Transcript Details
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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

How Early Decisions in Upper GI Cancer Shape Long-Term Outcomes

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by BeOne Medicines. Here's your host, Dr. Alexandria May.

Dr. May:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and joining me to discuss how earlier-line treatment decisions can influence outcomes and options for patients with upper GI cancer who progress to advanced disease is Dr. Sunnie Kim. She's an Associate Professor of Medicine at the University of Colorado Anschutz School of Medicine. Dr. Kim, thanks for being here today.

Dr. Kim:
Happy to be here. Thank you for inviting me.

Dr. May:
So, Dr. Kim, when you think about the current landscape of early stage and locally advanced upper GI cancers, what unmet needs remain most significant, and how might these early changes shape outcomes and treatment options for patients who later present with unresectable or metastatic disease?

Dr. Kim:
So we as a field have been doing better with giving patients more effective systemic therapy alongside surgical resection to hopefully help cure these patients of gastric and esophageal cancers. Currently, the newest standard of care is to give perioperative FLOT plus durvalumab. So FLOT is a triplet chemo regimen with 5-FU oxaliplatin docetaxel. And based on the MATTERHORN results that were presented last year, there is a survival benefit with adding durvalumab, which is a PD-L1 inhibitor, to perioperative FLOT. This data showed us that we achieved a higher pathological complete response rate for our patients and also improved event-free survival and overall survival for our patients. Having said that, we still struggle with having patients recur with disease even after this very aggressive systemic therapy regimen and life-changing surgery, whether it be an esophagectomy or gastrectomy. And I think a big need here is after they recur, our subsequent lines of therapy options for them in the recurrent metastatic setting are far inferior to the FLOT and durvalumab. And so as a field, we need to seek and study better treatment options for our patients after disease recurrence.

Dr. May:
From your perspective, how do current limitations in organ preserving and adjuvant approaches influence long-term outcomes like survival and quality of life? And what impacts do these early decisions have on systemic treatment options after recurrence?

Dr. Kim:
So we hope to get to a point where we can offer organ preservation to a majority of our patients. Unfortunately, we're not quite there yet. There are some patients, especially with MSI-high disease or mismatch repair deficient disease, where we can offer them immunotherapy-based treatments in the perioperative setting or neoadjuvant setting. We have noticed that when we give patients neoadjuvant immunotherapy-based treatments, upwards to 60 percent of patients may not need a surgical resection. We may be able to achieve a cure with just systemic therapy in the localized setting. But the vast majority of our patients don't have MSI-high disease in the localized setting. They have microsatellite stable disease, and in those situations, we do offer patients FLOT and durvalumab

perioperatively alongside surgical resection to be able to provide them with the highest chance of cure.

When they do have disease recurrence, we have limited options. So if a patient has disease recurrence over a year after receiving adjuvant therapy, we may be able to reintroduce the same drugs to see if we can induce a tumor response. However, if patients have disease recurrence within a short period of time after finishing adjuvant therapy, then we get concerned that they may not respond to that treatment any longer just given how quickly the disease recurred. In those situations, we often go for second-line and beyond therapy options or hopefully provide them with an opportunity to be on a clinical trial to have an experimental, promising therapy.

Dr. May:
Given that there's growing attention to PD-L1 status, MSI-high, HER2 expression, and Claudin 18.2 in upper GI cancers, how can earlier and more consistent use of biomarker testing help improve treatment alignment and informed decisions in the first-line unresectable setting?

Dr. Kim:
So biomarker testing is really key to providing our patients with optimal therapies. As you mentioned, those four biomarkers in my practice are must-haves, and we actually test for it even in earlier settings—not when patients necessarily present with metastatic advanced disease, but when they have localized disease so we can be prepared if the disease does become more advanced. So by having these biomarkers on hand, our patients are eligible for more targeted first-line therapies if they do become advanced disease.

So in the first-line setting, if someone has MSI-high disease, then we definitely want to make sure that we incorporate a PD-1 or PD-L1 inhibitor. If they're HER2 positive, most recently, we saw data come from GI ASCO of this year showing that a new therapy called zanidatamab in conjunction with chemotherapy and a PD-1 inhibitor, tislelizumab, can potentially improve survival over prior standard of care. If they're Claudin 18.2 positive, we now have a drug called zolbetuximab, which is a Claudin 18.2 monoclonal antibody, in conjunction with chemotherapy that can be offered to patients, showing a survival benefit over chemo alone. And then of course, if they're PD-L1 positive, we just want to make sure that they have a PD-1 inhibitor incorporated into their first-line chemotherapy backbone.

And by doing this, we offer patients that opportunity to have a better survival, to be on agents that are not necessarily chemotherapy, and to hopefully be able to prolong their lives.

Dr. May:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Sunnie Kim about how early treatment decisions can impact long-term planning and outcomes for patients who later develop advanced upper GI cancers.

Now, Dr. Kim, if we zero in on some recent clinical trial data, the final ASCO 2025 results from CheckMate 577 reported an overall median survival of 51.7 months with adjuvant nivolumab versus 35.3 months for placebo in resected esophageal or gastroesophageal junction cancer, with the most pronounced benefits seen in the squamous cell subgroup. How do you interpret these findings in your use of adjuvant immunotherapy, and what expectations do they set for first-line therapy if recurrence occurs?

Dr. Kim:
So CheckMate 577 was a global phase 3 trial evaluating patients who had GEJ and esophageal squamous or adenocarcinoma. And for patients who received chemoradiation followed by surgery, they were randomized to receive one year of adjuvant nivolumab or one year of placebo. And a few years ago, we found that there was disease-free survival benefits, and at ASCO last year, we finally received the median overall survival results.

And what we found was that in the overall population, despite a numerical benefit in median overall survival for the patients who received adjuvant nivolumab, this was not statistically significant, but when we looked at subgroups, we found that in the squamous cell population and in tumors that were PD-L1 positive, there was a median overall survival benefit. So in my practice, for patients who are receiving chemoradiation followed by surgery and have residual disease in the resected specimen, I do offer my patients who have squamous cell histology or PD-L1 positive tumors to receive the adjuvant nivolumab.

In terms of what I offer patients in the first-line setting, it really depends on when they experience disease recurrence. If it's over a year

after they finished the adjuvant nivolumab, then I will offer some version of fluoropyrimidine and a platinum agent plus or minus an immune checkpoint inhibitor or other targeted treatment depending on the biomarker status. But we don't really base early decisions on what could happen in the future if they experience disease progression.

Dr. May:
Another key trial was MATTERHORN, which showed that adding durvalumab to perioperative chemotherapy led to a significant improvement in event-free survival with manageable toxicity in resectable gastric and gastroesophageal junction cancers. So how do these findings influence your thinking on early immunotherapy integration, and what implications do you see for first-line strategies in patients who later develop advanced disease?

Dr. Kim:
So MATTERHORN was a practice-changing study, and we actually found that there was a median overall survival benefit at the 2025 ESMO conference in the fall. So right now, I am offering all my patients with locally advanced gastric and GEJ adenocarcinoma perioperative FLOT plus durvalumab. For patients who have disease recurrence after that regimen, I think it, again, really depends on when they experience disease recurrence. If they experienced disease recurrence a year after completing adjuvant FLOT durvalumab, then I will offer them some form of fluoropyrimidine and platinum drug plus or minus an immune checkpoint inhibitor or a targeted agent depending on their biomarker status. If they experience disease progression during adjuvant therapy or within six months of completing adjuvant FLOT durvalumab in those situations, then I'll go to more standard second-line therapy for advanced disease, or I'll try to offer them a clinical trial.

Dr. May:
As new survival and perioperative data continue to emerge, Dr. Kim, how can clinicians effectively align earlier decisions with future first-line planning to ensure consistent evidence-based and patient-centered care across the spectrum of upper GI cancer management?

Dr. Kim:
I think when someone presents with localized earlier-stage disease, they really have one chance to cure this, and so we do offer them very aggressive treatments. In the case of gastric and GEJ and distal esophageal adenocarcinoma, I'm offering them the triplet chemotherapy FLOT plus durvalumab. And if we do see a patient have disease recurrence, then we do go to second-line and beyond options, which we acknowledge are suboptimal, and so as a field, we're trying to develop new drugs and perform clinical trials to be able to provide patients with more effective second-line and beyond therapies. Having said that, I don't really base my earlier decisions in terms of systemic therapy options on what could happen in the future. We just want to offer patients the most effective treatments if they have curable disease.

Dr. May:
As those key strategies bring us to the end of today's program, I want to thank my guest, Dr. Sunnie Kim, for joining me to share her insights on improving outcomes for patients with advanced upper GI cancers. Dr. Kim, it was great speaking with you today.

Dr. Kim:
It was great to speak to you today. Thank you for having me.

Announcer:
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