Support for Yale Cancer Answers comes from AstraZeneca, a pharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com.

Welcome to Yale Cancer Answers with your host 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 gastroesophageal cancer with Doctor Jill Lacy.

Doctor Lacy is a professor of medicine and medical oncology at the Yale School of Medicine where Doctor Chagpar is a professor of surgical oncology.

Jill, we don’t often talk about gastroesophageal cancers much. So if you combine esophagus and...
gastric cancer in the United States, there’s about 46,000 cases a year, about 27,000 deaths. So it is quite a lethal cancer. And by contrast, lung cancer over 200,000 cases. Breast cancer, I believe over 270,000 cases. But interestingly, the death rate as I indicated, still is quite high. You compare this, say with breast cancer, where I believe we’re down to in the range of 40,000 deaths per year. So even though it’s not a common cancer, it is still a significant problem in terms of its lethality. What’s interesting about these cancers is that there’s quite a bit of geographic variation in incidence and gastric cancer actually is quite common worldwide and a significant public health problem. It’s actually the third leading cause of cancer related deaths globally. Over 1,000,000 cases and over 800,000 deaths. So it does remain, I think, a huge issue globally and still problematic in the United States. And on top of that, gastroesophageal cancers not only are
gastric cancers or cancers of the stomach, but also of the esophagus. But the esophagus is a long tube that goes all the way from essentially your mouth all the way down to your stomach.

So talk a little bit about whether those cancers, the cancers of the esophagus and the cancers of the stomach are similar or different, and whether there are different types of cancers even within that. Sure, so we often divide these cancers into two anatomic groups.

Esophagus cancer, as you alluded to, and gastric, or what we call stomach cancer. And esophageal cancer we now know really is comprised of two very distinct types, really essentially different diseases. One type is called squamous cell cancer an under the microscope and in terms of its molecular biology and risk factors, it’s actually quite similar to cancers of the throat and the head and neck region. The risk factor there is tobacco and alcohol in poverty.

And Interestingly, the incidence of squamous cell carcinoma of the esophagus has really dropped dramatically, particularly in the Western world,
so that’s the good news.
The other type of esophagus cancer is called adenocarcinoma, and then actually arises at the bottom of the esophagus where it connects in with the stomach, often referred to as gastroesophageal junction cancer, and looks much more like a typical gastric cancer under the microscope. And actually is much more similar to gastric cancer than it is to squamous cell cancers of the esophagus. And they are. They have different risk factors, so I alluded to the risk factors for squamous cell of these saw fickas it’s predominantly tobacco and alcohol as we see with head and neck cancer. For the adenocarcinomas of the esophagus that arise at the bottom of the esophagus. What’s interesting about that is that there actually has been quite a dramatic increase in the incidence of this particular entity. Particularly in Caucasian males, a great male predominant we don’t fully understand that increase some of the risk factors that are linked.
Two adenocarcinoma of the esophagus are high BMI or obesity. Possibly Dyett gastro oesophageal reflux disease is certainly risk factor in some cases, but smoking and alcohol do not seem to play a predominant role in risk. Then you get into the stomach and we’re talking about classic gastric cancer. And there what’s very interesting is that there’s been a progressive decline. Across the globe and in the United States. In the incidence of gastric cancer as it was the number one cause of cancer related deaths globally until about the 1980s, when it was surpassed by lung cancer and there are a lot of interesting theories about why that is. And we do know that there are some risk factors for stomach or gastric cancer, and these include some environmental and lifestyle risk factors. One of the most prominent is a bacteria called Helicobacter pylori, which is quite prevalent and some strains of that bacteria are cancer causing and do increase the risk of gastric cancer through been a lot of studies over the decades about diet.
So it does seem that.
Salt preserved and smoked foods increase the risk as well as dietze that are low in fresh fruits and vegetables.
Modest risks risk factors would be smoking and obesity and probably lower social economic status.
So there are a lot of differences, not only anatomically and in terms of the pathology under the microscope but also risk factors, and it’s interesting deals that you mentioned that the oesophageal cancer rate and the gastric cancer rate. Both seems to have dropped, but gastroesophageal cancers, those cancers that occur at that junction, the add node cancers.
Have increased Ann. You mentioned that we we don’t know exactly those have increased, but do we have any insight into what played a role in decreasing the incidence of oesophageal cancers and gastric cancers? So for squamous cell carcinoma of the esophagus it is related to a decrease in smoking. And improvements in social economic status and nutrition. Those seem to be quite linked to squamous
0:07:58.484 → 0:08:02.52 of the esophagus and for gastric cancer, we do think that it does relate to decreasing incidence of H. Pylori colonization or infection related, likely due to refrigeration over the last century or so. So in areas of the world that are underdeveloped we see a drop in the incidence of gastric cancer, so that’s the prevailing theory. But you know, it’s interesting that despite these advances, this is still, as you mentioned, a fairly lethal cancer when we think about gastroesophageal cancers as a whole, is that because they tend to present at late stages in general? I think it’s a combination of factors. Yes they are lethal cancers, and that’s why even though they’re not so common in the United States, they’re still very problematic. So the five year cure rate for esophageal cancer was only about 20%. It’s a little bit higher for gastric cancer, about 30%, and I think the reasons for this are multi factorial if you will. In some cases, due to a delay in diagnosis, but I don’t think that’s the major reason.
I think it has much to do with the inherent biology of these tumors. A propensity to disseminate or spread early on, and then the need for better and more effective therapies to deal with disseminated disease.

I would add that in contrast to the common cancers such as breast, colorectal, lung, and cervical there is no widespread screening at least in the Western world. But it is a little bit different in Asia and therefore early detection is less likely to happen with these cancers as opposed to breast cancer,

Usually we find screening to be more prevalent in the Western world than we do in less developed countries. In terms of screening in Asia for gastric cancer they do pretty sophisticated...
radiographic studies to look at the surface of the stomach to see if there are irregularities, and then for esophagus cancer screening modalities is to have patients swallow a balloon and sort patients swallow a balloon and sort patients swallow a balloon and sort and pull it up through the esophagus and you pull off abnormal cells in the lining of the esophagus. And those are two screening modalities. That can be applied widely in the United States because it is an uncommon cancer. I think there’s just not been a lot of focus on widespread screening for these cancers. So you mentioned that these cancers tend to, because of their biology, be more advanced at the time of presentation and more rapidly get to a more advanced or metastatic stage. what proportion of these patients present with advanced or metastatic disease, out of all the gastroesophageal cancers that you see? Still the majority of the patients are presenting with non disseminated or nonmetastatic disease, so that’s the good news.
oftentimes particularly with the more advanced but still nonmetastatic cases, there is what we call a cult dissemination, and that is where we look to additional therapies such as chemotherapy to try to increase security. You know, it’s something that we’ve been doing for several decades in the breast cancer world, and certainly has a role in these cancers as well. Even in those patients who appear to have localized and potentially curable disease. And I want to kind of get into how exactly we treat patients, and so with those patients with localized disease, can we treat these patients for curative intent? And how do we do that? Absolutely, patients who present with nonmetastatic disease, so no evidence of dissemination and that we determined simply by getting imaging, usually a CAT scan or in some cases a PET scan. And for those patients there is a path to cure for many of those patients,
and that often involves surgery as the centerpiece of the cure and then in many cases where the disease is more locally advanced, we will need adjunctive therapies in addition to surgery to further increase the cure rate. And that’s true both for esophagus cancer and for gastric cancer. When the disease has spread or is more advanced, I would imagine that therapies can be a little bit more challenging or problematic but I do understand that there are some new advances that may help patients who have more advanced or metastatic disease. So I want to get into all of that, but first we need to take a short break for a medical minute, so please stay tuned to learn more about gastroesophageal cancer with my guest Doctor Jill Lacy. Support or Yale Cancer Answers comes from AstraZeneca, a science LED biopharmaceutical company dedicated to partnering across the oncology community to improve outcomes across various stages of cancer. More at astrazeneca-us.com. This is a medical minute about breast cancer,
the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year, but thanks to earlier detection, non invasive treatments, and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. More information is available at yalecancercenter.org.

You’re listening to Connecticut Public Radio.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Jill Lacy. We’re talking about gastroesophageal cancer and right before the break Jill was telling us about
how this is a rare cancer, but one that really is fatal for some patients and especially difficult or perhaps more challenging to treat in the advanced and metastatic setting. So Jill tell us a little bit more about historically the options that we've had for advanced metastatic gastroesophageal cancers and some of the new developments that maybe can give patients more hope. For most of my career, when patients develop metastatic or disseminated esophageal or gastric cancers, we were able to offer some treatments, but the prognosis was poor and the survival was relatively short and those treatments up until relatively recently were basically the use of chemotherapy, or cytotoxic drugs. Traditional chemotherapy drugs. And those drugs, often provided some palliation and mostly prolong survival, but it was unusual to see long-term survivors, and we were not curing patients with those treatments. What changed more recently?
There have been some very exciting advances in the treatment of metastatic, or disseminated, both esophageal and gastric cancers. The first advance came about a decade ago and this was in the area of gastric and gastroesophageal adenocarcinomas. And what we had learned was that these are heterogeneous from a molecular perspective. And about 20 to 30% of these tumors carried high levels of a protein called Her 2, and we knew that this protein also was present in breast cancer. And a drug had been developed called an antibody that targeted her 2 in breast cancer and it was extraordinarily effective. That drug is trastuzumab, or Herceptin. And so it was theorized that perhaps Herceptin would have activity in the her 2 positive gastric and esophageal adenocarcinomas. So there was a large global effort to answer that question. Patients with advanced disease, metastatic or stage four were assigned to get the standard of care at that time, chemotherapy with two drugs the results of that study were really quite stunning.
in that survival was significantly improved for those patients who received Herceptin. So I would say that was the first big advance and changed the paradigm about how we think about these cancers in terms of looking at the molecular profile and thinking about using targeted therapies. So that was very exciting. And then what happened? It sounds like there’s another shoe that’s about to drop. There is, so in the breast cancer world what followed on after the discovery of Herceptin was the development of other drugs that targeted this protein Her 2 and there were additional drugs that were developed and approved and that were effective. But unfortunately when those drugs were tested in gastroesophageal cancers that were positive for her 2, they were not effective and that was disappointing and so we were learning that her 2 positive gastroesophageal cancer is not the same thing as her 2 positive breast cancer. That’s interesting. So wait a second, what you’re saying is that trust Herceptin worked in her
positive gastric cancer,
but Pertuzumab, I’m assuming
that you meant pertuzumab,
which also targets her 2, did not work.
It did not in the studies that were conducted as well
as the antibody
drug conjugate TDM one and lapatinib.
Any why was that?
I mean do they think that
there was something particular about
her 2 or was it or about Herceptin
versus the other drugs in terms
of what particular subunit of her 2
that we’re targeting?
Or what was the
hypothesis behind why
one drug would work, but the
others didn’t?
That is a great question and I don’t
know that we have all the answers.
We do know that gastroesophageal cancers
are much more heterogeneous in terms
of their levels of expression are
more likely to lose expression overtime,
so that’s one issue.
Some of it may have been related to how
the studies were designed and conducted,
but I don’t think we fully understand
why we don’t see the exact same activity
of some of these agents in gastric
and esophageal adenocarcinomas that we’re
seeing in breast cancer. Sorry to interrupt, but it still sounds like there was another shoe that was going to drop. Well, I think we’re very excited in that it does appear that there is going to be newer generations of her 2 targeting agents that are going to be effective in gastric cancer. So one of them is a very interesting drug that is also used in breast cancer now very recently where you take Herceptin and you link it up biochemically to a chemotherapeutic drug. And that has been approved in breast cancer. That’s her 2 positive and has been tested now and her 2 positive gastroesophageal adenocarcinomas in patients who have already been on trastuzumab and have failed treatment and the results really were stunning. With major shrinkage in more than half of the patients, which is not something that we typically see in this disease. Really with any line of therapy and very impressive survival. So this is very exciting. There was a New England Journal of Medicine paper regarding this
data earlier this year, and I do believe this new drug will be approved not only in breast cancer but also in her positive gastroesophageal cancer. So we’re very excited about that. And again, this is for our patients who have her two positive tumors. So it’s not for all comers. So that’s one development.

And then I think we will also see some newer generation antibodies that are similar to trastuzumab but more potent in recruiting the immune system into action to kill the cancer. And so one of those is called margetuximab, so quite similar to trastuzumab, but it enhances the immune response and we’ve already seen really positive and exciting preliminary data when it is combined with immunotherapy. And there’s a very exciting on going clinical trial looking at this combination of margetuximab in immunotherapy with chemotherapy in newly diagnosed patients. So we’re very excited about the second and third generation iterations and then there are other novel antibodies.
targeting her 2 that are being developed, so I do think that the field is really going to open up in terms of treatment of her 2 positive stage for gastroesophageal adenocarcinoma. I’m very hopeful that the prognosis for these patients will improve significantly with these therapies. But there’s still a large fraction of patients who are her 2 negative, So what about them? Does standard immunotherapy, for example with checkpoint inhibitors, help them? This is where there’s some excitement really just in the past few months. So we hear a lot about immune checkpoint inhibitors. Drugs like KEYTRUDA or Opdivo in colon cancer, lung cancer, Melanoma, and many other cancers where these immunotherapeutic agents have really been game changers. These agents in the way the studies have been done to date have not appeared to have a significant impact in gastroesophageal cancer. But there is some activity and we’re learning more about who should get these agents who will benefit
most when and how to use them.
And I think that’s where the field is moving forward in a very positive way.
So there are already FDA approvals for classical immune checkpoint inhibitors,
and gastroesophageal cancer,
so we can use KEYTRUDA in patients who failed standard several lines of standard therapy
if their tumor expresses the target PDL1 that’s for gastric and gastroesophageal adenocarcinomas and it is also approved in esophageal squamous cell carcinoma after standard initial chemotherapy works.
And the results are very impressive there and it’s also active in a very small subset of patients whose tumors are characterized by what we call microsatellite instability.
Or loss of a DNA repair mechanism.
These tumors are characterized by lots of mutations in abnormal proteins.
And respond very well to checkpoint inhibitors,
but that’s a small percentage in the range of three to 5%.
So what’s most exciting is data that we heard really just a few months ago regarding the incorporation of immune checkpoint inhibitors into
the initial treatment of stage four, gastric and esophageal cancers. And so there were a couple of studies that were presented at the major meeting in Europe. Both had similar designs. One was focused on gastroesophageal adenocarcinoma and in this study patients were given either the standard two drug chemotherapy, or those same two chemotherapy drugs with no OPDIVO and again really exciting results with the significant improvement in survival. A higher response rate and excellent tolerability. So lots of excitement about that. And then a second study with a very similar design of chemo or chemo, with in this case KEYTRUDA and here the focus was again on esophageal cancer, both squamous and adenocarcinoma, and again a similar exciting result showing a significant improvement in survival. Actually a doubling of survival at two years. So this is really great news for patients with these diseases, and I do think that these studies will ultimately lead to new indications and FDA approvals.
We’re not there yet, but I think we’re getting close.

What about in terms of other targeted therapies?

You know we have talked on this show with other people from other disease groups and other cancer types about looking at cancers and seeing what genes are turned on and turned off to try to target these?

How much of that goes on in gastroesophageal cancers?

Are we getting there in terms of genomic analysis of these cancers and being able to target them aside from her 2?

Yes, absolutely, so we routinely recommend that all patients with advanced gastroesophageal adenocarcinomas and squamous cell carcinomas undergo what is referred to as tumor profiling or molecular profiling to look at the genetic makeup of the tumor to see what makes it tick.

Now we haven’t identified a high frequency of recurring targets.

To date, other than her 2, but there are targets that are expressed with reasonable frequency that are what we call actionable or druggable where we can develop a
drug or have a drug that potentially could target that abnormality.

So we’ve talked at length today already about her 2, and that’s a critically important target in those 25 to 30% patients and again another exciting development that I think we are on the cusp of is another targeted therapy. This again is an antibody that is targeting another protein called fibroblast growth factor receptor and like her 2, is expressed on the surface and in about probably 20 to 30% of patients is expressed at very high levels or overexpressed and this has been a target for the development of an antibody, and we heard really just this week from a press release, so we haven’t seen the data, so we have to stay tuned, that a study looking at patients who have this target looking at these patients and combining the antibody that targets FG FR2 with chemotherapy and comparing that to standard of care chemotherapy alone. And at least based on the press release, this looks like it will be a positive study.
So again, quite a bit of excitement and buzz in the field.

So there’s one example, there are several others and drugs in the pipeline looking at other targets.

Doctor Jill Lacy is a professor of medicine and medical 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.