TRAVIS GROTZ: My name is Dr. Travis Grotz, and I am a cancer surgeon at Mayo Clinic in Rochester, Minnesota. My research and clinical expertise are in treating patients with gastric cancer and other malignancies of the gastrointestinal tract, as well as tumors that spread within the abdomen or peritoneum. The past year, 28,000 people were diagnosed with gastric cancer in the United States. Approximately, 1 in 95 men will develop stomach cancer in their lifetime, and for women that risk is 154.

However each individual person's risk is affected by certain risk factors, such as ethnicity, infection with bacteria, such as H pylori, or the Epstein-Barr virus, smoking, obesity, previous stomach surgery, pernicious anemia, hypertrophic gastropathy, and consuming a diet rich in smoked foods, salted fish, pickled vegetables, or cured meats.

Gastric cancer may also be inherited through familial syndromes. These include, hereditary diffuse gastric cancer, which is caused by inherited mutation in the CDH-1 gene, Lynch syndrome, or hereditary non-polyposis colorectal cancer, a syndrome associated with inherited defect in the body's ability to repair damaged DNA, and familial adenomatous polyposis syndrome, also known as FAP, which is associated with an inherited mutation in the APC gene, which leads to numerous, precancerous polyps of the upper and lower tract.

Inherited mutations in the DNA repair genes, BRCA and BRCA2, are also associated with an increased risk of gastric cancer. Lastly, Li-Fraumeni syndrome involves inherited mutation in the P53 gene, which places patients at risk for several different malignancies, including gastric cancer.

Gastric cancer often does not cause symptoms until it's become advanced. Some signs and symptoms of gastric cancer include, epigastric pain or discomfort, bleeding from the tumor which may lead to vomiting blood, or having dark, tarry stools. Persistent blood loss can lead to iron deficiency anemia, which may cause dizziness and light headedness. The tumor can also obstruct the stomach causing weight loss, nausea, vomiting, feeling full fast, or bloating.

Overall, gastric cancer is decreasing in frequency. However, it remains the seventh leading cause of cancer related death in the US. And we are seeing an alarming rise in the incidence of gastric cancer in young patients. Fortunately, new advances in systemic chemotherapy, sequencing of treatment, and improved surgical techniques, are allowing patients to live longer

than before with gastric cancer.

However, in order to realize these improvements patients must be treated by a multidisciplinary team experienced with the complex treatment of gastric cancer, such as at Mayo Clinic. Patients are typically diagnosed during upper endoscopy. The endoscopic findings may reveal a mass, or an ulcer in the stomach, which is then biopsied. A pathologist reviews the biopsy material and confirms the diagnosis. Patients should then undergo staging. Typically, this is performed by an endoscopy ultrasound, which tells the treating physician the depth of the tumor growth within the stomach wall. This is called the T stage of the tumor.

Enoscopists can also visualize nearby lymph nodes, and based on imaging characteristics or biopsy, can determine if the lymph nodes are involved with cancer. This is the end stage. Additional staging information is obtained by CT or PET scan, to see if the cancer has spread to other organs. This is called the M stage. If metastasis to other organs are identified on imaging, then patients are treated with systemic chemotherapy and/or immunotherapy. Surgery, or endoscopic stenting, can be helpful to relieve obstructive symptoms caused by the tumor.

Patients without distant metastasis on imaging should undergo a final staging test, a diagnostic laparoscopy. This is a minimally invasive procedure under general anesthesia to evaluate the abdominal cavity or peritoneum for any evidence of metastasis. These metastases are often too small to be detected on CT or PET scan. Peritoneum metastasises are identified in 20% of patients with gastric cancer.

At the same time, patients should also have their abdomen washed with saline and evaluated by a pathologist for microscopic circulating tumor cells. This fluid can be positive for cancer cells in another 14% of patients with gastric cancer. This procedure is done as an outpatient and can be combined with placement of a port for subsequent systemic chemotherapy and a feeding tube, if needed, for nutrition.

The treatment of patients with peritoneal disease remains an intense area of focus for us. Unfortunately, systemic chemotherapy has been only associated with a modest seven-month improvement in survival. And up until recently, the only benefit of surgery has been to palliate symptoms. However, recent research suggests that heated chemotherapy can be delivered directly to the tumor within the peritoneum using minimally invasive surgical techniques.

This treatment is called laparoscopic HIPEC and can be given safely in highly experienced

centers such as the Mayo Clinic. This treatment currently is given after systemic chemotherapy. Laparoscopic HIPEC can be repaired as necessary in order to clear the peritoneal disease, so that patients may go on to gastrectomy.

A recent study demonstrated a 37% response rate to this aggressive, multi-modality approach. Furthermore, patients who responded and went on to gastrectomy had survival outcomes similar to patients who had never had peritoneal disease. We offer this novel treatment strategy at Mayo Clinic and are working to further refine the technique and treatment in order to obtain improved outcomes for more patients.

For those patients whose tumors are locally advanced, we recommend perioperative systemic chemotherapy. Traditionally, this has been given in clinical trials as a sandwich approach, with half the chemotherapy treatment given before surgery, and the remaining half of chemotherapy given after surgery. Although this does result in improved outcomes compared to surgery alone, only 45% of patients are able to complete systemic chemotherapy following surgery. Therefore, at Mayo Clinic we favor a completely new adjuvant or upfront approach, where patients receive all their chemotherapy prior to surgery. This ensures that more people actually receive the beneficial effects of chemotherapy.

Fortunately we now have an even more effective combination of systemic chemotherapy agents that has dramatically improved response rates, as well as survival outcomes. In addition, we are starting to understand the molecular characteristics of gastric cancer, and some of the underlying mutations that drive tumor growth and metastasis. This has led to an effective utilization of targeted agents for some patients.

Similarly, it has been recognized that the amount of mutations a tumor has directly correlates with the likelihood of successful treatment with immunotherapy, such as immune checkpoint blockade. Gastric cancer has the third highest mutation tumor burden, right behind melanoma and lung cancer. Two malignancies that have significantly benefited from immunotherapy with checkpoint inhibitors. Immunotherapy for gastric cancer is now FDA approved, and is an active area of research for us.

Chemoradiation can also be utilized in specific instances where surgical margins, or extensive neural metastasis are a concern. This often consists of a few cycles of low dose chemotherapy to sensitize the cancer cells, with concurrent daily radiation treatments for five weeks. Once patients have completed their chemotherapy and radiation treatments, we recommend

restage and imaging to evaluate for response to treatment and for surgical planning. Patients may need a subtotal, or a total gastrectomy, depending on the tumor location and size. A 5 cm margin is recommended, and we routinely utilize intraoperative pathologic analysis to confirm negative margins.

The lymph node dissection is also critical, as more than 50% of patients will have lymph node metastasis. Lymph node metastasis is one of the main drivers of outcome following gastrectomy. Clinical trials show that an extended lymphnadectomy, also called a D2 lymphnadectomy, is necessary to remove all the possible draining lymph nodes. If this is done safely without removing the spleen or pancreas, then it can decrease the patient's risk of regional recurrence and death from gastric cancer. Unfortunately, an adequate lymphnadectomy is rarely performed in the United States, outside of large, tertiary academic referral centers, such as Mayo Clinic.

At Mayo Clinic, we have the experience and advanced surgical techniques and instruments allowing us to expand the application of minimally invasive surgery, from early gastric cancers to now include more advanced gastric cancers. The minimally invasive approach is beneficial to patients. It's associated with less post-operative pain, early return of bowel function, and a shorter hospital length of stay, while achieving similar long term oncologic outcomes to the traditional open gastrectomy.

Malnutrition and weight loss can be a concern after surgery, as well as dumping syndrome, malabsorption, and feeling full fast, which can make it difficult to get enough calories to maintain or regain weight. Patients may lose approximately 20% of their total body weight within the first three to six months after gastrectomy. As a result, we selectively place feeding tubes at the time of surgery to help maintain nutrition while patients advance their oral intake. Patients will meet with a dietitian for a comprehensive nutritional plan.

Depending on the extent of gastric resection, patients may need monthly vitamin B12 intramuscular injections and oral iron vitamin D and folate supplementation. Other recommendations are to make every bite count by eating calorie dense foods and protein supplements, eating a variety of foods from all the food groups, and eating small, frequent meals.

After completing chemotherapy and surgery patients are followed in surveillance, with routine imaging and nutritional follow-up. Outcomes following surgery or depend on the stage of the

gastric cancer. 80% to 90% of patients with early stage 1 gastric cancer are alive five years. Approximately 70% to 80% of patients with stage 2 gastric cancer are alive five years. And approximately 40% of patients with stage 3 gastric cancer are alive at five years.

We are continually working at Mayo Clinic to improve upon these results, by studying the incorporation of immunotherapy, targeted therapy and other novel treatments, as well as methods to improve patient recovery, and long term nutritional parameters, and quality of life. Patients may consider participating in clinical trials to receive the latest advances in multi-modality therapy.