Welcome to Yale Cancer Answers with Doctor Anees Chagpar.

Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer.

This week it’s a conversation about the evolution of HIPEC and the treatment of cancer with Doctor Kiran Turaga.

Doctor Turaga is a professor and division chief of surgical oncology at the Yale School of Medicine.
where Doctor Chagpar is also a professor of surgical oncology.

Dr. Turaga, maybe we can start off by you telling us a little bit more about yourself and what it is you do.

I’m a surgical oncologist, which means I’m a cancer surgeon, cancer first, surgeon second. But I use surgical techniques to remove cancers and my focus has always been on cancers that spread or are advanced. Typically these cancers are called Stage 4 cancers.
cancers and potentially lead to cures even in stage 4 settings. You know, it’s interesting that you start in that way because you said a couple of things that really tweaked my interest. First, you said cancer first, surgery 2nd. And the second thing you said which was of interest was the fact that you’re interested in advanced cancers and metastatic cancers. For most cancers that we deal with most of the time surgery is limited to the early setting. So can you talk a little bit about...
00:01:44.160 --> 00:01:46.692 how you got interested in advanced
and metastatic cancers even though
you’re a surgeon or did that interest
in surgery come after the interest
in advanced and metastatic cancers?
That’s a great question.
And my evolution
and interest of both cancer and
surgery was sort of parallel.
You know, I’ve personally
been affected by cancer.
My grandfather died of lung cancer,
my dad died of liver cancer.
And so there’s certainly
a significant personal commitment
to wanting to do better for cancer.

I like doing things with my hands.

In fact, for the longest time I wanted to be a medical doctor like an oncologist.

And then when I started doing my rotations in surgery, I really enjoyed it and I felt the impact that we could have as surgeons. And so it was just a marrying of my two interests that brought me together to doing oncologic surgery. And I think you make a very good point that surgery is generally applied to tumors that are early stage or even sometimes for prevention of cancers.
But I think I was very affected by many patients that I encountered during both my training and then even as a young attending where I felt that patients who had cancers that had spread were often treated with purely palliative intent where you're trying to help them live a little bit longer with good quality of life, but perhaps not really thinking about curative approaches. And so I started thinking about the problem and I was fortunate to have interacted with numerous individuals.
that have had similar interests. And so we were able to think together about who are the patients that we can actually be aggressive even surgically to help think about more curative intent approaches.

So that’s sort of how my journey evolved. And so that leads us into the whole world of HIPEC.

Can you tell us a little bit about what exactly it is and for which patients it is appropriate? HIPEC is hyperthermic intraperitoneal chemotherapy.
Way back even in the 18th century, there were patients that were developing malignant ascites. So they had fluid fill up inside their abdomen and were very distressed. And there was a surgeon who actually put wine or alcohol inside the abdomen with an intention of seeing if it would dry up the fluid. And it did, but unfortunately caused such a significant reaction that patients didn’t do well from that. But over the years, there was this appreciation that cancers, especially many cancers that start both in the gastrointestinal tract,
so like our digestive system and the genital urinary, essentially in ovarian cancers, can actually spread to the lining of the abdomen. And as surgeons, it was sort of overwhelming to see the number of tumors that were inside the abdomen. And so back in the 1980s, a concept was developed at the NIH/NCI where chemotherapy was introduced directly inside the abdomen at high concentrations and high temperatures with the understanding that when it was delivered like that,
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NOTE Confidence: 0.652222856285714
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00:05:31.435 --> 00:05:33.200 and it started being called HIPEC.
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high temperatures inside the abdomen to essentially affect cancer cells that are there after surgery with an intention of trying to cure it. It is a technique that’s used for many cancers, like I said. But the common cancers that are routinely treated with cytoreductive surgery are ovarian cancers, colon cancers, appendix cancers, mesothelioma, and gastric cancer. So those are sort of the big cancer groups that are often treated with this technique.
we think about metastatic cancer, most often we think that the cancer has spread to a different part of the body, often through the bloodstream. And so it’s interesting that you mentioned that HIPEC is really designed to be delivered topically into the abdomen so that it has its effect on peritoneal surfaces, which seems kind of counter to how we often think about distant metastatic spread in the sense that we want to get it into the systemic absorption. Can you kind of talk about the rationale behind that and how that plays in?
Yeah, you know, I think this is actually a fascinating story of how medicine has evolved over the century. So as you know, William Halsted was a very famous cancer surgeon or a surgeon at the Johns Hopkins Hospital and he was of the belief that cancer went in a very linear progression and that if there was cancer, the more aggressive and radical your surgery, the better the chance of curing it. And that was sort of the way a lot
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00:07:29.176 --> 00:07:30.947 of cancers were treated all the way
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00:07:43.714 --> 00:07:44.999 the concept was,
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00:07:44.999 --> 00:07:47.153 all cancer is metastatic at diagnosis
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00:07:48.929 --> 00:07:50.843 or cancer DNA floating around in
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00:07:50.843 --> 00:07:52.000 your blood streams,
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00:07:52.000 --> 00:07:54.520 even if it’s a very early stage cancer.
NOTE Confidence: 0.965544569230769
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treated with a combination of chemotherapy, maybe surgery, and that is sort of how you’re trying to affect this entire system.

I think in the 1990s, a concept called oligometastasis was proposed by one of my close friends and colleagues, Ralph Weichselbaum and Sam Hellman who noted that maybe the reality wasn’t one of these two hypothesis, but actually somewhere in the middle where there were clearly groups of patients who had cancers that had spread but had spread in a very unique way where the spread was limited, it was limited to a few areas and
when treated locally, meaning with surgery or radiation or ablation. So when you’re actually working on these, you can actually potentially cure these patients of the cancer and this observation led to the coining of the word oligometastases.

And since then there have been numerous investigations in this space and it’s very fascinating to think about the peritoneum itself. The peritoneum is a remarkable barrier, but if you actually look at it, the peritoneum is like Saran wrap. I tell patients it’s sort of like wallpaper on the walls of your rooms.
So it’s a very, very thin layer. But remarkably, all cancer that generally start in the peritoneum or in the peritoneal cavity are actually limited to that peritoneum. It rarely invades beyond the peritoneum into the abdominal wall or musculature, things like that. It’s interesting when you actually measure the DNA of cancer that’s present in the blood. And this is some of our own work where we’ve found that the DNA that’s shed by these tumors, you might have a ton of
cancer inside the peritoneum, but you barely will have any DNA or cancer DNA in the blood as opposed to if you have one spot in the liver, one spot in the lungs, you know, the amount of DNA that’s shed in the blood, especially for colon cancer is tremendous. So it’s a very interesting phenomenon where this may almost be a sequestered form of metastases that is happening, you know, in a certain region. So I think that is where the appeal of surgery and delivering intraperitoneal chemotherapy.
00:10:05.920 --> 00:10:07.320 is significant in this area.

00:10:07.840 --> 00:10:10.156 Yeah, it certainly makes

00:10:10.156 --> 00:10:12.958 a whole lot more sense as to why

00:10:12.960 --> 00:10:15.360 delivering chemotherapy in a more

00:10:15.360 --> 00:10:18.256 topical way for people who have

00:10:18.256 --> 00:10:20.676 peritoneal metastases may be beneficial.

00:10:20.680 --> 00:10:24.088 Can you talk a little bit about how

00:10:24.088 --> 00:10:26.816 efficacious it is in terms of the

00:10:26.816 --> 00:10:29.240 response that patients have to HIPEC?

00:10:30.160 --> 00:10:32.050 Yeah, I think that’s a good

00:10:32.050 --> 00:10:33.894 question and it’s a complicated

00:10:33.894 --> 00:10:35.760 answer because there are numerous

00:10:35.760 --> 00:10:38.560 different cancers that are treated

00:10:38.560 --> 00:10:39.986 with intraperitoneal chemotherapy.

00:10:39.986 --> 00:10:41.718 But for instance,

00:10:41.720 --> 00:10:43.745 one of the cancers or one of the
00:10:43.745 --> 00:10:45.802 diseases that is often treated with this is
00:10:45.802 --> 00:10:47.720 a condition called pseudomyxoma peritonei.
00:10:47.720 --> 00:10:49.876 And this is a condition where patients’
00:10:49.880 --> 00:10:52.260 abdomens are full of mucus that is
00:10:52.260 --> 00:10:54.290 arising either from the appendix or
00:10:54.290 --> 00:10:56.138 the ovary and it causes the entire
00:10:56.138 --> 00:10:58.336 abdomen to fill up with mucus.
00:10:58.336 --> 00:11:01.032 Folks often look like they’re
00:11:01.032 --> 00:11:03.240 39 weeks pregnant and it’s just a very,
00:11:03.240 --> 00:11:05.640 very tremendous burden on our patients.
00:11:05.640 --> 00:11:10.240 especially the low grade tumors,
00:11:10.240 --> 00:11:12.208 70% of the patients are cured of this
00:11:12.208 --> 00:11:13.793 disease with cytoreductive surgery
00:11:13.793 --> 00:11:15.356 and intraperitoneal chemotherapy.
So it is a very remarkable effect on these tumors. On the other hand, when cancers are more high grade, so they’re more aggressive, the cure rates are a lot lower. So it’s much harder to reach, you know, 10 year survivals. But I think for colon cancer, for instance, if it’s detected very early, almost 60% of the patients will live 5 to 10 years, which I think is a good marker for considering cure as opposed to when it’s detected late, you know only 20% of the
patients will live five years.

So I think a lot depends on when it’s detected and then of course how it is treated.

Also, the other thing that is often misunderstood or mischaracterized is HIPEC is not treatment by itself without considering the agent itself that’s delivered. It’s merely a technology by which you know therapy is delivered. The effects are dependent on what the intraparitonal chemotherapy agent is. The problem with truly understanding
how efficacious or even effective

HIPEC itself is a little complicated because the first thing to consider is that it is often delivered with surgery called cytoreductive surgery.

So I give patients the example, like if you have grease that’s spilt in your room, you know, instead of just spraying Lysol or Febreze on it, you first have to clean it all out. You have to pick up all that grease, and then you spray the Lysol and then scrub it. So that’s really sort of the way HIPEC
works and it’s in its core and you know there are many components to it. There’s heat, there’s flow, there’s the drug that’s delivered, there’s the duration that this is given. And so it’s very hard to experimentally differentiate which one of these components is efficacious in which part. But in randomized trials such as in ovarian cancer and gastric cancer, it has clearly been found to be efficacious when certain agents are given. But in colon cancer, when oxaliplatin,
one of the agents that’s given, it wasn’t effective, but mitomycin, another agent was very effective. So I think it’s very individualized based on the disease.

Fantastic. So we’re going to pick up this conversation right after we take a short break for a medical minute. Please stay tuned to learn more about HIPEC and the treatment of cancer with my guest doctor Kiran Turaga.

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while respecting the unique philosophies,

spiritualities, and religions

of patients and caregivers.

Smilowcancerhospital.org.

There are over 16.9 million

in the US and

here in Connecticut.

Completing treatment for cancer

is a very exciting milestone,

but cancer and its treatment can

be a life changing experience.

The return to normal activities

and relationships may be difficult

and cancer survivors may face
other long term side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated Comprehensive Cancer Centers, such as Yale Cancer Center and Smilow Cancer Hospital. The Smilow Cancer Hospital Survivorship Clinic focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life, and longevity.
00:14:53.840 --> 00:14:56.176 More information is available at yalecancercenter.org.

00:14:56.176 --> 00:14:57.194 You’re listening to Connecticut Public Radio.

00:15:00.720 --> 00:15:02.598 Welcome back to Yale Cancer Answers.

00:15:02.600 --> 00:15:04.120 This is Doctor Anees Chagpar,

00:15:06.160 --> 00:15:07.321 and I’m joined tonight by my guest, Doctor Kiran Turaga.

00:15:07.321 --> 00:15:09.643 We’re talking about the evolution of HIPEC in the treatment of cancer.

00:15:12.040 --> 00:15:14.375 And right before the break, Kiran, you were talking about the fact that delivering this particular drug depending on the disease in question,

00:15:20.416 --> 00:15:25.120 delivering chemotherapy at a high temperature into the peritoneal space,
it can potentially be curative when coupled with surgery for patients with metastatic disease, which is something that a lot of people may not really think about. When we think about metastatic disease, the words curative and metastatic usually don’t go together. So a couple of questions just to wrap up what we were talking about before you had mentioned that the peritoneal cavity is kind of like saran wrap. And so one can imagine that the chemotherapy may help to reduce that amount of disease in people who have significant burden of
metastases in their abdominal cavity.

The question then becomes, can you really remove all of that with surgery? And if not, how do you decide what to remove and how do you decide if that’s good enough?

Yeah, they’re very, very good questions. And I think the answer is a process in evolution. So the lining which is essentially in the same example of the room for instance, being your abdominal cavity with
furniture inside it,

it's very easy to remove the wallpaper,

the flooring, the roof lining,

which is the the anterior peritoneum

or the parietal peritoneum.

So I think that’s a fairly straightforward procedure and

when I say straightforward you know

developed and you require expertise

but with training I think it’s

possible for experts to do.

I think the part where it becomes

a little bit more challenging is

when the peritoneum overlying the

organs called the visceral peritoneum

especially over the intestines
00:17:17.759 --> 00:17:19.839 is involved with the disease.

00:17:19.840 --> 00:17:23.848 And so I think the key thing

00:17:23.848 --> 00:17:26.584 that we know is that

00:17:26.584 --> 00:17:29.319 removing tumors part way, halfway,

00:17:29.320 --> 00:17:31.315 a little bit, doesn’t help.

00:17:31.320 --> 00:17:33.640 So I think the key part is in

00:17:33.640 --> 00:17:35.278 selecting the patients in whom

00:17:35.278 --> 00:17:37.588 such that the chemotherapy can work.

00:17:37.660 --> 00:17:40.048 reduce it to a microscopic level

00:17:40.048 --> 00:17:42.218 such that the chemotherapy can work.

00:17:42.218 --> 00:17:44.241 So I think the selection of patients

00:17:44.241 --> 00:17:46.914 is very important and I think the big

00:17:46.914 --> 00:17:48.924 factors that actually prevent many of

00:17:48.924 --> 00:17:50.838 us from doing these surgeries would

00:17:50.838 --> 00:17:53.045 be if there is extensive involvement

00:17:53.045 --> 00:17:55.066
of the visceral peritoneum which is the lining on the intestines or the surfaces of the intestines that cannot be feasibly removed.

I think the other thing also as cancer surgeons, we all think about very carefully with our patients and shared decision making is making sure that we are hitting the goals, it’s not just adequate to live long or get cured, if you’re going to be living a miserable life. So I think it is very important to balance both quality and quantity of life when these decisions are being made.
Which of course brings us to the next question, which is can you talk about some of the side effects of this procedure? Yeah. So I think these side effects are again broken down into the two components. So one is the cytoreductive surgery and these surgeries can be very, very big where we’re doing long operations, 8 to 10 hours trying to clean out tumors from every nook and cranny inside the abdominal cavity requiring resecting organs, sometimes many organs. And so it could be very dramatic or it could be very minor. We’re actually now doing
In fact we just published along with a bunch of other institutions a group of laparoscopic procedures where you can do these with little poke holes and remove a lot of the cancers and still achieve the same benefits. The premise being you can identify these cancers early, which I think is the key to thinking about the future of this. And so the side effect profile of the surgery is something that is well known and well understood.
many randomized trials adds very little to the complication profile when studied in trial. So essentially, it can increase the risk of bleeding, leakages when we make connections. But I think one of the things that we notice often in clinics is that it does knock the wind out of our patients a little bit more than just surgery. And so you know patients will typically feel about 80% of their pre surgery quality of life at about six weeks and it takes about 3 months for people to really start feeling as
As they did before the surgery.

However, interestingly in many quality of life studies at six months, most patients actually feel better, like 120% as compared to prior to surgery obviously because the cancer has been removed and they're doing well at that point.

Getting back to the question or the point that you made earlier which was that removing a little bit doesn’t really help. I think a lot of listeners may have the question that goes something like this.
If you have this peritoneum, which is a barrier, right?
You had mentioned before the break that people who have peritoneal metastases often times don’t have a large burden of circulating cancer that it really acts to confine that. So then I wonder if you remove the peritoneum, do you then remove that barrier such that patients who get a recurrence may be more likely to get distant metastatic disease? That’s a fascinating question. And the answer is we don’t know completely,
but I can give you some data that might help us think about this.

So if you think and again remember unfortunately there’s a very heterogeneous group of tumors.

So it matters which cancer we’re talking about.

But let’s take the example of colon cancer for instance.

And so in colon cancer, when the lining is removed, the peritoneum is removed. Depending on when the cancer comes back, often the cancer will still come back inside the abdominal cavity.
So even though the barrier or the lining has been removed, it still tends to come back to the cavity.

Now the caveat is that in colon cancer we rarely remove the entire lining, the parietal peritoneum.

And so perhaps there still is that evidence of a barrier that’s keeping things at bay.

On the other hand, there are tumors like mesothelioma appendix tumors where we actually take out the entire lining.

And even in those scenarios very often if it does come back, it still tends to come back.
inside the abdominal cavity. However, one of the observations we started noticing as a group most of us that treat patients with this disease was that we were now keeping patients alive longer and longer to the point where now we started seeing metastasis or spread of cancer in locations that we wouldn’t conventionally see. So for instance in appendix cancer we started seeing bone metastasis or brain metastasis five years after an operation.
So just a very unusual pattern. So perhaps there may be some effect of removing the peritoneum, but not something that is immediately observable or has been seen by datum. And you know presumably this will take longer study because distant metastases won’t occur in the short term. And so it’s interesting to kind of think about getting these distant metastases that we may not have seen before. Which brings us to the next big question I think, which is can you talk a little bit about ongoing research and things that are most exciting for
you moving forward in this area?

Yeah. So I think this is perhaps where we have the opportunity for greatest impact, which is number one, I think knowing what this disease is. So I think finally now there’s enough awareness and there’s a lot of folks that are learning more about peritoneal metastases early. And what is fascinating is a study that was recently published where patients with colon cancer without metastases were treated with intraperitoneal chemotherapy with HIPEC.
at the time of their operation.

So remember, no peritoneal metastases and they actually demonstrated that at three years, 97% of these patients who got the chemo didn’t have peritoneal metastases versus 84 or 85% of patients in the other arm who developed metastases. So it’s a remarkable concept of thinking about can we act in a preventative way or can we act in a way where we find these diseases early. I think the other thing is using novel technologies like CFDN, A/C, TDNA, advanced MRI, advanced PET scans to find these.
peritoneal metastases early so that they can be treated earlier. And then I think more importantly finding better agents that can be put inside the abdomen in better ways. So there’s technologies like HIPEC, which is aerosolized chemotherapy, but there’s also other things such as delivering immunotherapy inside the abdomen, viruses inside the abdomen, vaccines that I think have really moved the field forward and are are exciting. And what I tell a lot of my patients is that while we try our best to cure these cancers we’re not successful all the time,
our goal is to at least keep people alive long enough with good quality of life such that our science advances at a pace that we are able to see this. And in my own lifetime, as I’m sure you have seen Anees, the advances in cancer care have been dramatic. You know for the first time we’re seeing reduction in cancer deaths nationally. We’re seeing almost two to three new drugs being approved by the FDA every month for many of these conditions. And so I think it is remarkable to be at this phase of science where I feel much more hopeful about our goals.
of using HIPEC for preventing peritoneal metastases is certainly intriguing especially when you couple it with this idea of you know the peritoneum being a barrier. So has anybody looked at using just the chemotherapy part of HIPEC in terms of the prevention or in the preventative trial that you mentioned, were they also removing the entire parietal peritoneum? No. So I think 2 parts to the answer. First for the trial specifically called the HIPEC T4 trial, it was removing the colon cancer.
and then doing the hot chemo, not removing the parietal peritoneum. And so I think that was purely a study where delivering the intraparitonal chemotherapy with mitomycin worked in colon cancer. A similar study with oxaliplatin actually didn’t work. So again going to the concept that the actual drug that is delivered matters a lot in these diseases. I think the concept of putting chemotherapy alone in the abdomen is something that is being explored both by a technology or technique.
called intraperitoneal aerosol chemotherapy (PI-PAC).

In both of these concepts, if you think of the analogy I'd given earlier of grease on the floor and you know cytoreductive surgeries, removing the grease and HIPEC is sort of the Lysol or the Febreeze spray. There is a concept where you actually don’t remove the tumor at all. So you don’t actually scrub the grease and you just put the chemotherapy inside the abdomen. You let it deliver either through HIPEC which is heated and delivered inside.
the abdomen or through normal
thermic intravertinal chemotherapy.
So you just put a catheter and you
put chemo inside it or with PIPEC
in which you actually aerosolize
the chemotherapy and put it inside.
And there are numerous trials that
are ongoing across the world where
these concepts are being studied not
just to improve quality of life, but also to see if these are helpful
in controlling the cancers.
It is a little difficult to believe
that these therapies alone,

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And so many of these are trials designed with the end point of being able to get to cytoreductive surgery or some other modality. But it has been very interesting to see many preliminary reports where intraparitonal chemotherapy delivered in different forms seems to have a significant oncological benefit. And to your earlier point of you know the whole concept of HIPEC and cytoreductive surgery being kind of studied as a bundle, right, with the heat and the intraparitoneal chemotherapy and the cytoreductive surgery. One can only imagine that these trials
that are now ongoing which are looking at, well what if we don’t heat the chemotherapy, what if we don’t do the cytoreductive surgery might give us some insight into, you know, which of these elements of HIPEC are really the most efficacious? Absolutely. Doctor Kiran Turaga is a professor and division Chief of Surgical Oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at yalecancercenter.org.
We hope you'll join us next week to learn more about the fight against cancer here on Connecticut Public Radio. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.