.204 --> 00:04:01.640 in this early stage of the disease.

NOTE Confidence: 0.91091260125

00:04:01.640 --> 00:04:02.858 Unfortunately though recurrences

NOTE Confidence: 0.91091260125

00:04:02.858 --> 00:04:04.076 are very common.

NOTE Confidence: 0.91091260125

00:04:04.080 --> 00:04:06.208 Bladder cancer has a very not especially

NOTE Confidence: 0.91091260125

00:04:06.208 --> 00:04:07.771 non muscle invasive bladder cancer

NOTE Confidence: 0.91091260125

00:04:07.771 --> 00:04:09.559 has a very high recurrence rate.

NOTE Confidence: 0.91091260125

00:04:09.560 --> 00:04:11.436 So this is a study from the

NOTE Confidence: 0.91091260125

00:04:11.436 --> 00:04:12.960 University of Miami, Rich ET al.

NOTE Confidence: 0.91091260125

00:04:12.960 --> 00:04:14.640 And it's a really well done study.

NOTE Confidence: 0.91091260125

00:04:14.640 --> 00:04:16.428 It's approximately 500 patients

NOTE Confidence: 0.91091260125

00:04:16.428 --> 00:04:19.110 that they've taken care of with

NOTE Confidence: 0.91091260125

00:04:19.182 --> 00:04:21.606 really meticulous data review and

NOTE Confidence: 0.91091260125

00:04:21.606 --> 00:04:23.070 these patients were stratified

NOTE Confidence: 0.91091260125

00:04:23.070 --> 00:04:25.421 into risk strata that we use in non

NOTE Confidence: 0.91091260125

00:04:25.421 --> 00:04:27.056 muscle invasive bladder cancer and

NOTE Confidence: 0.91091260125

00:04:27.056 --> 00:04:28.504 they tracked progression despite

NOTE Confidence: 0.91091260125

00:04:28.504 --> 00:04:29.952 standard of care therapy.

NOTE Confidence: 0.91091260125

00:04:29.960 --> 00:04:32.016 And what you can see here is progression

NOTE Confidence: 0.91091260125

00:04:32.016 --> 00:04:33.500 free survival or recurrence free

NOTE Confidence: 0.91091260125

00:04:33.500 --> 00:04:35.330 survival I should say rather than

NOTE Confidence: 0.91091260125

00:04:35.330 --> 00:04:36.882 progression is pretty significant.

NOTE Confidence: 0.91091260125

00:04:36.882 --> 00:04:40.261 The very top line here the the black

NOTE Confidence: 0.91091260125

00:04:40.261 --> 00:04:43.186 line is low risk patients and you can

NOTE Confidence: 0.91091260125

00:04:43.186 --> 00:04:44.998 see after a few years approximately

NOTE Confidence: 0.91091260125

00:04:44.998 --> 00:04:47.344 half of them will have experienced a

NOTE Confidence: 0.91091260125

00:04:47.344 --> 00:04:49.065 recurrence in the bladder requiring

NOTE Confidence: 0.91091260125

00:04:49.065 --> 00:04:50.755 repeat surgery and so on.

NOTE Confidence: 0.91091260125

00:04:50.760 --> 00:04:52.758 High risk patients have even higher

NOTE Confidence: 0.91091260125

00:04:52.758 --> 00:04:54.986 recurrence rates in in this series

NOTE Confidence: 0.91091260125

00:04:54.986 --> 00:04:57.076 pretty significant rates of recurrence.

NOTE Confidence: 0.91091260125

00:04:57.080 --> 00:04:59.640 So to deal with this,

NOTE Confidence: 0.91091260125

00:04:59.640 --> 00:05:01.962 one of the things we do is we put

NOTE Confidence: 0.91091260125

00:05:01.962 --> 00:05:03.717 patients on long term surveillance

NOTE Confidence: 0.91091260125

00:05:03.717 --> 00:05:05.859 of their bladder cancer and this

NOTE Confidence: 0.91091260125

00:05:05.924 --> 00:05:08.079 is done through routine cystoscopy.

NOTE Confidence: 0.91091260125

00:05:08.080 --> 00:05:10.705 And I like this image image because

NOTE Confidence: 0.91091260125

00:05:10.705 --> 00:05:12.000 it it makes me feel uncomfortable

NOTE Confidence: 0.91091260125

00:05:12.000 --> 00:05:12.920 when I look at it.

NOTE Confidence: 0.91091260125

00:05:12.920 --> 00:05:15.517 It's sort of highlights I think the

NOTE Confidence: 0.91091260125

00:05:15.517 --> 00:05:17.249 discomfort that patients experience

NOTE Confidence: 0.91091260125

00:05:17.249 --> 00:05:19.594 undergoing this procedure And cystoscopy

NOTE Confidence: 0.91091260125

00:05:19.594 --> 00:05:21.953 is really a useful tool in urology,

NOTE Confidence: 0.91091260125

00:05:21.960 --> 00:05:24.440 but it's got major limitations.

NOTE Confidence: 0.91091260125

00:05:24.440 --> 00:05:25.128 For one,

NOTE Confidence: 0.91091260125

00:05:25.128 --> 00:05:26.160 it's not perfect.

NOTE Confidence: 0.91091260125

00:05:26.160 --> 00:05:28.398 It has you know approximately a

NOTE Confidence: 0.91091260125

00:05:28.398 --> 00:05:31.086 70 to 80% sensitivity for bladder

NOTE Confidence: 0.91091260125

00:05:31.086 --> 00:05:33.174 cancer recurrence depending on

NOTE Confidence: 0.91091260125

00:05:33.174 --> 00:05:35.759 the series that's looked at it,

NOTE Confidence: 0.91091260125

00:05:35.760 --> 00:05:36.760 it's uncomfortable.

NOTE Confidence: 0.91091260125

00:05:36.760 --> 00:05:40.040 Approximately 30 to 35% of patients

NOTE Confidence: 0.91091260125

00:05:40.040 --> 00:05:42.600 report experiencing significant anxieties

NOTE Confidence: 0.91091260125

00:05:42.600 --> 00:05:46.280 from cystoscopy and it's expensive.

NOTE Confidence: 0.91091260125

00:05:46.280 --> 00:05:47.736 So here are a couple of references

NOTE Confidence: 0.91091260125

00:05:47.736 --> 00:05:48.760 that we won't go into,

NOTE Confidence: 0.91091260125

00:05:48.760 --> 00:05:50.420 but these are references that

NOTE Confidence: 0.91091260125

00:05:50.420 --> 00:05:51.748 really highlight the significant

NOTE Confidence: 0.91091260125

00:05:51.748 --> 00:05:53.665 cost to the healthcare system for

NOTE Confidence: 0.91091260125

00:05:53.665 --> 00:05:55.200 long term surveillance of bladder

NOTE Confidence: 0.91091260125

00:05:55.253 --> 00:05:57.087 cancer making it one of the most

NOTE Confidence: 0.91091260125

00:05:57.087 --> 00:06:00.199 expensive cancers to to care for.

NOTE Confidence: 0.91091260125

00:06:00.200 --> 00:06:01.400 And so for those reasons I,

NOTE Confidence: 0.91091260125

00:06:01.400 --> 00:06:03.580 I I think there are lots of reasons why we

NOTE Confidence: 0.82512236826087

00:06:03.634 --> 00:06:04.943 sort of you can see I made

NOTE Confidence: 0.82512236826087

00:06:04.943 --> 00:06:06.439 my own my own figures here.

NOTE Confidence: 0.82512236826087

00:06:06.440 --> 00:06:08.424 But you can see that there's a real

NOTE Confidence: 0.82512236826087

00:06:08.424 --> 00:06:10.149 strong indication for biomarkers in the

NOTE Confidence: 0.82512236826087

00:06:10.149 --> 00:06:11.919 non muscle invasive bladder cancer space.

NOTE Confidence: 0.82512236826087

00:06:11.920 --> 00:06:14.602 Ideally a sensitive and specific marker

00:06:14.602 --> 00:06:17.765 that can identify non invasively when

00:06:17.765 --> 00:06:21.155 patients have recurred with bladder cancer.

00:06:21.160 --> 00:06:23.197 There are ones that we use currently.

00:06:23.200 --> 00:06:25.719 So cytology is a commonly used urinary

00:06:25.719 --> 00:06:27.114 biomarker and and again without

00:06:27.114 --> 00:06:28.919 sort of going too much into it,

00:06:28.920 --> 00:06:31.608 cytology has its own major limitations

00:06:31.608 --> 00:06:34.168 for for one it's it's quite,

00:06:34.168 --> 00:06:35.320 it's quite intensive,

00:06:35.320 --> 00:06:37.405 it requires A cytopathologist to

00:06:37.405 --> 00:06:39.490 review their significant inter reader

00:06:39.554 --> 00:06:41.759 variability between cytopathologists.

00:06:41.760 --> 00:06:44.078 And on top of that it's despite

00:06:44.078 --> 00:06:45.392 being labour intensive,

00:06:45.392 --> 00:06:48.600 the performance of cytology is quite lacking.

00:06:48.600 --> 00:06:50.360 Sensitivities have been reported

NOTE Confidence: 0.82512236826087

00:06:50.360 --> 00:06:53.759 in the 50s to 60 percents with with

NOTE Confidence: 0.82512236826087

00:06:53.760 --> 00:06:56.052 in all comers with bladder cancer

NOTE Confidence: 0.82512236826087

00:06:56.052 --> 00:06:57.580 and then obviously substratifying

NOTE Confidence: 0.82512236826087

00:06:57.646 --> 00:06:59.600 we had a little more granularity.

NOTE Confidence: 0.82512236826087

00:06:59.600 --> 00:07:00.800 There are other biomarkers that

NOTE Confidence: 0.82512236826087

00:07:00.800 --> 00:07:02.217 have been reported and I'm going

NOTE Confidence: 0.82512236826087

00:07:02.217 --> 00:07:03.545 to just sort of show you a list

NOTE Confidence: 0.82512236826087

00:07:03.545 --> 00:07:05.302 of what's been out there that are

NOTE Confidence: 0.82512236826087

00:07:05.302 --> 00:07:06.076 protein based biomarkers,

NOTE Confidence: 0.82512236826087

00:07:06.080 --> 00:07:08.350 cell based biomarkers and the sort of

NOTE Confidence: 0.82512236826087

00:07:08.350 --> 00:07:10.390 in the interest of time what I would

NOTE Confidence: 0.82512236826087

00:07:10.452 --> 00:07:12.475 say is none of them are recommended

NOTE Confidence: 0.82512236826087

00:07:12.475 --> 00:07:14.600 for routine use or certainly for

NOTE Confidence: 0.82512236826087

00:07:14.600 --> 00:07:16.555 replacement of cystoscopy because of

NOTE Confidence: 0.82512236826087

00:07:16.560 --> 00:07:18.845 poor performance of these relative

NOTE Confidence: 0.82512236826087

00:07:18.845 --> 00:07:19.759 to cystoscopies.

NOTE Confidence: 0.894374198333334

00:07:22.280 --> 00:07:24.456 One real Ave. that's come to light in

NOTE Confidence: 0.894374198333334

00:07:24.456 --> 00:07:26.720 the last several years especially with

NOTE Confidence: 0.894374198333334

00:07:26.720 --> 00:07:29.204 the advent of widespread next generation

NOTE Confidence: 0.894374198333334

00:07:29.270 --> 00:07:31.965 sequencing is the the question about urinary

NOTE Confidence: 0.894374198333334

00:07:31.965 --> 00:07:33.918 tumor associated DNA as a biomarker.

NOTE Confidence: 0.894374198333334

00:07:33.918 --> 00:07:36.165 And so I'm going to spend just a

NOTE Confidence: 0.894374198333334

00:07:36.165 --> 00:07:37.760 few minutes talking about this.

NOTE Confidence: 0.894374198333334

00:07:37.760 --> 00:07:39.520 This has been reported as a proof of

NOTE Confidence: 0.894374198333334

00:07:39.520 --> 00:07:41.236 principle and several, several reports.

NOTE Confidence: 0.894374198333334

00:07:41.236 --> 00:07:44.302 And so there are versions that have

NOTE Confidence: 0.894374198333334

00:07:44.302 --> 00:07:46.802 been tested in the past and the

NOTE Confidence: 0.894374198333334

00:07:46.802 --> 00:07:48.212 proof of principle does demonstrate

NOTE Confidence: 0.894374198333334

00:07:48.212 --> 00:07:49.640 that it's a useful tool.

NOTE Confidence: 0.894374198333334

00:07:49.640 --> 00:07:50.600 There are sensitivities

NOTE Confidence: 0.894374198333334

00:07:50.600 --> 00:07:52.200 sometimes in the high 80s,

NOTE Confidence: 0.894374198333334

00:07:52.200 --> 00:07:55.080 mid to high 80s for urinary DNA biomarkers,

NOTE Confidence: 0.894374198333334

00:07:55.080 --> 00:07:56.800 especially in a tumor

NOTE Confidence: 0.894374198333334

00:07:56.800 --> 00:07:58.520 informed mechanism for it.

NOTE Confidence: 0.894374198333334

00:07:58.520 --> 00:07:59.354 But ultimately,

NOTE Confidence: 0.894374198333334

00:07:59.354 --> 00:08:01.022 the sensitivities and specificities

NOTE Confidence: 0.894374198333334

00:08:01.022 --> 00:08:04.254 don't seem to to be good enough to

NOTE Confidence: 0.894374198333334

00:08:04.254 --> 00:08:06.448 replace cystoscopy with current with

NOTE Confidence: 0.894374198333334

00:08:06.448 --> 00:08:09.200 current DNA sequencing technologies.

NOTE Confidence: 0.894374198333334

00:08:09.200 --> 00:08:10.831 And one of the reasons for this

NOTE Confidence: 0.894374198333334

00:08:10.831 --> 00:08:12.009 is some inherent limitations

NOTE Confidence: 0.894374198333334

00:08:12.009 --> 00:08:13.717 with next generation sequencing.

NOTE Confidence: 0.894374198333334

00:08:13.720 --> 00:08:15.316 So I'm going to talk just a

NOTE Confidence: 0.894374198333334

00:08:15.316 --> 00:08:16.320 little bit about that.

NOTE Confidence: 0.894374198333334

00:08:16.320 --> 00:08:17.136 This is a paper,

NOTE Confidence: 0.894374198333334

00:08:17.136 --> 00:08:18.360 it's a little bit old now,

NOTE Confidence: 0.894374198333334

00:08:18.360 --> 00:08:20.166 but it's a nice paper because it

NOTE Confidence: 0.894374198333334

00:08:20.166 --> 00:08:21.480 reviews some various platforms.

NOTE Confidence: 0.894374198333334

00:08:21.480 --> 00:08:22.404 I'm not going to go through

NOTE Confidence: 0.894374198333334

00:08:22.404 --> 00:08:23.240 in detail all of this,

NOTE Confidence: 0.894374198333334

00:08:23.240 --> 00:08:24.997 but what you can see here in

NOTE Confidence: 0.894374198333334

00:08:24.997 --> 00:08:26.593 this column is actually just

NOTE Confidence: 0.894374198333334

00:08:26.593 --> 00:08:28.157 various sequencing platforms here

NOTE Confidence: 0.894374198333334

00:08:28.157 --> 00:08:30.398 and the error rates associated

NOTE Confidence: 0.894374198333334

00:08:30.398 --> 00:08:32.237 with polymerase amplifications.

NOTE Confidence: 0.894374198333334

00:08:32.240 --> 00:08:33.661 And what you can see is error

NOTE Confidence: 0.894374198333334

00:08:33.661 --> 00:08:35.001 rates just from the amplification

NOTE Confidence: 0.894374198333334

00:08:35.001 --> 00:08:36.357 process of next generation.

NOTE Confidence: 0.894374198333334

00:08:36.360 --> 00:08:38.200 Sequencing can vary based on

NOTE Confidence: 0.894374198333334

00:08:38.200 --> 00:08:40.640 the platform but it's can be

NOTE Confidence: 0.894374198333334

00:08:40.640 --> 00:08:43.520 somewhere between point O1 to 1%

NOTE Confidence: 0.894374198333334

00:08:43.520 --> 00:08:47.318 amplification error rates which is

NOTE Confidence: 0.894374198333334

00:08:47.318 --> 00:08:49.713 not significant if you're checking

NOTE Confidence: 0.894374198333334

00:08:49.713 --> 00:08:52.020 for somatic mutations or really

NOTE Confidence: 0.894374198333334

00:08:52.020 --> 00:08:54.396 high volume mutations in a tumor.

NOTE Confidence: 0.894374198333334

00:08:54.400 --> 00:08:57.152 But it can be a problem if you're

NOTE Confidence: 0.894374198333334

00:08:57.152 --> 00:08:59.792 looking for heterogeneous low,

NOTE Confidence: 0.894374198333334

00:08:59.792 --> 00:09:03.781 you know really infrequent mutations

NOTE Confidence: 0.894374198333334

00:09:03.781 --> 00:09:07.288 in in something like a dilute sample

NOTE Confidence: 0.894374198333334

00:09:07.288 --> 00:09:10.080 like urinary like a urine sample.

NOTE Confidence: 0.894374198333334

00:09:10.080 --> 00:09:12.264 And so one example of I think a

NOTE Confidence: 0.894374198333334

00:09:12.264 --> 00:09:14.185 helpful figure for me is if you look

NOTE Confidence: 0.894374198333334

00:09:14.185 --> 00:09:16.102 at this sort of hundred well image

NOTE Confidence: 0.894374198333334

00:09:16.102 --> 00:09:17.936 here and you could see that tumors

NOTE Confidence: 0.894374198333334

00:09:17.936 --> 00:09:20.199 are we know tumors are heterogeneous,

NOTE Confidence: 0.894374198333334

00:09:20.200 --> 00:09:21.964 they present different populate,

NOTE Confidence: 0.894374198333334

00:09:21.964 --> 00:09:23.728 they have different populations

18

NOTE Confidence: 0.894374198333334

00:09:23.728 --> 00:09:25.029 with different expressions

NOTE Confidence: 0.894374198333334

00:09:25.029 --> 00:09:26.799 of tumor associated DN as.

NOTE Confidence: 0.894374198333334

00:09:26.800 --> 00:09:29.264 And if you look at standard next generation

NOTE Confidence: 0.894374198333334

00:09:29.264 --> 00:09:31.080 sequencing with the known error rates,

NOTE Confidence: 0.894374198333334

00:09:31.080 --> 00:09:32.352 what you can see is that a lot

NOTE Confidence: 0.894374198333334

00:09:32.352 --> 00:09:33.758 of the heterogeneity is missed.

NOTE Confidence: 0.894374198333334

00:09:33.760 --> 00:09:35.840 There are certain subpopulations that

NOTE Confidence: 0.894374198333334

00:09:35.840 --> 00:09:38.090 can't be captured very effectively and

NOTE Confidence: 0.894374198333334

00:09:38.090 --> 00:09:39.280 there are tools to get around this.

NOTE Confidence: 0.894374198333334

00:09:39.280 --> 00:09:41.268 We can do micro dissection for example

NOTE Confidence: 0.894374198333334

00:09:41.268 --> 00:09:43.719 and then do next generation sequencing,

NOTE Confidence: 0.894374198333334

00:09:43.720 --> 00:09:45.554 which adds a little bit of Labor.

NOTE Confidence: 0.894374198333334

00:09:45.560 --> 00:09:47.576 It's has difficulty with scalability and

NOTE Confidence: 0.894374198333334

00:09:47.576 --> 00:09:49.960 maybe capture some of these populations.

NOTE Confidence: 0.894374198333334

00:09:49.960 --> 00:09:51.790 But again some of the heterogeneity

NOTE Confidence: 0.894374198333334

00:09:51.790 --> 00:09:52.400 is missed.

NOTE Confidence: 0.94406696

00:09:54.560 --> 00:09:55.600 What about single cell sequencing?

NOTE Confidence: 0.94406696

00:09:55.600 --> 00:09:57.622 And again single single cell next

NOTE Confidence: 0.94406696

00:09:57.622 --> 00:09:58.970 generation sequencing is really

NOTE Confidence: 0.94406696

00:09:59.024 --> 00:10:00.839 effective at capturing rare events,

NOTE Confidence: 0.94406696

00:10:00.840 --> 00:10:03.600 but scalability becomes an issue.

NOTE Confidence: 0.94406696

00:10:03.600 --> 00:10:05.882 And when 1 zooms out and thinks

NOTE Confidence: 0.94406696

00:10:05.882 --> 00:10:07.696 about the challenge that faces

NOTE Confidence: 0.94406696

00:10:07.696 --> 00:10:09.505 urinary detecting tumor DNA in the

NOTE Confidence: 0.94406696

00:10:09.505 --> 00:10:11.468 urine the the picture starts to look

NOTE Confidence: 0.94406696

00:10:11.468 --> 00:10:13.169 a little bit more like this where

NOTE Confidence: 0.94406696

00:10:13.169 --> 00:10:14.919 we're trying to capture very very,

NOTE Confidence: 0.94406696

00:10:14.920 --> 00:10:16.880 very rare events and quite,

NOTE Confidence: 0.94406696

00:10:16.880 --> 00:10:20.198 quite dilute solutions And and this,

NOTE Confidence: 0.94406696

00:10:20.200 --> 00:10:21.880 this really can limit the

NOTE Confidence: 0.94406696

00:10:21.880 --> 00:10:23.560 sensitivity and of an assay.

NOTE Confidence: 0.94406696

00:10:23.560 --> 00:10:25.548 And and I think that's what's been

NOTE Confidence: 0.94406696

00:10:25.548 --> 00:10:28.078 shown in in previous attempts at this.

NOTE Confidence: 0.94406696

00:10:28.080 --> 00:10:29.760 One thing we've been looking at that

NOTE Confidence: 0.94406696

00:10:29.760 --> 00:10:31.657 we looked at at the University of

NOTE Confidence: 0.94406696

00:10:31.657 --> 00:10:33.652 Washington and are trying to develop is

NOTE Confidence: 0.94406696

00:10:33.652 --> 00:10:35.242 using a tool called duplex sequencing

NOTE Confidence: 0.94406696

00:10:35.242 --> 00:10:37.505 which was new to me as a fellows

NOTE Confidence: 0.94406696

00:10:37.505 --> 00:10:39.996 developed in the lab in the labs at

NOTE Confidence: 0.94406696

00:10:39.996 --> 00:10:41.641 the University of Washington with

NOTE Confidence: 0.94406696

00:10:41.641 --> 00:10:43.678 Scott Kennedy and and colleagues.

NOTE Confidence: 0.94406696

00:10:43.680 --> 00:10:45.640 And this is a tool that's really

NOTE Confidence: 0.94406696

00:10:45.640 --> 00:10:47.878 helpful for the detection of ultra rare

NOTE Confidence: 0.94406696

00:10:47.880 --> 00:10:51.040 mutations with quite high accuracy.

NOTE Confidence: 0.94406696

00:10:51.040 --> 00:10:53.422 The reason this is helpful is

NOTE Confidence: 0.94406696

00:10:53.422 --> 00:10:55.440 because of a computational tool.

NOTE Confidence: 0.94406696

00:10:55.440 --> 00:10:57.580 Duplex sequencing is primarily A

NOTE Confidence: 0.94406696

00:10:57.580 --> 00:10:59.403 computational tool which starts off

NOTE Confidence: 0.94406696

00:10:59.403 --> 00:11:01.650 by using a sort of standard error

NOTE Confidence: 0.94406696

00:11:01.717 --> 00:11:04.477 corrected next generation sequencing tools.

NOTE Confidence: 0.94406696

00:11:04.480 --> 00:11:06.368 So you know DNA,

NOTE Confidence: 0.94406696

00:11:06.368 --> 00:11:09.200 the DNA from specimens are fragmented.

NOTE Confidence: 0.94406696

00:11:09.200 --> 00:11:11.180 We use a unique molecular identifier

NOTE Confidence: 0.94406696

00:11:11.180 --> 00:11:13.400 that's ligated to the fragments and

NOTE Confidence: 0.94406696

00:11:13.400 --> 00:11:15.920 then next generation sequencing is performed.

NOTE Confidence: 0.94406696

00:11:15.920 --> 00:11:17.999 And if you can see here in this panel,

NOTE Confidence: 0.94406696

00:11:18.000 --> 00:11:19.500 there's a true mutation demonstrated

NOTE Confidence: 0.94406696

00:11:19.500 --> 00:11:20.400 here in green.

NOTE Confidence: 0.94406696

00:11:20.400 --> 00:11:22.960 And then as amplification occurs,

NOTE Confidence: 0.94406696

00:11:22.960 --> 00:11:24.816 there are amplification errors

NOTE Confidence: 0.94406696

00:11:24.816 --> 00:11:27.136 that accumulate during the during

NOTE Confidence: 0.94406696

00:11:27.136 --> 00:11:28.919 in various amplicons.

22

NOTE Confidence: 0.94406696

00:11:28.920 --> 00:11:31.134 And sort of a standard pathway

NOTE Confidence: 0.94406696

00:11:31.134 --> 00:11:33.524 would be to perform single strand

NOTE Confidence: 0.94406696

00:11:33.524 --> 00:11:36.418 consensus so that if all of the

NOTE Confidence: 0.94406696

00:11:36.418 --> 00:11:38.448 amplicons don't have a demonstrated

NOTE Confidence: 0.94406696

00:11:38.448 --> 00:11:40.880 mutation that mutation is sort of

NOTE Confidence: 0.94406696

00:11:40.880 --> 00:11:43.196 assumed to be an amplification error.

NOTE Confidence: 0.94406696

00:11:43.200 --> 00:11:45.630 The technology here is using the

NOTE Confidence: 0.94406696

00:11:45.630 --> 00:11:47.732 inherent complementarity of DNA to

NOTE Confidence: 0.94406696

00:11:47.732 --> 00:11:49.380 identify double strand consensus

NOTE Confidence: 0.94406696

00:11:49.380 --> 00:11:51.440 so that even early mutations,

NOTE Confidence: 0.94406696

00:11:51.440 --> 00:11:53.765 even founder mutations in the

NOTE Confidence: 0.94406696

00:11:53.765 --> 00:11:55.625 amplification process can be

NOTE Confidence: 0.94406696

00:11:55.625 --> 00:11:57.924 identified and and sort of deleted

NOTE Confidence: 0.94406696

00:11:57.924 --> 00:11:59.879 out of the final analysis.

NOTE Confidence: 0.94406696

00:11:59.880 --> 00:12:01.440 And so only true mutations,

NOTE Confidence: 0.94406696

00:12:01.440 --> 00:12:03.265 even very rare mutations are

NOTE Confidence: 0.94406696

00:12:03.265 --> 00:12:05.266 identified in this that has been

NOTE Confidence: 0.94406696

00:12:05.266 --> 00:12:07.078 reported on several times and and

NOTE Confidence: 0.94406696

00:12:07.078 --> 00:12:09.254 it moves the error rate from one in

NOTE Confidence: 0.94406696

00:12:09.254 --> 00:12:11.354 100 and to 1 to one in 1000 to one

NOTE Confidence: 0.94406696

00:12:11.354 --> 00:12:13.237 in 10,000 in some series of standard

NOTE Confidence: 0.94406696

00:12:13.237 --> 00:12:14.609 next generation sequencing to

NOTE Confidence: 0.94406696

00:12:14.609 --> 00:12:16.560 something like one in 10 to the 7th.

NOTE Confidence: 0.94406696

00:12:16.560 --> 00:12:18.864 So it really adds quite a significant amount

NOTE Confidence: 0.94406696

00:12:18.864 --> 00:12:22.838 of quite a significant amount of accuracy.

NOTE Confidence: 0.94406696

00:12:22.840 --> 00:12:24.160 So how would we use this?

NOTE Confidence: 0.94406696

00:12:24.160 --> 00:12:26.455 I think the next step for us was if

NOTE Confidence: 0.94406696

00:12:26.455 --> 00:12:28.596 we're going to try to apply this

NOTE Confidence: 0.94406696

00:12:28.596 --> 00:12:31.139 technology to a screen to a surveillance

NOTE Confidence: 0.94406696

00:12:31.139 --> 00:12:33.234 program for bladder cancer patients,

NOTE Confidence: 0.94406696

00:12:33.240 --> 00:12:35.680 what genes are we going to look for?

00:12:35.680 --> 00:12:37.892 Luckily there have been a couple of

00:12:37.892 --> 00:12:39.609 publicly available and published series

00:12:39.609 --> 00:12:41.436 that have sequenced very large number

00:12:41.436 --> 00:12:43.485 or not very large numbers but large

00:12:43.485 --> 00:12:45.080 numbers of bladder cancer tumors.

00:12:45.080 --> 00:12:47.411 So this is the TCGA which was

00:12:47.411 --> 00:12:48.876 published and updated several

00:12:48.876 --> 00:12:50.836 times most recently in 2018.

00:12:50.840 --> 00:12:53.780 This is a series from Memorial Sloan

00:12:53.780 --> 00:12:56.147 Kettering which has sequenced some

00:12:56.147 --> 00:12:59.280 non muscle invasive tumors and some

00:12:59.280 --> 00:13:02.520 of the frequently mutated genes were

00:13:02.520 --> 00:13:04.668 sort of analyzed from these data

00:13:04.668 --> 00:13:07.224 and we came up with a list of some

00:13:07.224 --> 00:13:09.296 pretty frequent genes and you all will

00:13:09.363 --> 00:13:11.397 recognize many of these genes here.

NOTE Confidence: 0.89193125

00:13:11.400 --> 00:13:14.192 So the the basic approach that we took

NOTE Confidence: 0.89193125

00:13:14.192 --> 00:13:16.373 to developing at least the preliminary

NOTE Confidence: 0.89193125

00:13:16.373 --> 00:13:19.400 data for our our surveillance study was

NOTE Confidence: 0.89193125

00:13:19.400 --> 00:13:23.152 patients present with a a mass or hematuria,

NOTE Confidence: 0.89193125

00:13:23.152 --> 00:13:24.944 they undergo transurethral resection

NOTE Confidence: 0.89193125

00:13:24.944 --> 00:13:27.164 of bladder tumor and then after

NOTE Confidence: 0.89193125

00:13:27.164 --> 00:13:28.396 the diagnosis is made,

NOTE Confidence: 0.89193125

00:13:28.400 --> 00:13:31.228 a urine sample is taken immediately or

NOTE Confidence: 0.89193125

00:13:31.228 --> 00:13:33.538 soon after surgery they receive therapy

NOTE Confidence: 0.89193125

00:13:33.538 --> 00:13:35.734 intravesically and then a urine sample

NOTE Confidence: 0.89193125

00:13:35.734 --> 00:13:38.896 is taken after their therapy and then

NOTE Confidence: 0.89193125

00:13:38.896 --> 00:13:40.716 patients undergo cystoscopic surveillance.

NOTE Confidence: 0.89193125

00:13:40.720 --> 00:13:42.592 And the goal of this was

NOTE Confidence: 0.89193125

00:13:42.592 --> 00:13:43.840 to just understand one,

NOTE Confidence: 0.89193125

00:13:43.840 --> 00:13:46.102 are we able to reliably detect

NOTE Confidence: 0.89193125

00:13:46.102 --> 00:13:47.233 tumor associated genes?

NOTE Confidence: 0.89193125

00:13:47.240 --> 00:13:47.798 And two,

NOTE Confidence: 0.89193125

00:13:47.798 --> 00:13:50.030 do the do the levels of these tumor

NOTE Confidence: 0.89193125

00:13:50.101 --> 00:13:52.226 associated genes relate to their

NOTE Confidence: 0.89193125

00:13:52.226 --> 00:13:54.351 risk of recurrence moving forward?

NOTE Confidence: 0.89193125

00:13:54.360 --> 00:13:55.480 So I'm going to show you some examples.

NOTE Confidence: 0.89193125

00:13:55.480 --> 00:13:56.640 This is quite early work,

NOTE Confidence: 0.89193125

00:13:56.640 --> 00:13:58.696 but I'd like to show you some examples

NOTE Confidence: 0.89193125

00:13:58.696 --> 00:14:00.477 that got us excited about this.

NOTE Confidence: 0.89193125

00:14:00.480 --> 00:14:01.028 This is,

NOTE Confidence: 0.89193125

00:14:01.028 --> 00:14:03.220 this is data from a 77 year old

NOTE Confidence: 0.89193125

00:14:03.296 --> 00:14:05.746 male who presented to us with high

NOTE Confidence: 0.89193125

00:14:05.746 --> 00:14:08.534 grade T1 bladder cancer with no CIS.

NOTE Confidence: 0.89193125

00:14:08.534 --> 00:14:11.460 And this is just an analysis of

NOTE Confidence: 0.89193125

00:14:11.555 --> 00:14:13.960 their their pre and post urine

NOTE Confidence: 0.89193125

00:14:13.960 --> 00:14:16.800 for the 10 genes that we analyzed.

NOTE Confidence: 0.89193125

00:14:16.800 --> 00:14:17.970 It's important to note here that

NOTE Confidence: 0.89193125

00:14:17.970 --> 00:14:19.399 this is a tumor naive approach.

NOTE Confidence: 0.89193125

00:14:19.400 --> 00:14:21.494 So we're not sequencing the initial

NOTE Confidence: 0.89193125

00:14:21.494 --> 00:14:23.867 tumor and then going on to try

NOTE Confidence: 0.89193125

00:14:23.867 --> 00:14:25.079 to detect these lesions.

NOTE Confidence: 0.89193125

00:14:25.080 --> 00:14:28.075 This is an off the shelf approach

NOTE Confidence: 0.89193125

00:14:28.075 --> 00:14:30.464 which I think is really useful for

NOTE Confidence: 0.89193125

00:14:30.464 --> 00:14:32.720 scalability in a setting like this.

NOTE Confidence: 0.89193125

00:14:32.720 --> 00:14:34.952 And what you can see is the blue is

NOTE Confidence: 0.89193125

00:14:34.952 --> 00:14:37.336 the levels of of the variants detected

NOTE Confidence: 0.89193125

00:14:37.336 --> 00:14:40.320 for the common genes that we're detecting.

NOTE Confidence: 0.89193125

00:14:40.320 --> 00:14:43.480 The blue is before and the orange which

NOTE Confidence: 0.89193125

00:14:43.480 --> 00:14:46.364 is really almost difficult to see,

NOTE Confidence: 0.89193125

00:14:46.364 --> 00:14:48.396 is the after treatment.

NOTE Confidence: 0.89193125

00:14:48.400 --> 00:14:50.472 And I'll just I'll just point get

NOTE Confidence: 0.89193125

00:14:50.472 --> 00:14:52.360 your attention here to the Y axis

NOTE Confidence: 0.89193125

00:14:52.360 --> 00:14:54.116 and you could see that these are

NOTE Confidence: 0.89193125

00:14:54.116 --> 00:14:55.276 very very rare events.

NOTE Confidence: 0.89193125

00:14:55.280 --> 00:14:56.860 These varying allele fractions

NOTE Confidence: 0.89193125

00:14:56.860 --> 00:14:58.440 are really quite low.

NOTE Confidence: 0.89193125

00:14:58.440 --> 00:15:01.177 You know a a common varying allele

NOTE Confidence: 0.89193125

00:15:01.177 --> 00:15:02.960 fraction for previously reported

NOTE Confidence: 0.89193125

00:15:02.960 --> 00:15:06.524 assays would be .3 to .5 and so.

NOTE Confidence: 0.89193125

00:15:06.524 --> 00:15:08.456 So we're detecting really low levels

NOTE Confidence: 0.89193125

00:15:08.456 --> 00:15:11.133 and what you can see here is that

NOTE Confidence: 0.89193125

00:15:11.133 --> 00:15:12.753 there's clearly some dynamics at

NOTE Confidence: 0.89193125

00:15:12.753 --> 00:15:14.665 play here and this is the total

NOTE Confidence: 0.89193125

00:15:14.665 --> 00:15:15.235 variolial fraction.

NOTE Confidence: 0.89193125

00:15:15.240 --> 00:15:18.096 And you can see that this patient had

NOTE Confidence: 0.89193125

00:15:18.096 --> 00:15:20.672 a significant reduction in the total

NOTE Confidence: 0.89193125

00:15:20.672 --> 00:15:22.912 amount of detectable tumor associated

NOTE Confidence: 0.89193125

00:15:22.912 --> 00:15:25.598 DNA and they're now 18 months out,

NOTE Confidence: 0.89193125

00:15:25.600 --> 00:15:26.668 no, no recurrence.

NOTE Confidence: 0.89193125

00:15:26.668 --> 00:15:28.804 And you can sort of contrast

NOTE Confidence: 0.89193125

00:15:28.804 --> 00:15:30.914 that with this patient who had

NOTE Confidence: 0.89193125

00:15:30.914 --> 00:15:33.280 quite low levels at the beginning

NOTE Confidence: 0.89193125

00:15:33.280 --> 00:15:35.240 after surveillance or excuse me,

NOTE Confidence: 0.89193125

00:15:35.240 --> 00:15:35.998 after therapy,

NOTE Confidence: 0.89193125

00:15:35.998 --> 00:15:38.651 we were able to detect low levels

NOTE Confidence: 0.89193125

00:15:38.651 --> 00:15:41.220 of of stack two ERD 1A and quite

NOTE Confidence: 0.89193125

00:15:41.220 --> 00:15:43.320 significant levels of PIC three CA.

NOTE Confidence: 0.89193125

00:15:43.320 --> 00:15:46.029 And this is sort of demonstrated here

NOTE Confidence: 0.89193125

00:15:46.029 --> 00:15:49.199 really driven by this PIC three CA mutation.

NOTE Confidence: 0.89193125

00:15:49.200 --> 00:15:51.065 And ultimately the patient in

NOTE Confidence: 0.89193125

00:15:51.065 --> 00:15:52.930 about 6 1/2 months later

NOTE Confidence: 0.935023914736842

00:15:53.005 --> 00:15:55.585 was found to have a detectable

NOTE Confidence: 0.935023914736842

00:15:55.585 --> 00:15:56.875 recurrence on cystoscopy.

NOTE Confidence: 0.935023914736842

00:15:56.880 --> 00:15:59.070 Obviously these are specific examples that

NOTE Confidence: 0.935023914736842

00:15:59.070 --> 00:16:01.558 sort of just demonstrated this was feasible.

NOTE Confidence: 0.935023914736842

00:16:01.560 --> 00:16:04.180 And so we have now collected a total of 50

NOTE Confidence: 0.935023914736842

00:16:04.251 --> 00:16:06.876 patients and are working through the data.

NOTE Confidence: 0.935023914736842

00:16:06.880 --> 00:16:09.337 Now this is just a a heat map showing

NOTE Confidence: 0.935023914736842

00:16:09.337 --> 00:16:12.260 some of their some of their demographic

NOTE Confidence: 0.935023914736842

00:16:12.260 --> 00:16:15.040 and and pathologic data and approximately

NOTE Confidence: 0.935023914736842

00:16:15.040 --> 00:16:17.200 20 of them have experienced recurrences.

NOTE Confidence: 0.935023914736842

00:16:17.200 --> 00:16:21.592 And the the future of this is we're now

NOTE Confidence: 0.935023914736842

00:16:21.592 --> 00:16:24.498 working through their their clinical

NOTE Confidence: 0.935023914736842

00:16:24.498 --> 00:16:26.188 outcomes and trying to understand

NOTE Confidence: 0.935023914736842

00:16:26.188 --> 00:16:28.677 if we can reliably identify a lead

NOTE Confidence: 0.935023914736842

00:16:28.677 --> 00:16:30.477 time for identifying these patients.

NOTE Confidence: 0.935023914736842

00:16:30.480 --> 00:16:32.640 And so the the future of this is

NOTE Confidence: 0.935023914736842

00:16:32.640 --> 00:16:34.343 we're working through the data now

NOTE Confidence: 0.935023914736842

00:16:34.343 --> 00:16:36.586 trying to develop a a reliable way

NOTE Confidence: 0.935023914736842

00:16:36.586 --> 00:16:38.318 to detect treatment response,

NOTE Confidence: 0.935023914736842

00:16:38.320 --> 00:16:40.284 identify recurrences before they're

NOTE Confidence: 0.935023914736842

00:16:40.284 --> 00:16:42.739 grossly visible and maybe identify

NOTE Confidence: 0.935023914736842

00:16:42.739 --> 00:16:44.792 patients for whom early switching

NOTE Confidence: 0.935023914736842

00:16:44.792 --> 00:16:47.030 of therapy before a visible tumours

NOTE Confidence: 0.935023914736842

00:16:47.097 --> 00:16:49.610 identified and maybe be able to spare

NOTE Confidence: 0.935023914736842

00:16:49.610 --> 00:16:50.870 those patients subsequent surgery

NOTE Confidence: 0.935023914736842

00:16:50.929 --> 00:16:52.555 for example if we switch early.

NOTE Confidence: 0.935023914736842

00:16:52.560 --> 00:16:54.943 And I just wanted to highlight Jonathan

NOTE Confidence: 0.935023914736842

00:16:54.943 --> 00:16:57.344 Wright who's a a bladder cancer surgeon

NOTE Confidence: 0.935023914736842

00:16:57.344 --> 00:16:58.982 and researcher at the University

NOTE Confidence: 0.935023914736842

00:16:58.982 --> 00:17:00.776 of Washington who's my mentor and

NOTE Confidence: 0.935023914736842

00:17:00.776 --> 00:17:02.180 and developed this project with

NOTE Confidence: 0.935023914736842

00:17:02.180 --> 00:17:03.600 me and Scott Kennedy of course,

NOTE Confidence: 0.935023914736842

00:17:03.600 --> 00:17:06.570 who was part of the development

NOTE Confidence: 0.935023914736842

00:17:06.570 --> 00:17:07.556 of this technology.

NOTE Confidence: 0.935023914736842

00:17:07.556 --> 00:17:09.692 And Doctor Blaha is a biostatistician

NOTE Confidence: 0.935023914736842

00:17:09.692 --> 00:17:12.315 here at Yale who as soon as I got here,

NOTE Confidence: 0.935023914736842

00:17:12.320 --> 00:17:13.800 I was lucky enough to get to meet

NOTE Confidence: 0.935023914736842

00:17:13.800 --> 00:17:15.349 him and and recruited him to work

NOTE Confidence: 0.935023914736842

00:17:15.349 --> 00:17:16.479 on this project with us.

NOTE Confidence: 0.935023914736842

00:17:16.480 --> 00:17:18.700 So have been really looking forward

NOTE Confidence: 0.935023914736842

00:17:18.700 --> 00:17:20.880 to this And as we analyze this data,

NOTE Confidence: 0.935023914736842

00:17:20.880 --> 00:17:23.987 the goal will be to develop a a larger

NOTE Confidence: 0.935023914736842

00:17:23.987 --> 00:17:26.441 study where we can collect ongoing

NOTE Confidence: 0.935023914736842

00:17:26.441 --> 00:17:28.723 urines with every cystoscopy and

NOTE Confidence: 0.935023914736842

00:17:28.723 --> 00:17:32.172 hopefully be able to follow and monitor

NOTE Confidence: 0.935023914736842

00:17:32.172 --> 00:17:34.876 these patients more longitudinally.

NOTE Confidence: 0.935023914736842

00:17:34.880 --> 00:17:36.154 I think that data will be richer.

NOTE Confidence: 0.935023914736842

00:17:36.160 --> 00:17:37.744 So we're preparing these,

NOTE Confidence: 0.935023914736842

00:17:37.744 --> 00:17:39.328 we're preparing this analysis

NOTE Confidence: 0.935023914736842

00:17:39.328 --> 00:17:41.476 now for hopefully some extramural

NOTE Confidence: 0.935023914736842

00:17:41.476 --> 00:17:43.200 funding in the spring.

NOTE Confidence: 0.935023914736842

00:17:43.200 --> 00:17:45.174 The thing that we're all trying to

NOTE Confidence: 0.935023914736842

00:17:45.174 --> 00:17:46.699 prevent is progression of these

NOTE Confidence: 0.935023914736842

00:17:46.699 --> 00:17:47.960 patients because progressing to

NOTE Confidence: 0.935023914736842

00:17:47.960 --> 00:17:49.560 muscle invasive bladder cancer is,

NOTE Confidence: 0.935023914736842

00:17:49.560 --> 00:17:50.294 is almost,

NOTE Confidence: 0.935023914736842

00:17:50.294 --> 00:17:52.496 it's an entirely really a different

NOTE Confidence: 0.935023914736842

00:17:52.496 --> 00:17:54.885 kind of clinical entity and it's

NOTE Confidence: 0.935023914736842

00:17:54.885 --> 00:17:57.060 it's has significantly poor outcomes

NOTE Confidence: 0.935023914736842

00:17:57.060 --> 00:17:58.395 associated with it.

NOTE Confidence: 0.935023914736842

00:17:58.400 --> 00:17:59.562 So this is that same paper that

NOTE Confidence: 0.935023914736842

00:17:59.562 --> 00:18:00.400 I showed you earlier,

NOTE Confidence: 0.935023914736842

00:18:00.400 --> 00:18:02.787 those same 400 patients and this is

NOTE Confidence: 0.935023914736842

00:18:02.787 --> 00:18:04.760 now progression rather than recurrence

NOTE Confidence: 0.935023914736842

00:18:04.760 --> 00:18:06.496 and you can see that low risk patients

NOTE Confidence: 0.935023914736842

00:18:06.496 --> 00:18:08.477 have a pretty low risk of progression,

NOTE Confidence: 0.935023914736842

00:18:08.480 --> 00:18:10.510 but high risk patients especially

NOTE Confidence: 0.935023914736842

00:18:10.510 --> 00:18:12.540 do progress significantly and many

NOTE Confidence: 0.935023914736842

00:18:12.605 --> 00:18:14.924 of them will progress to like I

NOTE Confidence: 0.935023914736842

00:18:14.924 --> 00:18:17.134 say this muscle invasive bladder

NOTE Confidence: 0.935023914736842

00:18:17.134 --> 00:18:19.695 cancer phase in invading the muscle

NOTE Confidence: 0.935023914736842

00:18:19.695 --> 00:18:21.999 or fat or or or onward.

NOTE Confidence: 0.935023914736842

00:18:22.000 --> 00:18:24.424 And for those patients therapy really

NOTE Confidence: 0.935023914736842

00:18:24.424 --> 00:18:26.979 does transition standard of care therapy

NOTE Confidence: 0.935023914736842

00:18:26.979 --> 00:18:29.154 really transitions from the bladder,

NOTE Confidence: 0.935023914736842

00:18:29.160 --> 00:18:31.536 you know the the less invasive

NOTE Confidence: 0.935023914736842

00:18:31.536 --> 00:18:33.578 endoscopic approaches to therapy too

NOTE Confidence: 0.935023914736842

00:18:33.578 --> 00:18:35.518 often much more involved therapy.

NOTE Confidence: 0.935023914736842

00:18:35.520 --> 00:18:38.474 So I'll I'll talk briefly about that.

NOTE Confidence: 0.935023914736842

00:18:38.480 --> 00:18:40.175 The management of muscle invasive

NOTE Confidence: 0.935023914736842

00:18:40.175 --> 00:18:42.230 bladder cancer generally falls into two

NOTE Confidence: 0.935023914736842

00:18:42.230 --> 00:18:44.066 broad categories for patients who are

NOTE Confidence: 0.935023914736842

00:18:44.066 --> 00:18:46.210 candidates for for radical treatment.

NOTE Confidence: 0.935023914736842

00:18:46.210 --> 00:18:48.760 The 1st is radical surgery,

NOTE Confidence: 0.935023914736842

00:18:48.760 --> 00:18:50.808 radical cystectomy with lymph

NOTE Confidence: 0.935023914736842

00:18:50.808 --> 00:18:52.856 node dissection preceded by

NOTE Confidence: 0.935023914736842

00:18:52.856 --> 00:18:53.880 neoadjuvant chemotherapy.

NOTE Confidence: 0.872237478888889

00:18:53.880 --> 00:18:55.462 And the other is what we call

NOTE Confidence: 0.872237478888889

00:18:55.462 --> 00:18:57.264 trimodal therapy, which is the

NOTE Confidence: 0.872237478888889

00:18:57.264 --> 00:18:59.504 first mode is maximal endoscopic

NOTE Confidence: 0.872237478888889

00:18:59.504 --> 00:19:01.624 resection followed by chemo radiation.

NOTE Confidence: 0.872237478888889

00:19:01.624 --> 00:19:04.448 So those are the three modes outcomes

NOTE Confidence: 0.872237478888889

00:19:04.448 --> 00:19:06.088 are significantly poorer for patients

NOTE Confidence: 0.872237478888889

00:19:06.088 --> 00:19:07.760 with muscle invasive bladder cancer.

NOTE Confidence: 0.872237478888889

00:19:07.760 --> 00:19:09.904 This is a study that looked at data

NOTE Confidence: 0.872237478888889

00:19:09.904 --> 00:19:11.756 from from the VA of all places.

NOTE Confidence: 0.872237478888889

00:19:11.760 --> 00:19:14.112 These are Vinci data from the University

NOTE Confidence: 0.872237478888889

00:19:14.112 --> 00:19:16.348 of California in San Diego and these

NOTE Confidence: 0.872237478888889

00:19:16.348 --> 00:19:17.918 are multiple thousands of patients.

NOTE Confidence: 0.872237478888889

00:19:17.920 --> 00:19:20.176 And you could see overall survival

NOTE Confidence: 0.872237478888889

00:19:20.176 --> 00:19:22.399 plots for radical cystectomy with chemo,

NOTE Confidence: 0.872237478888889

00:19:22.400 --> 00:19:24.268 radical cystectomy without neoadjuvant

NOTE Confidence: 0.872237478888889

00:19:24.268 --> 00:19:26.603 chemotherapy are demonstrated here in

NOTE Confidence: 0.872237478888889

00:19:26.603 --> 00:19:29.082 the in the dashed orange and the dark

NOTE Confidence: 0.872237478888889

00:19:29.082 --> 00:19:31.400 blue line and trimodal therapy with

NOTE Confidence: 0.872237478888889

00:19:31.400 --> 00:19:33.600 preferred chemotherapy regimens up here.

NOTE Confidence: 0.872237478888889

00:19:33.600 --> 00:19:36.128 And you can see that survival is at

NOTE Confidence: 0.872237478888889

00:19:36.128 --> 00:19:39.100 at best at least from these real world

NOTE Confidence: 0.872237478888889

00:19:39.100 --> 00:19:41.250 data and admittedly somewhat sicker

NOTE Confidence: 0.872237478888889

00:19:41.250 --> 00:19:43.359 patients are somewhere in the 40 to

NOTE Confidence: 0.872237478888889

00:19:43.360 --> 00:19:45.520 5545 to 55% range in the five year

NOTE Confidence: 0.872237478888889

00:19:45.520 --> 00:19:47.357 survival data that they report here.

NOTE Confidence: 0.872237478888889

00:19:47.360 --> 00:19:48.865 This varies a little bit based on

NOTE Confidence: 0.872237478888889

00:19:48.865 --> 00:19:50.199 you know some other factors,

NOTE Confidence: 0.872237478888889

00:19:50.200 --> 00:19:52.640 but that's what's reported here.

NOTE Confidence: 0.872237478888889

00:19:52.640 --> 00:19:54.684 One thing to note is that trimodal

NOTE Confidence: 0.872237478888889

00:19:54.684 --> 00:19:56.406 therapy with non preferred regimens

NOTE Confidence: 0.872237478888889

00:19:56.406 --> 00:19:58.746 in these data show a significantly

NOTE Confidence: 0.872237478888889

00:19:58.746 --> 00:20:01.439 poorer outcome that they were able to

NOTE Confidence: 0.872237478888889

00:20:01.439 --> 00:20:02.919 detect a statistically significant.

NOTE Confidence: 0.872237478888889

00:20:02.920 --> 00:20:05.432 So for for many decades now management of

NOTE Confidence: 0.872237478888889

00:20:05.432 --> 00:20:07.720 muscle invasive bladder cancer has this this.

NOTE Confidence: 0.872237478888889

00:20:07.720 --> 00:20:09.680 The central feature of it in the United

NOTE Confidence: 0.872237478888889

00:20:09.680 --> 00:20:11.413 States at least has been radical

NOTE Confidence: 0.872237478888889

00:20:11.413 --> 00:20:13.878 cystectomy with lymph node dissection.

NOTE Confidence: 0.872237478888889

00:20:13.880 --> 00:20:15.994 We have learned in the last several

NOTE Confidence: 0.872237478888889

00:20:15.994 --> 00:20:18.448 decades that chemotherapy prior to radical

NOTE Confidence: 0.872237478888889

00:20:18.448 --> 00:20:20.758 surgery doesn't prove overall survival.

NOTE Confidence: 0.872237478888889

00:20:20.760 --> 00:20:22.615 This was first shown in with level

NOTE Confidence: 0.872237478888889

00:20:22.615 --> 00:20:24.956 one evidence in a study in 2003 which

NOTE Confidence: 0.872237478888889

00:20:24.956 --> 00:20:27.824 administered M VAC prior to radical

NOTE Confidence: 0.872237478888889

00:20:27.824 --> 00:20:30.577 cystectomy and locally advanced muscle

NOTE Confidence: 0.872237478888889

00:20:30.577 --> 00:20:32.862 invasive bladder cancer and demonstrated

NOTE Confidence: 0.872237478888889

00:20:32.862 --> 00:20:35.155 about a 5% overall survival benefit.

NOTE Confidence: 0.872237478888889

00:20:35.155 --> 00:20:37.594 So you can see that's that top line

NOTE Confidence: 0.872237478888889

00:20:37.594 --> 00:20:40.996 here and and the the charts separate.

NOTE Confidence: 0.872237478888889

00:20:41.000 --> 00:20:42.086 Despite these data,

NOTE Confidence: 0.872237478888889

00:20:42.086 --> 00:20:44.258 they're good real world data that

NOTE Confidence: 0.872237478888889

00:20:44.258 --> 00:20:47.242 we do not use chemotherapy in the

NOTE Confidence: 0.872237478888889

00:20:47.242 --> 00:20:48.946 neoadjuvant setting very frequently

NOTE Confidence: 0.872237478888889

00:20:49.020 --> 00:20:50.958 or as frequently as we should.

NOTE Confidence: 0.872237478888889

00:20:50.960 --> 00:20:53.120 So this is a study looking at SEER data,

NOTE Confidence: 0.872237478888889

00:20:53.120 --> 00:20:54.880 It's now a little bit old 'cause it stops in.

NOTE Confidence: 0.872237478888889

00:20:54.880 --> 00:20:56.752 It stopped in 2011 and we could see

NOTE Confidence: 0.872237478888889

00:20:56.752 --> 00:20:59.205 sort of a trend upwards in the use

NOTE Confidence: 0.872237478888889

00:20:59.205 --> 00:21:00.489 of neoadjuvant chemotherapy with

NOTE Confidence: 0.872237478888889

00:21:00.550 --> 00:21:02.238 muscle invasive bladder cancer,

NOTE Confidence: 0.872237478888889

00:21:02.240 --> 00:21:04.466 but it peaks at around in this

NOTE Confidence: 0.872237478888889

00:21:04.466 --> 00:21:07.960 data here about around 23 to 25%.

NOTE Confidence: 0.872237478888889

00:21:07.960 --> 00:21:10.504 More recent data using the National

NOTE Confidence: 0.872237478888889

00:21:10.504 --> 00:21:12.552 Cancer Database reported that while

NOTE Confidence: 0.872237478888889

00:21:12.552 --> 00:21:14.312 again it's still increasing the

NOTE Confidence: 0.872237478888889

00:21:14.312 --> 00:21:15.720 use of neoadjuvant chemotherapy,

NOTE Confidence: 0.872237478888889

00:21:15.720 --> 00:21:17.244 the highest that they were able

NOTE Confidence: 0.872237478888889

00:21:17.244 --> 00:21:19.368 to detect was in the 35% range.

NOTE Confidence: 0.872237478888889

00:21:19.368 --> 00:21:22.920 And and so we're not using it nearly

NOTE Confidence: 0.872237478888889

00:21:23.016 --> 00:21:26.040 as frequently as as we could be.

NOTE Confidence: 0.872237478888889

00:21:26.040 --> 00:21:28.638 And this is a potential real

NOTE Confidence: 0.872237478888889

00:21:28.638 --> 00:21:30.370 opportunity for improving survival

NOTE Confidence: 0.872237478888889

00:21:30.439 --> 00:21:32.378 without major new interventions,

NOTE Confidence: 0.872237478888889

00:21:32.378 --> 00:21:33.836 without major new,

NOTE Confidence: 0.872237478888889

00:21:33.840 --> 00:21:35.912 you know all of the new fancy drugs

NOTE Confidence: 0.872237478888889

00:21:35.912 --> 00:21:36.800 that we have.

NOTE Confidence: 0.872237478888889

00:21:36.800 --> 00:21:39.518 This is tried and true and and we're just

NOTE Confidence: 0.872237478888889

00:21:39.518 --> 00:21:42.439 are not very effective at implementing it.

NOTE Confidence: 0.872237478888889

00:21:42.440 --> 00:21:43.775 What about radiation?

NOTE Confidence: 0.872237478888889

00:21:43.775 --> 00:21:46.445 And similarly there is high quality

NOTE Confidence: 0.872237478888889

00:21:46.445 --> 00:21:49.080 data that suggests that chemotherapy

NOTE Confidence: 0.872237478888889

00:21:49.080 --> 00:21:51.593 with radiation does improve outcomes

NOTE Confidence: 0.872237478888889

00:21:51.593 --> 00:21:53.558 for muscle invasive bladder cancer.

NOTE Confidence: 0.668353058333333

00:21:53.560 --> 00:21:55.000 This is the study out of

NOTE Confidence: 0.668353058333333

00:21:55.000 --> 00:21:56.680 from 2012 James ET al.

NOTE Confidence: 0.668353058333333

00:21:56.680 --> 00:21:59.170 But there's several others that have

NOTE Confidence: 0.668353058333333

00:21:59.170 --> 00:22:00.830 also demonstrated that chemotherapy

NOTE Confidence: 0.668353058333333

00:22:00.889 --> 00:22:02.733 administered with radiotherapy improves

NOTE Confidence: 0.668353058333333

00:22:02.733 --> 00:22:05.038 at least local regional control.

NOTE Confidence: 0.668353058333333

00:22:05.040 --> 00:22:06.867 And this is an overall survival plot

NOTE Confidence: 0.668353058333333

00:22:06.867 --> 00:22:08.200 that wasn't statistically significant.

NOTE Confidence: 0.668353058333333

00:22:08.200 --> 00:22:10.402 But you could see that chemoradiotherapy

NOTE Confidence: 0.668353058333333

00:22:10.402 --> 00:22:11.870 out outperforms radiotherapy alone

NOTE Confidence: 0.668353058333333

00:22:11.925 --> 00:22:13.635 at least in local regional control,

NOTE Confidence: 0.668353058333333

00:22:13.640 --> 00:22:15.998 if not both.

NOTE Confidence: 0.668353058333333

00:22:16.000 --> 00:22:17.925 Are we doing better with administering

NOTE Confidence: 0.668353058333333

00:22:17.925 --> 00:22:19.860 chemotherapy with radiation?

NOTE Confidence: 0.668353058333333

00:22:19.860 --> 00:22:21.795 We're doing better.

NOTE Confidence: 0.668353058333333

00:22:21.800 --> 00:22:25.280 We looked at this at using the SEER,

NOTE Confidence: 0.668353058333333

00:22:25.280 --> 00:22:27.160 the SEER Medicare data set.

NOTE Confidence: 0.668353058333333

00:22:27.160 --> 00:22:28.714 We looked at a cohort of about

NOTE Confidence: 0.668353058333333

00:22:28.720 --> 00:22:31.634 2200 patients and sort of the

NOTE Confidence: 0.668353058333333

00:22:31.634 --> 00:22:33.518 kind of summary of this data,

NOTE Confidence: 0.668353058333333

00:22:33.520 --> 00:22:35.496 of the data that we found is that

NOTE Confidence: 0.668353058333333

00:22:35.496 --> 00:22:37.389 in 2200 patients with muscle

NOTE Confidence: 0.668353058333333

00:22:37.389 --> 00:22:39.176 invasive bladder cancer with

NOTE Confidence: 0.668353058333333

00:22:39.176 --> 00:22:41.000 undergoing curative intent radiation,

NOTE Confidence: 0.668353058333333

00:22:41.000 --> 00:22:43.388 approximately 40% of patients do not

NOTE Confidence: 0.668353058333333

00:22:43.388 --> 00:22:45.840 receive any radiotherapy in in the

NOTE Confidence: 0.668353058333333

00:22:45.840 --> 00:22:47.835 time that they're receiving radiation.

NOTE Confidence: 0.668353058333333

00:22:47.840 --> 00:22:50.125 So again a significant opportunity

NOTE Confidence: 0.668353058333333

00:22:50.125 --> 00:22:51.039 for improving,

NOTE Confidence: 0.668353058333333

00:22:51.040 --> 00:22:53.400 improving care for these folks.

NOTE Confidence: 0.668353058333333

00:22:53.400 --> 00:22:56.764 Similarly many about 20 to 25% of

NOTE Confidence: 0.668353058333333

00:22:56.764 --> 00:22:58.816 patients are receiving what we would

NOTE Confidence: 0.668353058333333

00:22:58.816 --> 00:23:00.760 call non preferred chemotherapeutic

NOTE Confidence: 0.668353058333333

00:23:00.760 --> 00:23:04.318 regimens like carboplatin or dosataxel alone.

NOTE Confidence: 0.668353058333333

00:23:04.320 --> 00:23:07.112 And these are therapies that that we

NOTE Confidence: 0.668353058333333

00:23:07.112 --> 00:23:09.320 there are good data that they do not

NOTE Confidence: 0.668353058333333

00:23:09.384 --> 00:23:11.340 perform quite as well as cisplatin

NOTE Confidence: 0.668353058333333

00:23:11.340 --> 00:23:13.880 for example in in the setting and so.

NOTE Confidence: 0.668353058333333

00:23:13.880 --> 00:23:15.800 So again these are this is just an

NOTE Confidence: 0.668353058333333

00:23:15.861 --> 00:23:18.181 opportunity for for improvement in

NOTE Confidence: 0.668353058333333

00:23:18.181 --> 00:23:20.037 patients undergoing radiation therapy.

NOTE Confidence: 0.668353058333333

00:23:20.040 --> 00:23:21.558 This is a chart over time.

NOTE Confidence: 0.668353058333333

00:23:21.560 --> 00:23:22.290 We're not.

NOTE Confidence: 0.668353058333333

00:23:22.290 --> 00:23:23.750 We're getting better at

NOTE Confidence: 0.668353058333333

00:23:23.750 --> 00:23:24.480 administering therapy,

NOTE Confidence: 0.668353058333333

00:23:24.480 --> 00:23:26.280 but it's not significantly better

NOTE Confidence: 0.668353058333333

00:23:26.280 --> 00:23:28.303 in terms of preferred regimens and

NOTE Confidence: 0.668353058333333

00:23:28.303 --> 00:23:29.641 we did detect the difference in

NOTE Confidence: 0.668353058333333

00:23:29.641 --> 00:23:30.960 overall survival in these patients,

NOTE Confidence: 0.668353058333333

00:23:30.960 --> 00:23:33.074 although we should note that I should

NOTE Confidence: 0.668353058333333

00:23:33.074 --> 00:23:35.348 note that level one evidence doesn't

NOTE Confidence: 0.668353058333333

00:23:35.348 --> 00:23:37.433 demonstrate a clear survival benefit,

NOTE Confidence: 0.668353058333333

00:23:37.440 --> 00:23:38.157 mostly local, regional,

NOTE Confidence: 0.668353058333333

00:23:38.157 --> 00:23:39.830 but we did see an overall survival

NOTE Confidence: 0.668353058333333

00:23:39.875 --> 00:23:41.320 benefit in these retrospective data

NOTE Confidence: 0.896319028571429

00:23:43.600 --> 00:23:45.012 for patients undergoing bladder

NOTE Confidence: 0.896319028571429

00:23:45.012 --> 00:23:46.777 sparing therapy or radical cystectomy

NOTE Confidence: 0.896319028571429

00:23:46.777 --> 00:23:48.680 for muscle invasive bladder cancer.

NOTE Confidence: 0.896319028571429

00:23:48.680 --> 00:23:51.112 The goal would be to also expand the

NOTE Confidence: 0.896319028571429

00:23:51.112 --> 00:23:53.881 the idea of does urinary DNA play a role

NOTE Confidence: 0.896319028571429

00:23:53.881 --> 00:23:56.398 in these for these patients as well,

NOTE Confidence: 0.896319028571429

00:23:56.400 --> 00:23:57.885 establishing the utility of urinary

NOTE Confidence: 0.896319028571429

00:23:57.885 --> 00:24:00.076 DNA as a biomarker in muscle invasive

NOTE Confidence: 0.896319028571429

00:24:00.076 --> 00:24:02.014 bladder cancer could play a role

NOTE Confidence: 0.896319028571429

00:24:02.014 --> 00:24:03.744 in predicting complete response

NOTE Confidence: 0.896319028571429

00:24:03.744 --> 00:24:05.280 after neoadjuvant chemotherapy,

NOTE Confidence: 0.896319028571429

00:24:05.280 --> 00:24:06.638 which I didn't show you data for,

NOTE Confidence: 0.896319028571429

00:24:06.640 --> 00:24:08.791 but is known to be a good marker for

NOTE Confidence: 0.896319028571429

00:24:08.791 --> 00:24:11.116 a good outcome for these patients.

NOTE Confidence: 0.896319028571429

00:24:11.120 --> 00:24:12.975 And there's more and more interest in

NOTE Confidence: 0.896319028571429

00:24:12.975 --> 00:24:14.976 trying to avoid radical surgery in

NOTE Confidence: 0.896319028571429

00:24:14.976 --> 00:24:16.896 patients that respond to neoadjuvant

NOTE Confidence: 0.896319028571429

00:24:16.896 --> 00:24:17.280 chemotherapy.

NOTE Confidence: 0.896319028571429

00:24:17.280 --> 00:24:19.037 For those that are not responding well,

NOTE Confidence: 0.896319028571429

00:24:19.040 --> 00:24:21.062 there's a question of would they

NOTE Confidence: 0.896319028571429

00:24:21.062 --> 00:24:22.746 benefit from expedited surgery or

NOTE Confidence: 0.896319028571429

00:24:22.746 --> 00:24:24.414 switching therapy and we don't know

NOTE Confidence: 0.896319028571429

00:24:24.414 --> 00:24:26.463 the answer to that because we've not

NOTE Confidence: 0.896319028571429

00:24:26.463 --> 00:24:28.588 had a good marker for assessing it.

00:24:28.588 --> 00:24:30.916 Currently we just use cross-sectional imaging

00:24:30.920 --> 00:24:34.119 which has a lot of limitations unfortunately.

00:24:34.120 --> 00:24:35.512 And then of course for those

00:24:35.512 --> 00:24:36.440 who retain their bladder,

00:24:36.440 --> 00:24:38.253 there's a question of whether or not

00:24:38.253 --> 00:24:40.026 a highly sensitive marker could be

00:24:40.026 --> 00:24:41.601 useful for monitoring and surveilling

00:24:41.601 --> 00:24:43.559 patients that underwent trimodal therapy.

00:24:43.560 --> 00:24:46.052 And so these are questions that we

00:24:46.052 --> 00:24:47.933 hope to interrogate in the future.

00:24:47.933 --> 00:24:49.559 We have about 20 patients that

00:24:49.559 --> 00:24:51.414 have muscle invasive bladder cancer

00:24:51.414 --> 00:24:53.314 before and after chemotherapy that

00:24:53.314 --> 00:24:54.977 have undergone radical cystectomy.

00:24:54.977 --> 00:24:57.353 So we're hoping to look into that at

00:24:57.353 --> 00:24:59.557 a small scale in the near future.

NOTE Confidence: 0.896319028571429

00:24:59.560 --> 00:25:01.710 And ultimately muscle that urinary

NOTE Confidence: 0.896319028571429

00:25:01.710 --> 00:25:04.503 DNA biomarker has to be integrated

NOTE Confidence: 0.896319028571429

00:25:04.503 --> 00:25:06.891 with broader with other biomarkers

NOTE Confidence: 0.896319028571429

00:25:06.891 --> 00:25:08.559 that are in development.

NOTE Confidence: 0.896319028571429

00:25:08.560 --> 00:25:10.814 So that would be another goal is

NOTE Confidence: 0.896319028571429

00:25:10.814 --> 00:25:13.041 to understand how it relates to

NOTE Confidence: 0.896319028571429

00:25:13.041 --> 00:25:13.839 other biomarkers.

NOTE Confidence: 0.896319028571429

00:25:13.840 --> 00:25:16.018 So I did want to talk about one other

NOTE Confidence: 0.896319028571429

00:25:16.018 --> 00:25:17.445 biomarker which was not probably new

NOTE Confidence: 0.896319028571429

00:25:17.445 --> 00:25:19.499 to to most of you as it's made-up quite

NOTE Confidence: 0.896319028571429

00:25:19.499 --> 00:25:21.336 a splash in a lot of different cancers.

NOTE Confidence: 0.896319028571429

00:25:21.336 --> 00:25:23.480 But I'm going to talk about its role

NOTE Confidence: 0.896319028571429

00:25:23.531 --> 00:25:25.290 in bladder cancer is circulating

NOTE Confidence: 0.896319028571429

00:25:25.290 --> 00:25:28.080 tumor DNA in in bladder cancer.

NOTE Confidence: 0.896319028571429

00:25:28.080 --> 00:25:31.184 This is also a very exciting area of

NOTE Confidence: 0.896319028571429

00:25:31.184 --> 00:25:33.788 our in this field in bladder cancer

NOTE Confidence: 0.896319028571429

00:25:33.788 --> 00:25:35.720 and it sort of started at least

NOTE Confidence: 0.896319028571429

00:25:35.720 --> 00:25:37.638 has come to the forefront in the

NOTE Confidence: 0.896319028571429

00:25:37.638 --> 00:25:39.320 setting of another clinical trial.

NOTE Confidence: 0.896319028571429

00:25:39.320 --> 00:25:41.874 This was a trial published in 2021,

NOTE Confidence: 0.896319028571429

00:25:41.874 --> 00:25:44.238 the use of adjuvant A tezalizumab

NOTE Confidence: 0.896319028571429

00:25:44.240 --> 00:25:47.120 for folks who have bladder cancer

NOTE Confidence: 0.896319028571429

00:25:47.120 --> 00:25:50.100 to try to reduce basically increased

NOTE Confidence: 0.896319028571429

00:25:50.100 --> 00:25:51.840 disease free survival in these folks.

NOTE Confidence: 0.896319028571429

00:25:51.840 --> 00:25:53.842 So these are high risk folks that

NOTE Confidence: 0.896319028571429

00:25:53.842 --> 00:25:55.986 had disease on final pathology after

NOTE Confidence: 0.896319028571429

00:25:55.986 --> 00:25:58.016 cystectomy and they were randomized

NOTE Confidence: 0.896319028571429

00:25:58.016 --> 00:26:00.832 to receipt the receipt of a checkpoint

NOTE Confidence: 0.896319028571429

00:26:00.832 --> 00:26:02.752 inhibitor at tesolizumab and the

NOTE Confidence: 0.896319028571429

00:26:02.752 --> 00:26:04.256 this trial unfortunately ultimately

NOTE Confidence: 0.896319028571429

00:26:04.256 --> 00:26:06.968 was a negative trial didn't show an

NOTE Confidence: 0.896319028571429

00:26:06.968 --> 00:26:08.878 improvement in disease free survival.

NOTE Confidence: 0.896319028571429

00:26:08.880 --> 00:26:11.616 But one subsequent study that resulted

NOTE Confidence: 0.896319028571429

00:26:11.616 --> 00:26:14.544 from analysis of these data was re

NOTE Confidence: 0.896319028571429

00:26:14.544 --> 00:26:16.664 analyzing the clinical data based

NOTE Confidence: 0.896319028571429

00:26:16.664 --> 00:26:18.886 on substrata for circulating tumor

NOTE Confidence: 0.896319028571429

00:26:18.886 --> 00:26:19.800 DNA positivity.

NOTE Confidence: 0.896319028571429

00:26:19.800 --> 00:26:21.564 And so I'm going to show you some of

NOTE Confidence: 0.896319028571429

00:26:21.564 --> 00:26:23.167 the data from this paper published

NOTE Confidence: 0.896319028571429

00:26:23.167 --> 00:26:26.800 in in in Nature 2021, May 2021.

NOTE Confidence: 0.896319028571429

00:26:26.800 --> 00:26:30.658 You can see here that the data are

NOTE Confidence: 0.896319028571429

00:26:30.658 --> 00:26:32.834 stratified by observation in the

NOTE Confidence: 0.896319028571429

00:26:32.834 --> 00:26:34.976 orange versus the blue receipt of

NOTE Confidence: 0.896319028571429

00:26:34.976 --> 00:26:35.690 a tesolizumab

NOTE Confidence: 0.824925120714286

00:26:35.758 --> 00:26:38.118 in the adjuvant setting and circulating

NOTE Confidence: 0.824925120714286

00:26:38.118 --> 00:26:40.632 tumor DNA negative up top and

NOTE Confidence: 0.824925120714286

00:26:40.632 --> 00:26:42.799 circulating tumor DNA positive below.

NOTE Confidence: 0.824925120714286

00:26:42.800 --> 00:26:44.508 And one thing that's clear is that

NOTE Confidence: 0.824925120714286

00:26:44.508 --> 00:26:46.485 CT DNA this is a tumor informed

NOTE Confidence: 0.824925120714286

00:26:46.485 --> 00:26:48.053 biomarker in this setting is

NOTE Confidence: 0.824925120714286

00:26:48.053 --> 00:26:49.918 quite prognostic if nothing else.

NOTE Confidence: 0.824925120714286

00:26:49.920 --> 00:26:51.412 It clearly distinguishes patients

NOTE Confidence: 0.824925120714286

00:26:51.412 --> 00:26:53.277 who have poorer outcomes from

NOTE Confidence: 0.824925120714286

00:26:53.277 --> 00:26:55.276 those who do better and it reflect,

NOTE Confidence: 0.824925120714286

00:26:55.280 --> 00:26:58.976 it seems to reflect some residual disease

NOTE Confidence: 0.824925120714286

00:26:58.976 --> 00:27:01.356 after cystectomy which is pretty intuitive.

NOTE Confidence: 0.824925120714286

00:27:01.356 --> 00:27:03.779 But one of the signals that's really

NOTE Confidence: 0.824925120714286

00:27:03.779 --> 00:27:06.453 important here is that the folks who

NOTE Confidence: 0.824925120714286

00:27:06.453 --> 00:27:07.958 received atesalizumab with CTDNA

NOTE Confidence: 0.824925120714286

00:27:07.958 --> 00:27:09.710 positivity clearly experienced the

NOTE Confidence: 0.824925120714286

00:27:09.710 --> 00:27:11.900 benefit in disease free survival

NOTE Confidence: 0.824925120714286

00:27:11.960 --> 00:27:13.970 based on this reanalysis and this

NOTE Confidence: 0.824925120714286

00:27:13.970 --> 00:27:15.395 is an overall survival reanalysis.

NOTE Confidence: 0.824925120714286

00:27:15.400 --> 00:27:16.835 Again, this is not a randomized trial.

NOTE Confidence: 0.824925120714286

00:27:16.840 --> 00:27:20.384 This is, this is a reinterpretation

NOTE Confidence: 0.824925120714286

00:27:20.384 --> 00:27:22.914 from this invigor 10 study.

NOTE Confidence: 0.824925120714286

00:27:22.920 --> 00:27:25.288 And what you can see here again is

NOTE Confidence: 0.824925120714286

00:27:25.288 --> 00:27:28.160 that is that adjuvant therapy for folks

NOTE Confidence: 0.824925120714286

00:27:28.160 --> 00:27:30.706 who have detectable circulating tumor

NOTE Confidence: 0.824925120714286

00:27:30.706 --> 00:27:34.225 DNA is is really seems to reflect

NOTE Confidence: 0.824925120714286

00:27:34.225 --> 00:27:36.400 a benefit for adjuvant therapy.

NOTE Confidence: 0.824925120714286

00:27:36.400 --> 00:27:39.118 It's pretty exciting because we know

NOTE Confidence: 0.824925120714286

00:27:39.118 --> 00:27:41.440 that with adjuvant therapy we are

NOTE Confidence: 0.824925120714286

00:27:41.440 --> 00:27:43.673 we're delivering a lot of therapy to

NOTE Confidence: 0.824925120714286

00:27:43.673 --> 00:27:45.997 some patients who don't have any cancer.

NOTE Confidence: 0.824925120714286

00:27:46.000 --> 00:27:47.440 These are all these patients have

NOTE Confidence: 0.824925120714286

00:27:47.440 --> 00:27:48.958 no evidence of disease at the time,

NOTE Confidence: 0.824925120714286

00:27:48.960 --> 00:27:51.074 they just have a risk of recurrence.

NOTE Confidence: 0.824925120714286

00:27:51.080 --> 00:27:53.888 And so the idea of being able to parse

NOTE Confidence: 0.824925120714286

00:27:53.888 --> 00:27:55.914 out residual disease and hopefully

NOTE Confidence: 0.824925120714286

00:27:55.914 --> 00:27:58.874 make sort of the idea of adjuvant

NOTE Confidence: 0.824925120714286

00:27:58.874 --> 00:28:01.200 therapy a little bit to move past

NOTE Confidence: 0.824925120714286

00:28:01.200 --> 00:28:02.400 that would is a really exciting

NOTE Confidence: 0.824925120714286

00:28:02.400 --> 00:28:03.480 thing I think for patients,

NOTE Confidence: 0.824925120714286

00:28:03.480 --> 00:28:05.358 hopefully minimizing over

NOTE Confidence: 0.824925120714286

00:28:05.358 --> 00:28:07.236 treatment of patients.

NOTE Confidence: 0.824925120714286

00:28:07.240 --> 00:28:08.800 These results have led to the

NOTE Confidence: 0.824925120714286

00:28:08.800 --> 00:28:10.837 development of a new study of Vigor 11,

NOTE Confidence: 0.824925120714286

00:28:10.840 --> 00:28:14.460 which is a a biomarker driven randomized

NOTE Confidence: 0.824925120714286

00:28:14.460 --> 00:28:16.460 trial to administer atizolizumab

NOTE Confidence: 0.824925120714286

00:28:16.460 --> 00:28:18.960 for CT DNA positive patients.

NOTE Confidence: 0.824925120714286

00:28:18.960 --> 00:28:20.688 So to try to validate these

NOTE Confidence: 0.824925120714286

00:28:20.688 --> 00:28:21.840 in a prospective fashion,

NOTE Confidence: 0.824925120714286

00:28:21.840 --> 00:28:22.880 I mean this is not,

NOTE Confidence: 0.824925120714286

00:28:22.880 --> 00:28:24.196 I know this is a busy slide,

NOTE Confidence: 0.824925120714286

00:28:24.200 --> 00:28:26.617 but this is not meant to be read just as

NOTE Confidence: 0.824925120714286

00:28:26.617 --> 00:28:28.639 a reference for anyone who's interested.

NOTE Confidence: 0.824925120714286

00:28:28.640 --> 00:28:30.360 So this is this trial's ongoing and it's,

NOTE Confidence: 0.824925120714286

00:28:30.360 --> 00:28:32.136 it's very exciting and many of

NOTE Confidence: 0.824925120714286

00:28:32.136 --> 00:28:34.050 you who treat other cancers will

NOTE Confidence: 0.824925120714286

00:28:34.050 --> 00:28:36.060 know that they're really good data

NOTE Confidence: 0.824925120714286

00:28:36.060 --> 00:28:37.340 for similar biomarkers,

NOTE Confidence: 0.824925120714286

00:28:37.340 --> 00:28:39.220 circulating tumor biomarkers now

NOTE Confidence: 0.824925120714286

00:28:39.220 --> 00:28:41.547 in colorectal cancer and lung

NOTE Confidence: 0.824925120714286

00:28:41.547 --> 00:28:43.477 cancer and several other cancers.

NOTE Confidence: 0.824925120714286

00:28:43.480 --> 00:28:46.112 This trial has a disease free survival

NOTE Confidence: 0.824925120714286

00:28:46.112 --> 00:28:48.197 primary endpoint and I I do want to

NOTE Confidence: 0.824925120714286

00:28:48.200 --> 00:28:51.023 touch on that a little bit because

54

NOTE Confidence: 0.824925120714286

00:28:51.023 --> 00:28:53.144 the right way to answer this question

NOTE Confidence: 0.824925120714286

00:28:53.144 --> 00:28:55.548 is a is a prospective clinical trial

NOTE Confidence: 0.824925120714286

00:28:55.548 --> 00:28:57.592 that is the gold standard therapy

NOTE Confidence: 0.824925120714286

00:28:57.592 --> 00:28:59.464 and excuse me gold standard approach

NOTE Confidence: 0.824925120714286

00:28:59.464 --> 00:29:01.616 to answering a question like a

NOTE Confidence: 0.824925120714286

00:29:01.616 --> 00:29:03.160 therapeutic intervention like this.

NOTE Confidence: 0.824925120714286

00:29:03.160 --> 00:29:05.162 But clinical trials as many of you

NOTE Confidence: 0.824925120714286

00:29:05.162 --> 00:29:06.415 know have significant challenges

NOTE Confidence: 0.824925120714286

00:29:06.415 --> 00:29:08.115 and are difficult to conduct.

NOTE Confidence: 0.824925120714286

00:29:08.120 --> 00:29:10.056 They're quite resource intensive

NOTE Confidence: 0.824925120714286

00:29:10.056 --> 00:29:12.960 and they do face challenges for

NOTE Confidence: 0.824925120714286

00:29:12.960 --> 00:29:16.173 accrual of patients and and and

NOTE Confidence: 0.824925120714286

00:29:16.173 --> 00:29:18.838 completion within certain time points.

NOTE Confidence: 0.824925120714286

00:29:18.840 --> 00:29:21.558 And so I did want to talk about one

NOTE Confidence: 0.824925120714286

00:29:21.558 --> 00:29:23.773 particular challenge with these is

NOTE Confidence: 0.824925120714286

00:29:23.773 --> 00:29:26.073 endpoint selection and clinical trials.

NOTE Confidence: 0.824925120714286

00:29:26.080 --> 00:29:27.868 So surrogate endpoints have been a

NOTE Confidence: 0.824925120714286

00:29:27.868 --> 00:29:30.885 a bit of a topic in clinical trial

NOTE Confidence: 0.824925120714286

00:29:30.885 --> 00:29:33.075 design and implementation science over

NOTE Confidence: 0.824925120714286

00:29:33.075 --> 00:29:35.742 the last 10-15 years or so at least.

NOTE Confidence: 0.824925120714286

00:29:35.742 --> 00:29:38.199 And and just to define the term,

NOTE Confidence: 0.880171584444444

00:29:38.200 --> 00:29:40.420 surrogate endpoints are are outcomes

NOTE Confidence: 0.880171584444444

00:29:40.420 --> 00:29:42.876 that themselves are not known to

NOTE Confidence: 0.880171584444444

00:29:42.876 --> 00:29:44.904 have a clinical benefit but are

NOTE Confidence: 0.880171584444444

00:29:44.904 --> 00:29:47.131 thought or known to predict an

NOTE Confidence: 0.880171584444444

00:29:47.131 --> 00:29:49.357 outcome that has a clinical benefit.

NOTE Confidence: 0.880171584444444

00:29:49.360 --> 00:29:51.880 So they do not themselves carry

NOTE Confidence: 0.880171584444444

00:29:51.880 --> 00:29:53.560 a lot of meaning.

NOTE Confidence: 0.880171584444444

00:29:53.560 --> 00:29:55.534 They carry meaning because we think they're

NOTE Confidence: 0.880171584444444

00:29:55.534 --> 00:29:57.359 related to something that carries meaning,

NOTE Confidence: 0.880171584444444

00:29:57.360 --> 00:29:59.752 does that pretty, pretty reasonable.

NOTE Confidence: 0.880171584444444

00:29:59.752 --> 00:30:02.160 So they're used as a substitute and

NOTE Confidence: 0.880171584444444

00:30:02.220 --> 00:30:04.300 they're thought to predict clinical

NOTE Confidence: 0.880171584444444

00:30:04.300 --> 00:30:07.680 endpoints and they're increasing in use,

NOTE Confidence: 0.880171584444444

00:30:07.680 --> 00:30:08.880 they're becoming more and more frequent.

NOTE Confidence: 0.880171584444444

00:30:08.880 --> 00:30:11.372 I really like this study from JAMA

NOTE Confidence: 0.880171584444444

00:30:11.372 --> 00:30:13.328 Oncology which tracks the proportion

NOTE Confidence: 0.880171584444444

00:30:13.328 --> 00:30:15.378 of randomized clinical trials and

NOTE Confidence: 0.880171584444444

00:30:15.378 --> 00:30:18.300 these are endpoints that are used in

NOTE Confidence: 0.880171584444444

00:30:18.300 --> 00:30:20.400 various clinical trials over time.

NOTE Confidence: 0.880171584444444

00:30:20.400 --> 00:30:22.286 And you could see that overall survival's

NOTE Confidence: 0.880171584444444

00:30:22.286 --> 00:30:23.716 the most common clinical endpoint.

NOTE Confidence: 0.880171584444444

00:30:23.720 --> 00:30:25.204 And then you could see that it's

NOTE Confidence: 0.880171584444444

00:30:25.204 --> 00:30:26.727 kind of become falling out of

NOTE Confidence: 0.880171584444444

00:30:26.727 --> 00:30:27.839 favour in randomized trials.

NOTE Confidence: 0.880171584444444

00:30:27.840 --> 00:30:29.645 While progression free survival for

NOTE Confidence: 0.880171584444444

00:30:29.645 --> 00:30:32.275 example in is becoming more and more

NOTE Confidence: 0.880171584444444

00:30:32.275 --> 00:30:34.195 popular in randomized clinical trials.

NOTE Confidence: 0.880171584444444

00:30:34.200 --> 00:30:36.139 And I I think not UN coincidentally

NOTE Confidence: 0.880171584444444

00:30:36.139 --> 00:30:37.671 industry funding is also significantly

NOTE Confidence: 0.880171584444444

00:30:37.671 --> 00:30:39.932 increasing in these in these studies and

NOTE Confidence: 0.880171584444444

00:30:39.932 --> 00:30:42.244 what the study concludes is that the use

NOTE Confidence: 0.880171584444444

00:30:42.244 --> 00:30:45.438 of progression free survival is increasing.

NOTE Confidence: 0.880171584444444

00:30:45.440 --> 00:30:47.624 Progression free survival is more likely

NOTE Confidence: 0.880171584444444

00:30:47.624 --> 00:30:50.419 to be a positive trial if you use PFS

NOTE Confidence: 0.880171584444444

00:30:50.419 --> 00:30:52.720 rather than OS in a clinical trial.

NOTE Confidence: 0.880171584444444

00:30:52.720 --> 00:30:56.932 And and and it's becoming like I say it's

NOTE Confidence: 0.880171584444444

00:30:56.932 --> 00:31:00.344 it's become the the major most common

NOTE Confidence: 0.880171584444444

00:31:00.344 --> 00:31:03.080 endpoint used in clinical trials now.

NOTE Confidence: 0.880171584444444

00:31:03.080 --> 00:31:05.864 So why should be should we be worried

NOTE Confidence: 0.880171584444444

00:31:05.864 --> 00:31:07.838 or cautious about this trend?

NOTE Confidence: 0.880171584444444

00:31:07.840 --> 00:31:08.376 Well,

NOTE Confidence: 0.880171584444444

00:31:08.376 --> 00:31:10.796 the assumption when a surrogate

NOTE Confidence: 0.880171584444444

00:31:10.796 --> 00:31:12.728 endpoint is used is that there's some

NOTE Confidence: 0.880171584444444

00:31:12.728 --> 00:31:14.398 cause for the patient's illness,

NOTE Confidence: 0.880171584444444

00:31:14.400 --> 00:31:16.056 you know their malignancy.

NOTE Confidence: 0.880171584444444

00:31:16.056 --> 00:31:18.540 We detect some surrogate endpoint like

NOTE Confidence: 0.880171584444444

00:31:18.607 --> 00:31:20.629 progression free survival and that in

NOTE Confidence: 0.880171584444444

00:31:20.629 --> 00:31:23.530 turn leads to a clinical endpoint like

NOTE Confidence: 0.880171584444444

00:31:23.530 --> 00:31:26.000 there's the patient's overall survival.

NOTE Confidence: 0.880171584444444

00:31:26.000 --> 00:31:28.240 But as we all know that 'cause

NOTE Confidence: 0.880171584444444

00:31:28.240 --> 00:31:29.826 this cause causality scheme,

NOTE Confidence: 0.880171584444444

00:31:29.826 --> 00:31:32.358 this causation scheme is not always

NOTE Confidence: 0.880171584444444

00:31:32.358 --> 00:31:34.995 quite as direct cause can be related to

NOTE Confidence: 0.880171584444444

00:31:34.995 --> 00:31:36.880 the endpoint in multiple different ways.

NOTE Confidence: 0.880171584444444

00:31:36.880 --> 00:31:39.382 And so we really have to be kind of

NOTE Confidence: 0.880171584444444

00:31:39.382 --> 00:31:41.098 cautious about assuming this level

NOTE Confidence: 0.880171584444444

00:31:41.098 --> 00:31:43.450 A and there are ways to validate

NOTE Confidence: 0.880171584444444

00:31:43.450 --> 00:31:44.120 surrogate endpoints.

NOTE Confidence: 0.880171584444444

00:31:44.120 --> 00:31:46.178 People have done this in the past

NOTE Confidence: 0.880171584444444

00:31:46.178 --> 00:31:48.049 where they we can look at clinical

NOTE Confidence: 0.880171584444444

00:31:48.049 --> 00:31:50.183 data and try to make sure to that

NOTE Confidence: 0.880171584444444

00:31:50.183 --> 00:31:52.048 the surrogate endpoint is truly

NOTE Confidence: 0.880171584444444

00:31:52.048 --> 00:31:53.540 causally linked or significantly

NOTE Confidence: 0.880171584444444

00:31:53.599 --> 00:31:55.439 predictive of a clinical endpoint.

NOTE Confidence: 0.880171584444444

00:31:55.440 --> 00:31:57.464 And the answer seems to be it kind

NOTE Confidence: 0.880171584444444

00:31:57.464 --> 00:31:59.464 of varies whether or not a surrogate

NOTE Confidence: 0.880171584444444

00:31:59.464 --> 00:32:02.000 endpoint is linked to a clinical endpoint.

NOTE Confidence: 0.880171584444444

00:32:02.000 --> 00:32:02.822 It varies on,

NOTE Confidence: 0.880171584444444

00:32:02.822 --> 00:32:04.740 it varies based on the cancer and

NOTE Confidence: 0.880171584444444

00:32:04.806 --> 00:32:06.558 the specific clinical details.

NOTE Confidence: 0.880171584444444

00:32:06.560 --> 00:32:08.704 So this is an another paper that looked

NOTE Confidence: 0.880171584444444

00:32:08.704 --> 00:32:10.767 at the meta analysis of surrogate

NOTE Confidence: 0.880171584444444

00:32:10.767 --> 00:32:12.969 endpoints in various trials and it's

NOTE Confidence: 0.880171584444444

00:32:13.029 --> 00:32:15.066 not always the case that they do

NOTE Confidence: 0.880171584444444

00:32:15.066 --> 00:32:18.344 predict the clinical endpoint with

NOTE Confidence: 0.880171584444444

00:32:18.344 --> 00:32:20.800 with reliability. This is a big table.

NOTE Confidence: 0.880171584444444

00:32:20.800 --> 00:32:21.152 We don't,

NOTE Confidence: 0.880171584444444

00:32:21.152 --> 00:32:22.800 I'm not going to go through all of that.

NOTE Confidence: 0.880171584444444

00:32:22.800 --> 00:32:24.312 This is not again not meant to be read,

NOTE Confidence: 0.880171584444444

00:32:24.320 --> 00:32:26.592 but just to say that this meta analysis

NOTE Confidence: 0.880171584444444

00:32:26.592 --> 00:32:28.201 looked at multiple various trials

NOTE Confidence: 0.880171584444444

00:32:28.201 --> 00:32:30.476 in the past in areas of medicine

NOTE Confidence: 0.880171584444444

00:32:30.480 --> 00:32:31.950 where we use the surrogate endpoint

NOTE Confidence: 0.880171584444444

00:32:31.950 --> 00:32:32.930 and we found that

NOTE Confidence: 0.813315816875

00:32:32.985 --> 00:32:34.839 when the clinical endpoint was measured,

NOTE Confidence: 0.813315816875

00:32:34.840 --> 00:32:37.114 we really did ultimately find that

NOTE Confidence: 0.813315816875

00:32:37.114 --> 00:32:39.599 they were not predictive of each other.

NOTE Confidence: 0.813315816875

00:32:39.600 --> 00:32:41.502 And I think one really telling

NOTE Confidence: 0.813315816875

00:32:41.502 --> 00:32:43.880 example of this is the cast trials.

NOTE Confidence: 0.813315816875

00:32:43.880 --> 00:32:46.239 This was a trial in cardiology which

NOTE Confidence: 0.813315816875

00:32:46.239 --> 00:32:48.440 looked at patients who would experience

NOTE Confidence: 0.813315816875

00:32:48.440 --> 00:32:50.340 myocardial infarctions in the past

NOTE Confidence: 0.813315816875

00:32:50.340 --> 00:32:52.824 who had had ventric experienced

NOTE Confidence: 0.813315816875

00:32:52.824 --> 00:32:54.357 intermittent ventricular arrhythmia.

NOTE Confidence: 0.813315816875

00:32:54.360 --> 00:32:56.929 And the common thought prior to this

NOTE Confidence: 0.813315816875

00:32:56.929 --> 00:32:59.274 publication of the study in 1991

NOTE Confidence: 0.813315816875

00:32:59.274 --> 00:33:01.810 was medications anti arrhythmics

NOTE Confidence: 0.813315816875

00:33:01.810 --> 00:33:03.744 that decrease ventricular arrhythmia

NOTE Confidence: 0.813315816875

00:33:03.744 --> 00:33:05.736 would also decrease the risk of

NOTE Confidence: 0.813315816875

00:33:05.736 --> 00:33:07.320 sudden cardiac death in patients.

NOTE Confidence: 0.813315816875

00:33:07.320 --> 00:33:09.120 And so these were quite commonly

NOTE Confidence: 0.813315816875

00:33:09.120 --> 00:33:11.424 used at the time until a a pretty

NOTE Confidence: 0.813315816875

00:33:11.424 --> 00:33:13.080 heroic I think and really brave

NOTE Confidence: 0.813315816875

00:33:13.147 --> 00:33:15.049 study was performed this CAST trial

NOTE Confidence: 0.813315816875

00:33:15.049 --> 00:33:17.895 it was published in 1991 and what

NOTE Confidence: 0.813315816875

00:33:17.895 --> 00:33:20.520 they found was pretty striking.

NOTE Confidence: 0.813315816875

00:33:20.520 --> 00:33:22.320 Patients who received placebo

NOTE Confidence: 0.813315816875

00:33:22.320 --> 00:33:24.120 did significantly better than

NOTE Confidence: 0.813315816875

00:33:24.120 --> 00:33:26.306 patients who did who received anti

NOTE Confidence: 0.813315816875

00:33:26.306 --> 00:33:28.358 arrhythmics in the post MI period.

NOTE Confidence: 0.813315816875

00:33:28.360 --> 00:33:30.250 In fact mortality was was almost

NOTE Confidence: 0.813315816875

00:33:30.250 --> 00:33:31.960 double in the patients who

NOTE Confidence: 0.813315816875

00:33:31.960 --> 00:33:33.516 received the intervention arm.

NOTE Confidence: 0.813315816875

00:33:33.520 --> 00:33:34.336 And in you know,

NOTE Confidence: 0.813315816875

00:33:34.336 --> 00:33:35.880 as I was learning about this trial,

NOTE Confidence: 0.813315816875

00:33:35.880 --> 00:33:38.078 I read an editorial by a cardiologist

NOTE Confidence: 0.813315816875

00:33:38.078 --> 00:33:40.040 who was reflecting on this and said,

NOTE Confidence: 0.813315816875

00:33:40.040 --> 00:33:41.350 you know most Americans can

NOTE Confidence: 0.813315816875

63

00:33:41.350 --> 00:33:42.660 remember where they were when

NOTE Confidence: 0.813315816875

00:33:42.709 --> 00:33:44.317 President Kennedy was assassinated.

NOTE Confidence: 0.813315816875

00:33:44.320 --> 00:33:45.775 And every cardiologist can remember

NOTE Confidence: 0.813315816875

00:33:45.775 --> 00:33:47.880 where they were when the cast trial

NOTE Confidence: 0.813315816875

00:33:47.880 --> 00:33:49.662 was published because it was really

NOTE Confidence: 0.813315816875

00:33:49.662 --> 00:33:51.850 striking and and and it sort of

NOTE Confidence: 0.813315816875

00:33:51.850 --> 00:33:54.211 highlights I think the importance of

NOTE Confidence: 0.813315816875

00:33:54.211 --> 00:33:56.771 validating any assumed benefit from

NOTE Confidence: 0.813315816875

00:33:56.771 --> 00:33:59.080 clinical from surrogate endpoints.

NOTE Confidence: 0.813315816875

00:33:59.080 --> 00:34:00.235 So people have tried to do this

NOTE Confidence: 0.813315816875

00:34:00.235 --> 00:34:01.639 and like I say it kind of varies.

NOTE Confidence: 0.813315816875

00:34:01.640 --> 00:34:03.740 So this is again a big trial is a big

NOTE Confidence: 0.813315816875

00:34:03.806 --> 00:34:06.200 table not again not meant to be read here,

NOTE Confidence: 0.813315816875

00:34:06.200 --> 00:34:08.097 but what you can see is that

NOTE Confidence: 0.813315816875

00:34:08.097 --> 00:34:09.664 whether a surrogate endpoint is

NOTE Confidence: 0.813315816875

00:34:09.664 --> 00:34:11.399 helpful depends on the setting.

NOTE Confidence: 0.813315816875

00:34:11.400 --> 00:34:13.871 So this multiple studies have shown that

NOTE Confidence: 0.813315816875

00:34:13.871 --> 00:34:15.796 progression free survival and advanced

NOTE Confidence: 0.813315816875

00:34:15.796 --> 00:34:17.404 through metastatic colorectal cancer

NOTE Confidence: 0.813315816875

00:34:17.404 --> 00:34:19.637 is a reasonable surrogate for overall

NOTE Confidence: 0.813315816875

00:34:19.637 --> 00:34:21.632 survival in in many of these trials.

NOTE Confidence: 0.813315816875

00:34:21.640 --> 00:34:23.467 Whereas in breast cancer it seems to

NOTE Confidence: 0.813315816875

00:34:23.467 --> 00:34:26.084 not be a a good surrogate and and

NOTE Confidence: 0.813315816875

00:34:26.084 --> 00:34:29.370 it has to be done on an individual

NOTE Confidence: 0.813315816875

00:34:29.370 --> 00:34:31.680 basis for each cancer for each stage.

NOTE Confidence: 0.813315816875

00:34:31.680 --> 00:34:33.522 It's really quite quite important work

NOTE Confidence: 0.813315816875

00:34:33.522 --> 00:34:35.840 because we rely on them significantly.

NOTE Confidence: 0.813315816875

00:34:35.840 --> 00:34:36.960 This is a paper demonstrating

NOTE Confidence: 0.813315816875

00:34:36.960 --> 00:34:38.360 how much we rely on them.

NOTE Confidence: 0.813315816875

00:34:38.360 --> 00:34:40.808 This is a paper published in JAMA in

NOTE Confidence: 0.813315816875

00:34:40.808 --> 00:34:43.262 2020 and what you what they demonstrate

NOTE Confidence: 0.813315816875

00:34:43.262 --> 00:34:45.079 by evaluating FDA acceptance based

NOTE Confidence: 0.813315816875

00:34:45.079 --> 00:34:47.017 on surrogate endpoints is that the

NOTE Confidence: 0.813315816875

00:34:47.017 --> 00:34:49.049 use of surrogate endpoints is is

NOTE Confidence: 0.813315816875

00:34:49.049 --> 00:34:50.714 increasing like we talked about

NOTE Confidence: 0.813315816875

00:34:50.720 --> 00:34:54.479 and 61% of new medication of of

NOTE Confidence: 0.813315816875

00:34:54.480 --> 00:34:56.295 medications that are approved based

NOTE Confidence: 0.813315816875

00:34:56.295 --> 00:34:58.110 on surrogate endpoints are based

NOTE Confidence: 0.813315816875

00:34:58.170 --> 00:35:00.080 on endpoints that have not been

NOTE Confidence: 0.813315816875

00:35:00.080 --> 00:35:02.680 validated or lack correlation studies.

NOTE Confidence: 0.813315816875

00:35:02.680 --> 00:35:04.648 So we really don't know if the surrogate

NOTE Confidence: 0.813315816875

00:35:04.648 --> 00:35:06.449 is related to the endpoint we really

NOTE Confidence: 0.813315816875

00:35:06.449 --> 00:35:08.077 care about which is making patients

NOTE Confidence: 0.813315816875

00:35:08.077 --> 00:35:10.317 live longer or making patients live happier,

NOTE Confidence: 0.813315816875

00:35:10.320 --> 00:35:12.054 healthier or you know lives that

NOTE Confidence: 0.813315816875

00:35:12.054 --> 00:35:13.680 are have better quality of life.

NOTE Confidence: 0.813315816875

00:35:13.680 --> 00:35:17.432 I guess 61% of the time we don't

NOTE Confidence: 0.813315816875

00:35:17.432 --> 00:35:18.680 have a a link,

NOTE Confidence: 0.813315816875

00:35:18.680 --> 00:35:20.661 16% of the time we use them

NOTE Confidence: 0.813315816875

00:35:20.661 --> 00:35:21.510 despite data demonstrating

NOTE Confidence: 0.850934634615385

00:35:21.571 --> 00:35:23.888 a poor connect, a poor link between

NOTE Confidence: 0.850934634615385

00:35:23.888 --> 00:35:25.798 surrogate endpoints and overall survival.

NOTE Confidence: 0.850934634615385

00:35:25.800 --> 00:35:29.088 And only 5% of the time is there

NOTE Confidence: 0.850934634615385

00:35:29.088 --> 00:35:31.519 a established high correlation.

NOTE Confidence: 0.850934634615385

00:35:31.520 --> 00:35:35.055 There is a a post marketing requirement

NOTE Confidence: 0.850934634615385

00:35:35.055 --> 00:35:37.160 for medications that are approved based

NOTE Confidence: 0.850934634615385

00:35:37.160 --> 00:35:39.032 on surrogate endpoints and this paper

NOTE Confidence: 0.850934634615385

00:35:39.032 --> 00:35:41.160 demonstrates that upwards of 1/3 of them,

NOTE Confidence: 0.850934634615385

00:35:41.160 --> 00:35:42.715 third of trials don't report

NOTE Confidence: 0.850934634615385

00:35:42.715 --> 00:35:43.959 within the time period.

NOTE Confidence: 0.850934634615385

00:35:43.960 --> 00:35:45.396 So in bladder cancer,

NOTE Confidence: 0.850934634615385

00:35:45.396 --> 00:35:47.999 we do use surrogate endpoints quite a bit.

NOTE Confidence: 0.850934634615385

00:35:48.000 --> 00:35:50.640 We rely on them really heavily.

NOTE Confidence: 0.850934634615385

00:35:50.640 --> 00:35:52.158 Here's an example from bladder cancer,

NOTE Confidence: 0.850934634615385

00:35:52.160 --> 00:35:54.200 which we won't go into a whole lot,

NOTE Confidence: 0.850934634615385

00:35:54.200 --> 00:35:56.200 but this is a paper published in 2017,

NOTE Confidence: 0.850934634615385

00:35:56.200 --> 00:35:58.300 which is a single arm phase two

NOTE Confidence: 0.850934634615385

00:35:58.300 --> 00:35:59.960 trial that evaluated atezalizumab

NOTE Confidence: 0.850934634615385

00:35:59.960 --> 00:36:02.360 in a very difficult population.

NOTE Confidence: 0.850934634615385

00:36:02.360 --> 00:36:04.472 This is cisplatin ineligible

NOTE Confidence: 0.850934634615385

00:36:04.472 --> 00:36:06.200 patients in the second line setting.

NOTE Confidence: 0.850934634615385

00:36:06.200 --> 00:36:09.399 This was about 119 patients were enrolled,

NOTE Confidence: 0.850934634615385

00:36:09.400 --> 00:36:11.225 102 of them discontinued therapy

NOTE Confidence: 0.850934634615385

00:36:11.225 --> 00:36:12.986 because of progression and objective

NOTE Confidence: 0.850934634615385

00:36:12.986 --> 00:36:15.355 response rates were in 23% or so at a

NOTE Confidence: 0.850934634615385

00:36:15.355 --> 00:36:16.960 median follow up of about 17 months.

NOTE Confidence: 0.850934634615385

00:36:16.960 --> 00:36:19.200 So this wasn't a home run thing,

NOTE Confidence: 0.850934634615385

00:36:19.200 --> 00:36:20.348 This wasn't, this was,

NOTE Confidence: 0.850934634615385

00:36:20.348 --> 00:36:22.954 this was a a signal and a difficult

NOTE Confidence: 0.850934634615385

00:36:22.954 --> 00:36:24.984 population and it resulted in

NOTE Confidence: 0.850934634615385

00:36:24.984 --> 00:36:27.006 accelerated approval by the FDA

NOTE Confidence: 0.850934634615385

00:36:27.006 --> 00:36:28.836 for atizalizumab in this setting.

NOTE Confidence: 0.850934634615385

00:36:28.840 --> 00:36:31.038 And this is just as an aside,

NOTE Confidence: 0.850934634615385

00:36:31.040 --> 00:36:32.680 multiple cost effectiveness analysis

NOTE Confidence: 0.850934634615385

00:36:32.680 --> 00:36:35.645 of this drug show that it it's

NOTE Confidence: 0.850934634615385

00:36:35.645 --> 00:36:37.795 really quite costly to administer,

NOTE Confidence: 0.850934634615385

00:36:37.800 --> 00:36:38.880 you know,

NOTE Confidence: 0.850934634615385

00:36:38.880 --> 00:36:41.620 upwards of $400,000 per quality adjusted

NOTE Confidence: 0.850934634615385

00:36:41.620 --> 00:36:45.079 life here for a tesolizumab in this setting.

NOTE Confidence: 0.850934634615385

00:36:45.080 --> 00:36:46.784 And we learned about five years

NOTE Confidence: 0.850934634615385

00:36:46.784 --> 00:36:48.560 later that it was withdrawn.

NOTE Confidence: 0.850934634615385

00:36:48.560 --> 00:36:50.807 And it was withdrawn because the final

NOTE Confidence: 0.850934634615385

00:36:50.807 --> 00:36:52.949 data reported out that overall survival

NOTE Confidence: 0.850934634615385

00:36:52.949 --> 00:36:55.560 benefits were not detected in this setting.

NOTE Confidence: 0.850934634615385

00:36:55.560 --> 00:36:56.252 Now some might say,

NOTE Confidence: 0.850934634615385

00:36:56.252 --> 00:36:57.304 all right, well that's,

NOTE Confidence: 0.850934634615385

00:36:57.304 --> 00:36:58.360 that's, that's showbiz.

NOTE Confidence: 0.850934634615385

00:36:58.360 --> 00:36:59.200 That's the cost of it.

NOTE Confidence: 0.850934634615385

00:36:59.200 --> 00:37:01.180 You know sometimes you approve drugs

NOTE Confidence: 0.850934634615385

00:37:01.180 --> 00:37:03.156 and you give patients drugs that

NOTE Confidence: 0.850934634615385

00:37:03.156 --> 00:37:05.235 don't do that much benefit for them,

NOTE Confidence: 0.850934634615385

00:37:05.240 --> 00:37:06.759 but at least they get them faster.

NOTE Confidence: 0.850934634615385

00:37:06.760 --> 00:37:08.560 You know and what I would say is

NOTE Confidence: 0.850934634615385

00:37:08.560 --> 00:37:10.790 that the the effect is can often be

NOTE Confidence: 0.850934634615385

00:37:10.790 --> 00:37:12.523 more widespread than than we really

NOTE Confidence: 0.850934634615385

00:37:12.523 --> 00:37:14.371 think about at least than than I

NOTE Confidence: 0.850934634615385

00:37:14.371 --> 00:37:18.784 think about this is a a paper that

NOTE Confidence: 0.850934634615385

00:37:18.784 --> 00:37:21.141 was published by the folks at the

NOTE Confidence: 0.850934634615385

00:37:21.141 --> 00:37:22.449 University of Pennsylvania which

NOTE Confidence: 0.850934634615385

00:37:22.449 --> 00:37:23.920 evaluated the Flatiron database.

NOTE Confidence: 0.850934634615385

00:37:23.920 --> 00:37:25.000 So a kind of a,

NOTE Confidence: 0.850934634615385

00:37:25.000 --> 00:37:27.952 a large national database for patients

NOTE Confidence: 0.850934634615385

00:37:27.952 --> 00:37:31.560 who are exposed to cancer medications

NOTE Confidence: 0.850934634615385

00:37:31.560 --> 00:37:33.600 that were then ultimately withdrawn.

NOTE Confidence: 0.850934634615385

00:37:33.600 --> 00:37:37.216 And what they find is that it takes

NOTE Confidence: 0.850934634615385

00:37:37.216 --> 00:37:38.856 about 46 months from accelerated

NOTE Confidence: 0.850934634615385

00:37:38.856 --> 00:37:39.840 approval to withdrawal.

NOTE Confidence: 0.850934634615385

00:37:39.840 --> 00:37:41.560 So we don't get, it's not a huge,

NOTE Confidence: 0.850934634615385

00:37:41.560 --> 00:37:42.667 huge time period,

NOTE Confidence: 0.850934634615385

00:37:42.667 --> 00:37:44.881 but it does result in approximately

NOTE Confidence: 0.850934634615385

00:37:44.881 --> 00:37:47.292 1/4 of patients with cancer in

NOTE Confidence: 0.850934634615385

00:37:47.292 --> 00:37:49.267 the United States getting exposure

NOTE Confidence: 0.850934634615385

00:37:49.334 --> 00:37:51.404 to therapy that ultimately is

NOTE Confidence: 0.850934634615385

00:37:51.404 --> 00:37:53.474 demonstrated to not be beneficial.

NOTE Confidence: 0.850934634615385

00:37:53.480 --> 00:37:55.770 And in bladder cancer, it's about 22%.

00:37:55.770 --> 00:37:58.360 So it's a significant number of patients.

00:37:58.360 --> 00:38:00.118 And this is an interesting editorial.

00:38:00.120 --> 00:38:01.328 This is an editorial.

00:38:01.328 --> 00:38:03.720 It's it's a letter that talks about

00:38:03.720 --> 00:38:06.360 what the global impact of this

00:38:06.360 --> 00:38:08.960 practice is for other countries,

00:38:08.960 --> 00:38:11.918 especially low and middle income countries.

00:38:11.920 --> 00:38:15.560 And here the the group Bashal Gawali's

00:38:15.560 --> 00:38:17.594 a medical oncologist who writes and

00:38:17.594 --> 00:38:19.840 thinks a lot about this problem.

00:38:19.840 --> 00:38:23.398 And he highlights that often times

00:38:23.400 --> 00:38:23.990 other countries,

00:38:23.990 --> 00:38:25.760 especially low and middle income countries,

00:38:25.760 --> 00:38:27.560 will approve medications

00:38:27.560 --> 00:38:29.960 based on FDA recommendations.

NOTE Confidence: 0.93442106

00:38:29.960 --> 00:38:32.120 And so the FDA approves these

NOTE Confidence: 0.93442106

00:38:32.120 --> 00:38:32.840 medications conditionally,

NOTE Confidence: 0.93442106

00:38:32.840 --> 00:38:35.170 they're accepted as FDA approved

NOTE Confidence: 0.93442106

00:38:35.170 --> 00:38:37.510 medications in other countries and then

NOTE Confidence: 0.93442106

00:38:37.510 --> 00:38:39.155 if they're withdrawn in the United States,

NOTE Confidence: 0.93442106

00:38:39.160 --> 00:38:41.463 they continue to be approved in these

NOTE Confidence: 0.93442106

00:38:41.463 --> 00:38:43.663 other countries and in fact are often

NOTE Confidence: 0.93442106

00:38:43.663 --> 00:38:45.840 continue to be marketed in these other

NOTE Confidence: 0.93442106

00:38:45.840 --> 00:38:48.132 countries for the indications for which

NOTE Confidence: 0.93442106

00:38:48.132 --> 00:38:50.638 they're withdrawn here in the United States.

NOTE Confidence: 0.93442106

00:38:50.640 --> 00:38:52.940 And that's a really striking

NOTE Confidence: 0.93442106

00:38:52.940 --> 00:38:54.051 fact that I'm gonna,

NOTE Confidence: 0.93442106

00:38:54.051 --> 00:38:54.919 these are long quotes,

NOTE Confidence: 0.93442106

00:38:54.920 --> 00:38:56.630 but I think it's worth just

NOTE Confidence: 0.93442106

00:38:56.630 --> 00:38:58.200 looking at this is from the paper.

NOTE Confidence: 0.93442106

00:38:58.200 --> 00:39:00.486 Thus once a drug is approved by the FDA

NOTE Confidence: 0.93442106

00:39:00.486 --> 00:39:02.758 via the accelerated approval pathway,

NOTE Confidence: 0.93442106

00:39:02.760 --> 00:39:04.398 the drug can be marketed and

NOTE Confidence: 0.93442106

00:39:04.398 --> 00:39:05.972 promoted in low middle income

NOTE Confidence: 0.93442106

00:39:05.972 --> 00:39:08.560 countries as an FDA approved drug.

NOTE Confidence: 0.93442106

00:39:08.560 --> 00:39:10.290 And then confirmatory trials confirm

NOTE Confidence: 0.93442106

00:39:10.290 --> 00:39:12.432 they're negative and these are not

NOTE Confidence: 0.93442106

00:39:12.432 --> 00:39:14.197 communicated to those same countries.

NOTE Confidence: 0.93442106

00:39:14.200 --> 00:39:15.840 And this is an example,

NOTE Confidence: 0.93442106

00:39:15.840 --> 00:39:17.265 example again from in this

NOTE Confidence: 0.93442106

00:39:17.265 --> 00:39:18.120 case a tezalizumab,

NOTE Confidence: 0.93442106

00:39:18.120 --> 00:39:20.676 which I've highlighted multiple Times Now,

NOTE Confidence: 0.93442106

00:39:20.680 --> 00:39:23.205 but immediately after the

NOTE Confidence: 0.93442106

00:39:23.205 --> 00:39:24.480 drugs withdraw from the market,

NOTE Confidence: 0.93442106

00:39:24.480 --> 00:39:26.358 the company issued letters in this

NOTE Confidence: 0.93442106

00:39:26.358 --> 00:39:28.354 case to India stating that the

NOTE Confidence: 0.93442106

00:39:28.354 --> 00:39:30.059 Tezalism A tezalizumab would continue

NOTE Confidence: 0.93442106

00:39:30.059 --> 00:39:32.038 to be marketed in that country.

NOTE Confidence: 0.93442106

00:39:32.040 --> 00:39:33.867 And it's not just this country or

NOTE Confidence: 0.93442106

00:39:33.867 --> 00:39:35.360 this medication or this company,

NOTE Confidence: 0.93442106

00:39:35.360 --> 00:39:37.264 but this is they show nine other

NOTE Confidence: 0.93442106

00:39:37.264 --> 00:39:38.918 examples in this in this paper.

NOTE Confidence: 0.93442106

00:39:38.920 --> 00:39:41.250 So my point in all of this is that this

NOTE Confidence: 0.93442106

00:39:41.310 --> 00:39:43.878 is a practice that has some real downsides,

NOTE Confidence: 0.93442106

00:39:43.880 --> 00:39:45.240 should be really thought about

NOTE Confidence: 0.93442106

00:39:45.240 --> 00:39:47.242 carefully and and of course many people

NOTE Confidence: 0.93442106

00:39:47.242 --> 00:39:48.717 are thinking about it carefully,

NOTE Confidence: 0.93442106

00:39:48.720 --> 00:39:51.396 but has does have global implications.

NOTE Confidence: 0.93442106

00:39:51.400 --> 00:39:52.653 We wanted to look at what some

NOTE Confidence: 0.93442106

00:39:52.653 --> 00:39:53.600 of these surrogate endpoints,

NOTE Confidence: 0.93442106

00:39:53.600 --> 00:39:56.260 how they behave in bladder cancer because

NOTE Confidence: 0.93442106

00:39:56.260 --> 00:39:58.884 again that's that's been my main interest.

NOTE Confidence: 0.93442106

00:39:58.884 --> 00:40:01.880 And so we took a look at this.

NOTE Confidence: 0.93442106

00:40:01.880 --> 00:40:03.555 We looked at the relationship

NOTE Confidence: 0.93442106

00:40:03.555 --> 00:40:04.895 between commonly used surrogate

NOTE Confidence: 0.93442106

00:40:04.895 --> 00:40:06.290 endpoints and overall survival

NOTE Confidence: 0.93442106

00:40:06.290 --> 00:40:07.638 in metastatic bladder cancer.

NOTE Confidence: 0.93442106

00:40:07.640 --> 00:40:09.836 And the methods were pretty straightforward.

NOTE Confidence: 0.93442106

00:40:09.840 --> 00:40:12.392 We just did a review of clinical

NOTE Confidence: 0.93442106

00:40:12.392 --> 00:40:13.640 trials in bladder cancer.

NOTE Confidence: 0.93442106

00:40:13.640 --> 00:40:15.932 We looked at progression free survival

NOTE Confidence: 0.93442106

00:40:15.932 --> 00:40:18.418 and response rate and some other

NOTE Confidence: 0.93442106

00:40:18.418 --> 00:40:20.948 information and determined determined how

NOTE Confidence: 0.93442106

00:40:20.948 --> 00:40:23.918 effectively it predicts overall survival.

NOTE Confidence: 0.93442106

00:40:23.920 --> 00:40:25.558 So this is a big table.

NOTE Confidence: 0.93442106

00:40:25.560 --> 00:40:27.275 We looked at all trials which were

NOTE Confidence: 0.93442106

00:40:27.280 --> 00:40:30.059 62 trials and split them up into

NOTE Confidence: 0.93442106

00:40:30.059 --> 00:40:31.719 immune checkpoint inhibitors and

NOTE Confidence: 0.93442106

00:40:31.719 --> 00:40:33.719 non immune checkpoint inhibitors and

NOTE Confidence: 0.93442106

00:40:33.719 --> 00:40:35.476 we can skip through some of this.

NOTE Confidence: 0.93442106

00:40:35.480 --> 00:40:37.976 But you can see that the immune checkpoint

NOTE Confidence: 0.93442106

00:40:37.976 --> 00:40:39.440 inhibition trials were performed,

NOTE Confidence: 0.93442106

00:40:39.440 --> 00:40:41.546 the median year of publication was

NOTE Confidence: 0.93442106

00:40:41.546 --> 00:40:44.020 later than the than the chemotherapy

NOTE Confidence: 0.93442106

00:40:44.020 --> 00:40:46.320 trials and and tended to have much

NOTE Confidence: 0.93442106

00:40:46.320 --> 00:40:48.092 larger ends compared to checkpoint

NOTE Confidence: 0.93442106

00:40:48.092 --> 00:40:50.120 non checkpoint inhibitor trials,

NOTE Confidence: 0.93442106

00:40:50.120 --> 00:40:52.576 which we can talk about why that matters

NOTE Confidence: 0.93442106

00:40:52.576 --> 00:40:55.359 and we reported this earlier this year.

NOTE Confidence: 0.93442106

00:40:55.360 --> 00:40:57.547 The first thing you can do to try to

NOTE Confidence: 0.93442106

00:40:57.547 --> 00:40:59.235 understand sort of how well these two,

NOTE Confidence: 0.93442106

00:40:59.240 --> 00:41:01.538 a surrogate endpoint and a clinical

NOTE Confidence: 0.93442106

00:41:01.538 --> 00:41:04.238 endpoint relate is you can ask well

NOTE Confidence: 0.93442106

00:41:04.238 --> 00:41:06.440 what is the R-squared coefficient for

NOTE Confidence: 0.93442106

00:41:06.440 --> 00:41:08.918 the hazard ratio for progression free

NOTE Confidence: 0.93442106

00:41:08.918 --> 00:41:11.200 survival compared to overall survival.

NOTE Confidence: 0.93442106

00:41:11.200 --> 00:41:12.285 And you you can see here that

NOTE Confidence: 0.93442106

00:41:12.285 --> 00:41:12.750 in this case

NOTE Confidence: 0.861889365

00:41:12.794 --> 00:41:13.718 it was pretty reasonable,

NOTE Confidence: 0.861889365

00:41:13.720 --> 00:41:15.016 it was about .6.

NOTE Confidence: 0.861889365

00:41:15.016 --> 00:41:16.960 So it's not a strong predictor,

NOTE Confidence: 0.861889365

00:41:16.960 --> 00:41:19.558 but it's not a strongly correlated,

NOTE Confidence: 0.861889365

00:41:19.560 --> 00:41:21.750 but it's it's I would say

NOTE Confidence: 0.861889365

00:41:21.750 --> 00:41:22.480 moderately correlated.

NOTE Confidence: 0.861889365

00:41:22.480 --> 00:41:23.920 1 can ask a second question,

NOTE Confidence: 0.861889365

00:41:23.920 --> 00:41:27.830 which is what it's a metric called

NOTE Confidence: 0.861889365

00:41:27.830 --> 00:41:29.120 surrogate threshold effect.

NOTE Confidence: 0.861889365

00:41:29.120 --> 00:41:30.758 And what surrogate threshold effect is,

NOTE Confidence: 0.861889365

00:41:30.760 --> 00:41:35.648 is what result from the hazard

NOTE Confidence: 0.861889365

00:41:35.648 --> 00:41:37.458 ratio of progression free survival

NOTE Confidence: 0.861889365

00:41:37.458 --> 00:41:39.519 do you need to see to give you

NOTE Confidence: 0.861889365

00:41:39.520 --> 00:41:41.860 95% confidence that it's going to

NOTE Confidence: 0.861889365

00:41:41.860 --> 00:41:44.000 reflect an overall survival benefit.

NOTE Confidence: 0.861889365

00:41:44.000 --> 00:41:45.728 So you observe the surrogate and

NOTE Confidence: 0.861889365

00:41:45.728 --> 00:41:47.800 it give and it gives you with

NOTE Confidence: 0.861889365

00:41:47.800 --> 00:41:50.040 95% confidence an OS benefit.

NOTE Confidence: 0.861889365

00:41:50.040 --> 00:41:51.279 And So what would that number be?

NOTE Confidence: 0.861889365

00:41:51.280 --> 00:41:52.520 And so that turns out to be pretty,

NOTE Confidence: 0.861889365

00:41:52.520 --> 00:41:53.660 again, pretty straightforward

NOTE Confidence: 0.861889365

00:41:53.660 --> 00:41:54.800 to actually calculate.

NOTE Confidence: 0.861889365

00:41:54.800 --> 00:41:57.170 The first thing you do is you get 95%

NOTE Confidence: 0.861889365

00:41:57.170 --> 00:42:00.652 predictive sort of confidence interval

NOTE Confidence: 0.861889365

00:42:00.652 --> 00:42:02.912 around your correlation line and

NOTE Confidence: 0.861889365

00:42:02.912 --> 00:42:06.440 then you want a value that is below 1.

NOTE Confidence: 0.861889365

00:42:06.440 --> 00:42:09.065 And so you see what hazard ratio

NOTE Confidence: 0.861889365

00:42:09.065 --> 00:42:11.220 that for progression free survival

NOTE Confidence: 0.861889365

00:42:11.220 --> 00:42:13.000 that number intersects at.

NOTE Confidence: 0.861889365

00:42:13.000 --> 00:42:14.316 And for bladder cancer,

NOTE Confidence: 0.861889365

00:42:14.316 --> 00:42:17.038 we found that that R-squared was .6 and

NOTE Confidence: 0.861889365

00:42:17.038 --> 00:42:19.166 the surrogate threshold effect was .41,

NOTE Confidence: 0.861889365

00:42:19.166 --> 00:42:22.376 which means if you want 95% confidence that

NOTE Confidence: 0.861889365

00:42:22.376 --> 00:42:25.120 the OS is improved without observing it,

NOTE Confidence: 0.861889365

00:42:25.120 --> 00:42:25.954 you should,

NOTE Confidence: 0.861889365

00:42:25.954 --> 00:42:28.356 you should see APFS of .41.

NOTE Confidence: 0.861889365

00:42:28.356 --> 00:42:30.884 It doesn't mean that you need to have

NOTE Confidence: 0.861889365

00:42:30.884 --> 00:42:33.678 a .41 PFS to have an OS benefit.

NOTE Confidence: 0.861889365

00:42:33.680 --> 00:42:35.479 It just means that if you're not

NOTE Confidence: 0.861889365

00:42:35.479 --> 00:42:37.214 going to measure OS directly and

NOTE Confidence: 0.861889365

00:42:37.214 --> 00:42:39.038 you want that confidence you that's

NOTE Confidence: 0.861889365

00:42:39.038 --> 00:42:40.758 that's the value you need to get.

NOTE Confidence: 0.861889365

00:42:40.760 --> 00:42:42.890 We did the same for objective

NOTE Confidence: 0.861889365

00:42:42.890 --> 00:42:43.955 response rate here.

NOTE Confidence: 0.861889365

00:42:43.960 --> 00:42:45.591 And what you can see is that

NOTE Confidence: 0.861889365

00:42:45.591 --> 00:42:46.680 for for hazard ratio,

NOTE Confidence: 0.861889365

00:42:46.680 --> 00:42:48.012 for objective response rate,

NOTE Confidence: 0.861889365

00:42:48.012 --> 00:42:49.677 it actually never hits that

NOTE Confidence: 0.861889365

00:42:49.680 --> 00:42:51.488 95% confidence interval line.

NOTE Confidence: 0.861889365

00:42:51.488 --> 00:42:54.980 So for that our R-squared was .03 and

NOTE Confidence: 0.861889365

00:42:54.980 --> 00:42:57.320 our surrogate threshold effect was not,

NOTE Confidence: 0.861889365

00:42:57.320 --> 00:42:58.960 was not actually not reached,

NOTE Confidence: 0.861889365

00:42:58.960 --> 00:43:00.484 it's it wasn't calculable.

NOTE Confidence: 0.861889365

00:43:00.484 --> 00:43:03.359 And so from this study we sort of

NOTE Confidence: 0.861889365

00:43:03.360 --> 00:43:05.195 conclude that you know surrogate

NOTE Confidence: 0.861889365

00:43:05.195 --> 00:43:06.663 surrogate endpoints are poorly

NOTE Confidence: 0.861889365

00:43:06.663 --> 00:43:07.975 characterized in bladder cancer and

NOTE Confidence: 0.861889365

00:43:07.975 --> 00:43:09.773 there's sort of a weak to moderate

NOTE Confidence: 0.861889365

00:43:09.773 --> 00:43:11.798 correlation for progression free survival,

NOTE Confidence: 0.861889365

00:43:11.800 --> 00:43:13.930 but really quite a poor correlation

NOTE Confidence: 0.861889365

00:43:13.930 --> 00:43:16.719 for response rate or tumor shrinkage

NOTE Confidence: 0.861889365

00:43:16.719 --> 00:43:18.438 on cross-sectional imaging.

NOTE Confidence: 0.861889365

00:43:18.440 --> 00:43:21.248 And so we really should be

NOTE Confidence: 0.861889365

00:43:21.248 --> 00:43:22.710 deemphasizing response rate we

NOTE Confidence: 0.861889365

00:43:22.710 --> 00:43:24.690 conclude as a primary endpoint when

NOTE Confidence: 0.861889365

00:43:24.690 --> 00:43:26.219 possible in metastatic bladder

NOTE Confidence: 0.861889365

00:43:26.219 --> 00:43:29.504 cancer clinical trials more broadly

NOTE Confidence: 0.861889365

00:43:29.504 --> 00:43:31.136 I think outside of bladder cancer

NOTE Confidence: 0.861889365

00:43:31.136 --> 00:43:33.229 sort of zooming out again you know

NOTE Confidence: 0.861889365

00:43:33.229 --> 00:43:34.719 the question of clinical trials,

NOTE Confidence: 0.861889365

00:43:34.720 --> 00:43:36.454 we've seen this trend of clinical

NOTE Confidence: 0.861889365

00:43:36.454 --> 00:43:37.610 trials changing pretty significantly

NOTE Confidence: 0.861889365

00:43:37.658 --> 00:43:38.924 and there it's responding to a

NOTE Confidence: 0.861889365

00:43:38.924 --> 00:43:40.429 lot of pressures and you know I'm

NOTE Confidence: 0.861889365

00:43:40.429 --> 00:43:41.665 not under the impression that this

NOTE Confidence: 0.861889365

00:43:41.665 --> 00:43:43.640 is an easy thing to do.

NOTE Confidence: 0.861889365

00:43:43.640 --> 00:43:45.607 But when you think about the major

NOTE Confidence: 0.861889365

00:43:45.607 --> 00:43:46.764 stakeholders in clinical trials

NOTE Confidence: 0.861889365

00:43:46.764 --> 00:43:48.318 that are involved in bringing a

NOTE Confidence: 0.861889365

00:43:48.320 --> 00:43:49.876 new medication to patients,

NOTE Confidence: 0.861889365

00:43:49.876 --> 00:43:52.560 you know you think about the FDA,

NOTE Confidence: 0.861889365

00:43:52.560 --> 00:43:54.798 you think about the Pharmaceutical industry,

NOTE Confidence: 0.861889365

00:43:54.800 --> 00:43:56.285 you think about the patients

NOTE Confidence: 0.861889365

00:43:56.285 --> 00:43:58.455 themselves and and patient advocacy

NOTE Confidence: 0.861889365

00:43:58.455 --> 00:44:00.555 groups and then physicians.

NOTE Confidence: 0.861889365

00:44:00.560 --> 00:44:02.163 And you know I'm happy to have

NOTE Confidence: 0.861889365

00:44:02.163 --> 00:44:03.455 a longer discussion about this

NOTE Confidence: 0.861889365

00:44:03.455 --> 00:44:04.555 if people are interested.

NOTE Confidence: 0.861889365

00:44:04.560 --> 00:44:06.950 But I think that if you look at each of

NOTE Confidence: 0.97590114

00:44:07.013 --> 00:44:08.040 these factors individually,

NOTE Confidence: 0.97590114

00:44:08.040 --> 00:44:10.892 I think that the onus really is and

NOTE Confidence: 0.97590114

00:44:10.892 --> 00:44:13.896 has to be on physicians to protect the

NOTE Confidence: 0.97590114

00:44:13.896 --> 00:44:15.916 scientific integrity of clinical trials

NOTE Confidence: 0.97590114

00:44:15.916 --> 00:44:18.090 and make sure that we're we're really

NOTE Confidence: 0.97590114

00:44:18.090 --> 00:44:19.680 cautious about some of these things.

NOTE Confidence: 0.97590114

00:44:19.680 --> 00:44:23.636 I think I think while all of these

NOTE Confidence: 0.97590114

00:44:23.636 --> 00:44:25.868 other factors are key players in

NOTE Confidence: 0.97590114

00:44:25.868 --> 00:44:28.799 in bringing medications to patients

NOTE Confidence: 0.97590114

00:44:28.800 --> 00:44:30.459 really we're we're we are the ones

NOTE Confidence: 0.97590114

00:44:30.459 --> 00:44:32.214 who really are I think best equipped

NOTE Confidence: 0.97590114

00:44:32.214 --> 00:44:34.315 and and the onus really falls on us to

NOTE Confidence: 0.97590114

00:44:34.315 --> 00:44:36.200 think about how to do this and protect

NOTE Confidence: 0.97590114

00:44:36.200 --> 00:44:38.440 patient clinical trial integrity.

NOTE Confidence: 0.97590114

00:44:38.440 --> 00:44:39.910 So this is the thing I'm interested

NOTE Confidence: 0.97590114

00:44:39.910 --> 00:44:41.597 in and I'd love to you know many,

NOTE Confidence: 0.97590114

00:44:41.600 --> 00:44:43.592 many of you have have thought about this

NOTE Confidence: 0.97590114

00:44:43.592 --> 00:44:45.959 of course and and and a lot of academic

NOTE Confidence: 0.97590114

00:44:45.959 --> 00:44:47.439 scholarship about this here at Yale.

NOTE Confidence: 0.97590114

00:44:47.440 --> 00:44:49.312 One of the first things I did when

NOTE Confidence: 0.97590114

00:44:49.312 --> 00:44:51.133 coming here is I connected with the

NOTE Confidence: 0.97590114

00:44:51.133 --> 00:44:52.700 copper Center and contacted Mike Leapin

NOTE Confidence: 0.97590114

00:44:52.700 --> 00:44:54.520 and Carrie Gross and reached out to

NOTE Confidence: 0.97590114

00:44:54.571 --> 00:44:56.293 him because Carrie Gross has of course

NOTE Confidence: 0.97590114

00:44:56.293 --> 00:44:57.962 written quite a bit about this and

NOTE Confidence: 0.97590114

00:44:57.962 --> 00:44:59.872 thought deeply about a lot of these problems.

NOTE Confidence: 0.97590114

00:44:59.872 --> 00:45:01.944 And so we have started to work

NOTE Confidence: 0.97590114

00:45:01.944 --> 00:45:03.158 together a little bit on,

NOTE Confidence: 0.97590114

00:45:03.160 --> 00:45:05.512 on some projects that look at

NOTE Confidence: 0.97590114

00:45:05.512 --> 00:45:07.080 topics related to this.

NOTE Confidence: 0.97590114

00:45:07.080 --> 00:45:09.328 And I also wanted to highlight one other

NOTE Confidence: 0.97590114

00:45:09.328 --> 00:45:10.912 organization with many of the folks

NOTE Confidence: 0.97590114

00:45:10.912 --> 00:45:12.760 that I referenced in these other papers,

NOTE Confidence: 0.97590114

00:45:12.760 --> 00:45:13.928 Christopher Booth and Bishal

NOTE Confidence: 0.97590114

00:45:13.928 --> 00:45:16.000 who's who's also a part of this.

NOTE Confidence: 0.97590114

00:45:16.000 --> 00:45:18.604 And this isn't not an organization

NOTE Confidence: 0.97590114

00:45:18.604 --> 00:45:20.016 I'm I'm a part of,

NOTE Confidence: 0.97590114

00:45:20.016 --> 00:45:21.996 but they did start up a program

NOTE Confidence: 0.97590114

00:45:21.996 --> 00:45:24.241 called Common Sense Oncology and

NOTE Confidence: 0.97590114

00:45:24.241 --> 00:45:26.431 it's for physicians primarily who

NOTE Confidence: 0.97590114

00:45:26.431 --> 00:45:28.920 are interested in taking on the the,

NOTE Confidence: 0.97590114

00:45:28.920 --> 00:45:32.280 the role of thinking about this

NOTE Confidence: 0.97590114

00:45:32.280 --> 00:45:34.356 and and moving, moving.

NOTE Confidence: 0.97590114

00:45:34.356 --> 00:45:36.732 I would say the conversation to

NOTE Confidence: 0.97590114

00:45:36.732 --> 00:45:38.440 talking about endpoint design,

NOTE Confidence: 0.97590114

00:45:38.440 --> 00:45:40.865 the appropriateness of crossover and

NOTE Confidence: 0.97590114

00:45:40.865 --> 00:45:43.800 clinical trials and and some of the

NOTE Confidence: 0.97590114

00:45:43.800 --> 00:45:46.152 sort of some of the implementation

NOTE Confidence: 0.97590114

00:45:46.152 --> 00:45:47.720 signs around clinical trials.

NOTE Confidence: 0.97590114

00:45:47.720 --> 00:45:50.915 So just wanted to make people aware of that.

NOTE Confidence: 0.97590114

00:45:50.920 --> 00:45:51.736 So in conclusion,

NOTE Confidence: 0.97590114

00:45:51.736 --> 00:45:53.368 there's a lot of important work

NOTE Confidence: 0.97590114

00:45:53.368 --> 00:45:55.646 to be done in bladder cancer as I

NOTE Confidence: 0.97590114

00:45:55.646 --> 00:45:56.480 hope I've highlighted,

NOTE Confidence: 0.97590114

00:45:56.480 --> 00:45:58.136 there's a lot of room to

NOTE Confidence: 0.97590114

00:45:58.136 --> 00:45:59.560 continue to improve patient care.

NOTE Confidence: 0.97590114

00:45:59.560 --> 00:46:02.360 I think that urinary DNA has has

NOTE Confidence: 0.97590114

00:46:02.360 --> 00:46:04.196 a potential role in that future.

NOTE Confidence: 0.97590114

00:46:04.200 --> 00:46:05.985 We have very early data and there's

NOTE Confidence: 0.97590114

00:46:05.985 --> 00:46:07.802 some more robust data out there and

NOTE Confidence: 0.97590114

00:46:07.802 --> 00:46:09.595 we're hoping to continue to work and

NOTE Confidence: 0.97590114

00:46:09.595 --> 00:46:11.275 validate this as a biomarker in in

NOTE Confidence: 0.97590114

00:46:11.275 --> 00:46:14.400 both early and late bladder cancer.

NOTE Confidence: 0.97590114

00:46:14.400 --> 00:46:16.080 We need to be giving more chemotherapy

NOTE Confidence: 0.97590114

00:46:16.080 --> 00:46:16.800 and bladder cancer.

NOTE Confidence: 0.97590114

00:46:16.800 --> 00:46:18.851 We need to be giving more chemotherapy

NOTE Confidence: 0.97590114

00:46:18.851 --> 00:46:20.625 in for patients undergoing surgery

NOTE Confidence: 0.97590114

00:46:20.625 --> 00:46:22.720 and for folks undergoing radiation.

NOTE Confidence: 0.97590114

00:46:22.720 --> 00:46:24.256 And I hope I I showed you some

NOTE Confidence: 0.97590114

00:46:24.256 --> 00:46:25.760 data to convince you of that.

NOTE Confidence: 0.97590114

00:46:25.760 --> 00:46:28.640 And finally clinical trials are key,

NOTE Confidence: 0.97590114

00:46:28.640 --> 00:46:29.925 they're really important for patients

NOTE Confidence: 0.97590114

00:46:29.925 --> 00:46:31.520 and and especially in bladder cancer.

NOTE Confidence: 0.97590114

00:46:31.520 --> 00:46:32.798 We've seen tremendous,

NOTE Confidence: 0.97590114

00:46:32.798 --> 00:46:34.502 tremendous work and really

NOTE Confidence: 0.97590114

00:46:34.502 --> 00:46:36.980 exciting data of late especially.

NOTE Confidence: 0.97590114

00:46:36.980 --> 00:46:39.872 But I think it is the role of

NOTE Confidence: 0.97590114

00:46:39.872 --> 00:46:41.500 physicians really to ensure the

NOTE Confidence: 0.97590114

00:46:41.500 --> 00:46:43.360 integrity of the of the scientific

NOTE Confidence: 0.97590114

00:46:43.360 --> 00:46:45.198 endeavour that is a clinical trial

NOTE Confidence: 0.97590114

00:46:45.198 --> 00:46:46.938 and design answers that really focus

NOTE Confidence: 0.97590114

00:46:46.990 --> 00:46:48.595 on questions that are meaningful

NOTE Confidence: 0.97590114

00:46:48.595 --> 00:46:50.200 for patients making them live

NOTE Confidence: 0.880049383333333

00:46:50.200 --> 00:46:51.880 longer, improving their quality of life.

NOTE Confidence: 0.970721174285714

00:46:53.920 --> 00:46:55.278 Thank you very much for your attention.

NOTE Confidence: 0.970721174285714

00:46:55.280 --> 00:46:56.610 I'm happy to to chat a bit

NOTE Confidence: 0.970721174285714

00:46:56.610 --> 00:46:57.680 and answer some questions.

NOTE Confidence: 0.613968978333333

00:47:04.400 --> 00:47:06.664 Thank you Doctor Gatley.

NOTE Confidence: 0.613968978333333

00:47:06.664 --> 00:47:08.800 Any questions audience?

NOTE Confidence: 0.613968978333333

00:47:08.800 --> 00:47:11.840 The Internet very good,

NOTE Confidence: 0.613968978333333

00:47:11.840 --> 00:47:13.520 maybe I will set up for questions.

NOTE Confidence: 0.613968978333333

00:47:13.520 --> 00:47:14.532 So it's very beautiful

NOTE Confidence: 0.613968978333333

00:47:14.532 --> 00:47:15.797 talk about the urine DNA,

NOTE Confidence: 0.613968978333333

00:47:15.800 --> 00:47:17.774 how it's being used for non most

NOTE Confidence: 0.613968978333333

00:47:17.774 --> 00:47:19.390 invasive bladder cancer and some work

NOTE Confidence: 0.613968978333333

00:47:19.390 --> 00:47:21.049 you did in in terms of visibility

NOTE Confidence: 0.613968978333333

00:47:21.104 --> 00:47:23.005 and you also mentioned about the the

NOTE Confidence: 0.613968978333333

00:47:23.005 --> 00:47:24.715 low sensitivity and the low yield,

NOTE Confidence: 0.613968978333333

00:47:24.720 --> 00:47:26.256 you know where it sort of makes sense

NOTE Confidence: 0.613968978333333

00:47:26.256 --> 00:47:27.720 because it's really superficial disease,

NOTE Confidence: 0.613968978333333

00:47:27.720 --> 00:47:29.320 very low volume of disease.

NOTE Confidence: 0.613968978333333

00:47:29.320 --> 00:47:30.713 I wonder if we can share any

NOTE Confidence: 0.613968978333333

00:47:30.713 --> 00:47:32.262 data or any insights on using

NOTE Confidence: 0.613968978333333

00:47:32.262 --> 00:47:33.757 that in most invasive disease,

NOTE Confidence: 0.613968978333333

00:47:33.760 --> 00:47:35.025 maybe this is better setting

NOTE Confidence: 0.613968978333333

00:47:35.025 --> 00:47:36.659 to use that in most invasive

NOTE Confidence: 0.613968978333333

00:47:36.659 --> 00:47:38.239 setting how we can monitor,

NOTE Confidence: 0.613968978333333

00:47:38.240 --> 00:47:38.774 you know,

NOTE Confidence: 0.613968978333333

00:47:38.774 --> 00:47:40.376 treatment response from your agent chemo

NOTE Confidence: 0.613968978333333

00:47:40.376 --> 00:47:42.197 or even chemo radiotherapy as well.

NOTE Confidence: 0.613968978333333

00:47:42.200 --> 00:47:42.520 Yeah,

NOTE Confidence: 0.831260071666667

00:47:44.160 --> 00:47:45.996 yeah, there's a couple of questions.

NOTE Confidence: 0.831260071666667

00:47:46.000 --> 00:47:48.702 I think when when asking what its

NOTE Confidence: 0.831260071666667

00:47:48.702 --> 00:47:51.438 role would what a marker like this,

NOTE Confidence: 0.831260071666667

00:47:51.440 --> 00:47:52.976 what role it would play in

NOTE Confidence: 0.831260071666667

00:47:52.976 --> 00:47:54.000 muscle invasive bladder cancer,

NOTE Confidence: 0.831260071666667

00:47:54.000 --> 00:47:55.524 I think the first obvious thing

NOTE Confidence: 0.831260071666667

00:47:55.524 --> 00:47:57.706 for me would be to ask for folks

NOTE Confidence: 0.831260071666667

00:47:57.706 --> 00:47:59.278 who receive chemotherapy and

NOTE Confidence: 0.831260071666667

00:47:59.278 --> 00:48:01.520 have a really strong response.

NOTE Confidence: 0.831260071666667

00:48:01.520 --> 00:48:04.694 Can we identify patients who are

NOTE Confidence: 0.831260071666667

00:48:04.694 --> 00:48:06.810 completely responded to chemotherapy

NOTE Confidence: 0.831260071666667

00:48:06.892 --> 00:48:09.296 and we can maybe de escalate their

NOTE Confidence: 0.831260071666667

00:48:09.296 --> 00:48:11.256 therapy and identify them for

NOTE Confidence: 0.831260071666667

00:48:11.256 --> 00:48:13.400 not having radical cystectomy.

NOTE Confidence: 0.831260071666667

00:48:13.400 --> 00:48:15.920 Right now people try to do this

NOTE Confidence: 0.831260071666667

00:48:15.920 --> 00:48:18.279 with cytology or bladder biopsies

NOTE Confidence: 0.831260071666667

00:48:18.280 --> 00:48:20.320 and it has reasonable sensitivities

NOTE Confidence: 0.831260071666667

00:48:20.320 --> 00:48:23.106 again somewhere in the 80% or so.

NOTE Confidence: 0.831260071666667

00:48:23.106 --> 00:48:25.717 But if you're going to forego cystectomy,

NOTE Confidence: 0.831260071666667

00:48:25.720 --> 00:48:26.920 you would want to be really,

NOTE Confidence: 0.831260071666667

00:48:26.920 --> 00:48:29.685 really sure that there is no residual

NOTE Confidence: 0.831260071666667

00:48:29.685 --> 00:48:31.858 cancer because being wrong about that

NOTE Confidence: 0.831260071666667

00:48:31.858 --> 00:48:34.960 has a real high cost I think for patients.

NOTE Confidence: 0.831260071666667

00:48:34.960 --> 00:48:37.208 And so I think that that's one real

NOTE Confidence: 0.831260071666667

00:48:37.208 --> 00:48:39.015 exciting place and I don't have any

NOTE Confidence: 0.831260071666667

00:48:39.015 --> 00:48:41.272 data here to show you except to say

NOTE Confidence: 0.831260071666667

00:48:41.272 --> 00:48:43.300 that we can definitely detect tumor

NOTE Confidence: 0.831260071666667

00:48:43.300 --> 00:48:45.296 associated DNA before chemotherapy,

NOTE Confidence: 0.831260071666667

00:48:45.296 --> 00:48:48.056 you know after resection but

NOTE Confidence: 0.831260071666667

00:48:48.056 --> 00:48:49.160 before chemotherapy.

NOTE Confidence: 0.831260071666667

00:48:49.160 --> 00:48:50.889 So those dynamics are at play and

NOTE Confidence: 0.831260071666667

00:48:50.889 --> 00:48:52.843 we have seen decreases in that

NOTE Confidence: 0.831260071666667

00:48:52.843 --> 00:48:53.998 number with chemotherapy,

NOTE Confidence: 0.831260071666667

00:48:54.000 --> 00:48:54.837 but we've only,

NOTE Confidence: 0.831260071666667

00:48:54.837 --> 00:48:57.160 I've only looked at about 10 patients or so.

NOTE Confidence: 0.831260071666667

00:48:57.160 --> 00:49:00.120 So not enough to be able to say

NOTE Confidence: 0.831260071666667

00:49:00.120 --> 00:49:01.380 yeah we can start eliminating

NOTE Confidence: 0.831260071666667

00:49:01.380 --> 00:49:02.640 cystectomy in some of those,

NOTE Confidence: 0.831260071666667

00:49:02.640 --> 00:49:04.236 but that I think that that

NOTE Confidence: 0.831260071666667

00:49:04.236 --> 00:49:05.960 would be a key question.

NOTE Confidence: 0.831260071666667

00:49:05.960 --> 00:49:06.160 Thank

NOTE Confidence: 0.86307606

00:49:06.160 --> 00:49:07.216 you. We should definitely

NOTE Confidence: 0.86307606

00:49:07.216 --> 00:49:08.800 do this study here as well.

NOTE Confidence: 0.86307606

00:49:08.800 --> 00:49:12.118 Any other questions,

NOTE Confidence: 0.86307606

00:49:12.120 --> 00:49:13.848 questions, so maybe I can ask

NOTE Confidence: 0.86307606

00:49:13.848 --> 00:49:15.000 another question about this.

NOTE Confidence: 0.86307606

00:49:15.000 --> 00:49:16.664 So with that design,

NOTE Confidence: 0.86307606

00:49:16.664 --> 00:49:19.920 what would be the adequate endpoints?

NOTE Confidence: 0.86307606

00:49:19.920 --> 00:49:21.360 You know you talked about

NOTE Confidence: 0.86307606

00:49:21.360 --> 00:49:22.512 endpoints in metastatic setting.

NOTE Confidence: 0.86307606

00:49:22.520 --> 00:49:24.060 You know we talked about the endpoints

NOTE Confidence: 0.86307606

00:49:24.060 --> 00:49:25.520 in non most invasive disease,

NOTE Confidence: 0.86307606

00:49:25.520 --> 00:49:26.888 most invasive disease.

NOTE Confidence: 0.86307606

00:49:26.888 --> 00:49:28.712 With the introduction of

NOTE Confidence: 0.86307606

00:49:28.712 --> 00:49:30.080 this novel biomarkers,

NOTE Confidence: 0.86307606

00:49:30.080 --> 00:49:32.131 What do you think will be adequate

NOTE Confidence: 0.86307606

00:49:32.131 --> 00:49:33.638 endpoints in studies like that?

NOTE Confidence: 0.956704044444444

00:49:34.760 --> 00:49:36.875 To start a study like that would have to,

94

NOTE Confidence: 0.956704044444444

00:49:36.880 --> 00:49:39.488 would have to be an I think a

NOTE Confidence: 0.956704044444444

00:49:39.488 --> 00:49:40.560 prospective observational study.

NOTE Confidence: 0.956704044444444

00:49:40.560 --> 00:49:42.720 I think I would start with urine

NOTE Confidence: 0.956704044444444

00:49:42.720 --> 00:49:45.120 collections data analysis and then

NOTE Confidence: 0.956704044444444

00:49:45.120 --> 00:49:46.560 undergoing radical cystectomy.

NOTE Confidence: 0.956704044444444

00:49:46.560 --> 00:49:48.471 And the main endpoint I'd look for

NOTE Confidence: 0.956704044444444

00:49:48.471 --> 00:49:49.595 is pathologic complete response

NOTE Confidence: 0.956704044444444

00:49:49.595 --> 00:49:51.380 and the reason I choose that is

NOTE Confidence: 0.956704044444444

00:49:51.380 --> 00:49:52.680 because I didn't share it here,

NOTE Confidence: 0.956704044444444

00:49:52.680 --> 00:49:55.920 but from that 2003 paper with Grossman ET al.

NOTE Confidence: 0.956704044444444

00:49:55.920 --> 00:49:58.368 That first showed us the benefit of M

NOTE Confidence: 0.956704044444444

00:49:58.368 --> 00:50:01.158 Vac and muscle invasive bladder cancer.

NOTE Confidence: 0.956704044444444

00:50:01.160 --> 00:50:03.645 But multiple other papers have shown that

NOTE Confidence: 0.956704044444444

00:50:03.645 --> 00:50:05.710 patients who have pathologic complete

NOTE Confidence: 0.956704044444444

00:50:05.710 --> 00:50:08.070 response on surgery do significantly,

NOTE Confidence: 0.956704044444444

00:50:08.070 --> 00:50:09.020 significantly better.

NOTE Confidence: 0.956704044444444

00:50:09.020 --> 00:50:11.395 It's a really nice surrogate.

NOTE Confidence: 0.956704044444444

00:50:11.400 --> 00:50:13.328 So this is and this kind of ties

NOTE Confidence: 0.956704044444444

00:50:13.328 --> 00:50:15.769 back to how we ended the talk is

NOTE Confidence: 0.956704044444444

00:50:15.769 --> 00:50:17.296 that surrogates aren't all bad,

NOTE Confidence: 0.956704044444444

00:50:17.296 --> 00:50:20.086 it just has to be a a validated useful

NOTE Confidence: 0.956704044444444

00:50:20.086 --> 00:50:22.001 surrogate and I think pathologic

NOTE Confidence: 0.956704044444444

00:50:22.001 --> 00:50:23.919 complete response is one of those.

NOTE Confidence: 0.956704044444444

00:50:23.920 --> 00:50:25.513 So that's how I would do it to start.

NOTE Confidence: 0.956704044444444

00:50:25.520 --> 00:50:27.518 And then ultimately I think that

NOTE Confidence: 0.956704044444444

00:50:27.520 --> 00:50:29.812 the goal would be a prospective

NOTE Confidence: 0.956704044444444

00:50:29.812 --> 00:50:31.632 study where you identify patients

NOTE Confidence: 0.956704044444444

00:50:31.632 --> 00:50:33.984 who sort of are positive and then

NOTE Confidence: 0.956704044444444

00:50:33.984 --> 00:50:35.998 become negative after chemotherapy.

NOTE Confidence: 0.956704044444444

00:50:36.000 --> 00:50:37.764 So you biomarker select them into a

NOTE Confidence: 0.956704044444444

00:50:37.764 --> 00:50:39.404 study and then you would randomize

NOTE Confidence: 0.956704044444444

00:50:39.404 --> 00:50:41.343 those patients or at least you know

NOTE Confidence: 0.956704044444444

00:50:41.398 --> 00:50:43.162 it's that's a tough thing to randomize

NOTE Confidence: 0.956704044444444

00:50:43.162 --> 00:50:45.915 too but you would as much as you

NOTE Confidence: 0.956704044444444

00:50:45.915 --> 00:50:48.390 can offer patients multiple arms to

NOTE Confidence: 0.956704044444444

00:50:48.390 --> 00:50:51.344 treatment or no treatment and and and

NOTE Confidence: 0.956704044444444

00:50:51.344 --> 00:50:53.720 then you know observe quite carefully

NOTE Confidence: 0.956704044444444

00:50:53.720 --> 00:50:55.640 afterwards but you we would need,

NOTE Confidence: 0.956704044444444

00:50:55.640 --> 00:50:57.888 I I think we'd need pretty good data

NOTE Confidence: 0.956704044444444

00:50:57.888 --> 00:51:00.000 before we would you know withhold

NOTE Confidence: 0.956704044444444

00:51:00.000 --> 00:51:02.232 surgery for patients in this setting.

NOTE Confidence: 0.956704044444444

00:51:02.240 --> 00:51:03.731 I should say there's a study out

NOTE Confidence: 0.956704044444444

00:51:03.731 --> 00:51:05.320 of Fox Chase that is doing this.

NOTE Confidence: 0.956704044444444

00:51:05.320 --> 00:51:07.200 There's the retain study that's

NOTE Confidence: 0.956704044444444

00:51:07.200 --> 00:51:09.320 looking at de escalating therapy and

NOTE Confidence: 0.956704044444444

00:51:09.320 --> 00:51:11.105 you know it'll be exciting to see

NOTE Confidence: 0.956704044444444

00:51:11.105 --> 00:51:12.968 the results but we got we we have

NOTE Confidence: 0.956704044444444

00:51:12.968 --> 00:51:14.952 to be really careful I think in in

NOTE Confidence: 0.956704044444444

00:51:14.952 --> 00:51:16.264 these patients because it's it's

NOTE Confidence: 0.956704044444444

00:51:16.264 --> 00:51:17.960 a bad disease if we miss a window

NOTE Confidence: 0.676747478181818

00:51:18.640 --> 00:51:20.235 very life changing treatment too

NOTE Confidence: 0.676747478181818

00:51:20.235 --> 00:51:22.120 especially with the cystectomy as well.

NOTE Confidence: 0.676747478181818

00:51:22.120 --> 00:51:24.720 Thank you. Any other questions,

NOTE Confidence: 0.676747478181818

00:51:24.720 --> 00:51:27.440 questions, any questions from the online

NOTE Confidence: 0.82926348

00:51:31.440 --> 00:51:33.008 do new therapies replace

NOTE Confidence: 0.82926348

00:51:33.008 --> 00:51:34.639 chemotherapy, give up chemotherapy.

NOTE Confidence: 0.91131397875

00:51:37.760 --> 00:51:41.640 So yeah that's a that's a good question.

NOTE Confidence: 0.91131397875

00:51:41.640 --> 00:51:43.635 I think the so bladder cancer has

NOTE Confidence: 0.91131397875

00:51:43.635 --> 00:51:46.223 seen I think like a lot of solid

NOTE Confidence: 0.91131397875

00:51:46.223 --> 00:51:47.893 organ malignancies has really seen

NOTE Confidence: 0.91131397875

00:51:47.962 --> 00:51:49.464 kind of a revolution and how we

NOTE Confidence: 0.91131397875

00:51:49.464 --> 00:51:51.240 treat it in the last 1015 years.

NOTE Confidence: 0.91131397875

00:51:51.240 --> 00:51:52.840 We've seen the importance

NOTE Confidence: 0.91131397875

00:51:52.840 --> 00:51:54.084 of checkpoint inhibitors.

NOTE Confidence: 0.91131397875

00:51:54.084 --> 00:51:56.616 We have antibody drug conjugates and

NOTE Confidence: 0.91131397875

00:51:56.616 --> 00:51:58.559 several other important classes.

NOTE Confidence: 0.91131397875

00:51:58.560 --> 00:52:00.738 And I have seen you know a lot of

NOTE Confidence: 0.91131397875

00:52:00.738 --> 00:52:02.785 these medications move earlier and

NOTE Confidence: 0.91131397875

00:52:02.785 --> 00:52:04.960 earlier in the treatment paradigm.

NOTE Confidence: 0.91131397875

00:52:04.960 --> 00:52:06.402 Cisplatin is really quite a useful drug

NOTE Confidence: 0.91131397875

00:52:06.402 --> 00:52:08.062 I think in bladder cancer and Doctor

NOTE Confidence: 0.91131397875

00:52:08.062 --> 00:52:09.550 Kim of course could probably speak

NOTE Confidence: 0.91131397875

00:52:09.593 --> 00:52:11.000 about this much more than I could.

NOTE Confidence: 0.91131397875

00:52:11.000 --> 00:52:12.582 But I don't think that we'll ever

NOTE Confidence: 0.91131397875

00:52:12.582 --> 00:52:14.614 be at a phase where or at least

NOTE Confidence: 0.91131397875

00:52:14.614 --> 00:52:16.576 not anytime soon that I can think

NOTE Confidence: 0.91131397875

00:52:16.576 --> 00:52:18.394 of where chemotherapy has no role,

NOTE Confidence: 0.91131397875

00:52:18.400 --> 00:52:20.085 but no doubt checkpoint inhibitors

NOTE Confidence: 0.91131397875

00:52:20.085 --> 00:52:21.770 and these other therapies are

NOTE Confidence: 0.91131397875

00:52:21.829 --> 00:52:23.200 definitely moving earlier.

NOTE Confidence: 0.91131397875

00:52:23.200 --> 00:52:24.148 I think they're going to play

NOTE Confidence: 0.91131397875

00:52:24.148 --> 00:52:25.079 a bigger and bigger role in,

NOTE Confidence: 0.91131397875

00:52:25.080 --> 00:52:26.232 in bladder cancer patients.

NOTE Confidence: 0.91131397875

00:52:26.232 --> 00:52:29.041 We just I think for the first time saw

NOTE Confidence: 0.91131397875

00:52:29.041 --> 00:52:31.075 data that there's an overall survival

NOTE Confidence: 0.91131397875

00:52:31.075 --> 00:52:33.117 benefit in the frontline setting to

NOTE Confidence: 0.91131397875

00:52:33.117 --> 00:52:35.037 a regimen that isn't cisplatin based.

NOTE Confidence: 0.91131397875

00:52:35.037 --> 00:52:36.976 So we've we beat cisplatin in the

NOTE Confidence: 0.91131397875

00:52:36.976 --> 00:52:38.715 first line setting for the first

NOTE Confidence: 0.91131397875

00:52:38.715 --> 00:52:40.770 time with a combination of inforimab

NOTE Confidence: 0.91131397875

00:52:40.770 --> 00:52:42.540 Vidotin which is antibody drug

NOTE Confidence: 0.91131397875

00:52:42.604 --> 00:52:44.720 conjugate coupled with pembrolizumab,

NOTE Confidence: 0.91131397875

00:52:44.720 --> 00:52:45.446 A checkpoint inhibitor.

NOTE Confidence: 0.91131397875

00:52:45.446 --> 00:52:46.898 So those two agents you know

NOTE Confidence: 0.91131397875

00:52:46.898 --> 00:52:48.360 and that's a that's a big deal.

NOTE Confidence: 0.91131397875

00:52:48.360 --> 00:52:50.436 We've been using cisplatin for for

NOTE Confidence: 0.91131397875

00:52:50.436 --> 00:52:52.628 decades now and and and so it's

NOTE Confidence: 0.91131397875

00:52:52.628 --> 00:52:53.998 proven a really resilient regimen.

NOTE Confidence: 0.91131397875

00:52:54.000 --> 00:52:54.480 So big,

NOTE Confidence: 0.704338187272727

00:52:54.760 --> 00:52:56.260 big news, they had a standing

NOTE Confidence: 0.704338187272727

00:52:56.260 --> 00:52:57.720 ovation at the ASIMO meeting.

NOTE Confidence: 0.704338187272727

00:52:57.720 --> 00:53:01.080 Yeah. All right, good again.

NOTE Confidence: 0.704338187272727

00:53:01.080 --> 00:53:02.022 Thanks Doctor Kelly,

NOTE Confidence: 0.704338187272727

00:53:02.022 --> 00:53:03.640 you have fantastic talk. Thank you.

NOTE Confidence: 0.16256665

00:53:15.040 --> 00:53:16.000 That's a

NOTE Confidence: 0.6084483

00:53:18.640 --> 00:53:21.000 funny one.