Subtitles and transcriptions

Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.

Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

Every effort has been made to faithfully reproduce the audio of the sessions as recorded. However, no responsibility is accepted for mistakes or omissions. ESO does not endorse any opinions expressed in the presentations.

e-Session n 617008 - 5th July 2021

Early development: preclinical studies and clinical implementation in phase II studies

Dr Gronchi: So, hello, everybody. I will be discussing the multidisciplinary approach to gastrointestinal stromal tumors. Gastrointestinal stromal tumors are the most common malignancy of the GI tract, or, mesenchymal malignancy of the GI tract, the gastrointestinal tract. The most common site of origin is the stomach, followed by the small intestine, then the rectum, it is colon-rectum but mostly rectum, and then, the esophagus. Surgery is the primary therapy in localized GIST, and adjuvant imatinib is standard in patients carrying a significant risk of recurrence, and we will discuss about this later. While imatinib is the primary therapy in metastatic GIST, an adjuvant surgery is an option in patients responding to therapy, or with limited progression on therapy. So, which is the approach? First of all, one needs learn the histology, and biopsy are indicated also in GIST like they are in all other malignancies. Ultrasound-guided biopsy in upper GI, esophagus, and stomach, as well as in rectal GIST are the preferred method for obtaining a histological diagnosis. The gastric GIST may have different appearance when they are small. These are multiple examples. This is one example of right here. This is another example of a tumor completely extrinsic to the stomach. This is another example. And again, this is an example of an intramural gastrointestinal stromal tumor. There are multiple mimics though, which make the need of a pathological assessment mandatory before making any surgical decision. This, for example, is a leiomyoma of the upper stomach close to the EG junction. Same here. Then you have also leiomyoma and, leiomyomas are more common in esophagus, but occur also in the upper stomach. Other mimics are cellular schwannomas, like this cellular schwannoma, which was treated in another center by a very aggressive approach. This type of approach is called a gastrectomy which is probably not indicated in such a tumor. And if the surgeon had learned the histological nature of the disease, the histological diagnosis before surgical resection, it would have spared the patient from an unnecessary morbid procedure. And probably he should have known it, instead, he didn't. And so, schwannomas are mimics, and also, they can be as small as the gastric GISTs that I showed you before. Also, benign glomus tumor may mimic certain schwannomas, or the pancreatic ectopia may mimic the GIST. Inflammatory polyp. Finally, there are also gastric leiomyosarcomas that may be treated in a different way. And desmoid-type fibromatosis. While in the lower division, most of the common malignancies of the rectum are in fact GISTs. So, in upper gastrointestinal lab, GI lab, gastrointestinal submucosal tumors and rectal tumors called submucosal rectal tumors, a biopsy is mandatory. On the contrary, conversely, when you have a simple small bowel lab, or a intra-abdominal lab, where a biopsy is needed because one may also consider an immediate

surgical resection because the likelihood of being other disease is very small. When to do trans-abdominal biopsy instead? We need to perform a trans-abdominal biopsy every time you have an abdominal mass, which requires multi-visualization even if the diagnosis of GIST may be possible. Why so, because abdominal masses may be different, may have, may be of very different nature, like in the example, again, this is a non-Hodgkin lymphoma which is seen as gastrointestinal stromal tumor. Even if it is resectable, it doesn't need to be resected, because their treatment approaches can be predicted. Again here, what you see, on the left, a non-Hodgkin's lymphoma, and on the right, a GIST. So, it's important to have a proper diagnosis. Here, leiomyosarcoma on the left and the GIST on the right. So, a biopsy does not compromise the outcome and this has been also shown here, in gastrointestinal stromal tumor. In this study where a patient undergoing biopsy, has the same locoregional recurrence as you have compared to those who did not undergo a biopsy and therefore, it does not harm your patient to perform a biopsy, but you, instead, achieve the information you need to design the best approach to the patient. Which is the surgical approach, then? Surgical approach in submucosal nodules. Are there any lesions benign? Basically, all submucosal nodules which are greater than two centimeters should be resected because a diagnosis is possible. Unless the histological diagnosis of benignity, or benign condition has been established. They should be removed because all GISTs that are greater than two-centimeter have a risk of recurring and metastasizing. Conversely, submucosal nodules that are less than two-centimeter can also be followed and can undergo a program of active surveillance, unless a diagnosis of GIST is established and therefore, a resection is usually suggested. Gastric small GISTs may have a very indolent course, rectal GISTs don't. So, it's very important to apply this policy of surveillance only to gastric GISTs and not to rectal GISTs because rectal GISTs can grow. And even if they don't grow to a large size, may metastasize to the liver and also, to the lung where they are located very close to the lungs. Minimally invasive approach is possible as an alternative to surveillance. Both laparoscopically, but also endoscopic resection of a small lesion can be performed, as an alternative to active surveillance in order to achieve, to obtain a proper diagnosis of the small tumor. There are different techniques that are used today and they are all viable. There's one difficult location for minimal invasive approaches, which is the lesser curvature of the GE junction. In this situation, oftentimes, a conventional surgical resection is required. In this case, even if you perform, for example, and we'll be discussing about this later, a preoperative therapy to reduce the size you still have to perform a conventional resection. So, your take-home message number one is that, if available a histological diagnosis of GIST, the tumor has to be resected for small lesions. If not, endoscopic surveillance is an option, same for rectal GIST. In favorably located lesions, endoscopic, laparoscopic resection may be discussed as an alternative to repeated endoscopies. When you have instead a tumor mass, when the tumor is larger than the two-centimeter, minimal organ resection with negative margins is the recommended approach. The difficult gastric location often requires limited resection with the exception of syndromic GIST. And so, the so-called, the previously called, pediatric GISTs. They are multifocal, located to the stomach, and in this specific case, a conventional gastrectomy was the indicated procedure. The same apply to a small bowel, usually segmental resection is the procedure of choice. This segmental resection may be more extended in case of unequal related GIST because they tend to be multifocal. And sometimes, in order to perform a removal of all multiple nodules, you need to perform more extended small bowel resection. In duodenal gastrointestinal stromal tumor, one may perform a segmental resection or in a situation where the tumor involves a second portion of duodenum on the pancreatic site, one may need also to perform pancreaticoduodenectomy, a conventional pancreaticoduodenectomy. These are the multiple different duodenal reconstructions one may put in place to perform segmental resection. However, in specific conditions segmental resections are not possible, then pancreaticoduodenectomy may be required. In the rectal resection, most of the time, one may need to perform a conventional rectal resection or in specific condition, even a local excision. Positive margin of a diagram-margins, variance with soft tissue sarcoma at the site may not be directly responsible for local lesion recurrences. Why? So, this has been shown in multiple studies. The first prospective study was the one of DeMatteo in the beginning of 2000, then, you have another study by DeMatteo, and the group of DeMatteo, performed on the first prospective randomized study on adjuvant imatinib showing no difference in outcome when a tumor rupture were

excluded from the R1 group. And the same results were obtained in the European study presented, and there is more recently published, comparing two years of imatinib with no further therapy in high-risk GIST. This study was recently published and an analysis on the outcome of a patient by surgical margins, was also published recently. And showed, in consistency with other studies, that there is no difference in outcome with tumor in patients who have undergone R0 or R1 resection if you remove from the R1 resection tumor rupture. Why I say so? Because the way tumor rupture was initially called was probably wrong, because tumor rupture does confer a higher risk of recurrences. So, while the presence or absence of microscopic tumor cells at the resection margin may not be associated to a higher-risk, seems not to be associated to a higher-risk. Why so? In this indication, again, may not be the same, according to a different presentation, because most of the time GISTs tend to grow towards abdominal cavity. So, whether the margins are negative or positive at this level doesn't make a difference because you cannot control all this madness. On the contrary, GISTs that are completely confined into the, for example, gastric wall, like in this case, negative margins are important because they will avoid the even minimal risk of local recurrence that will eventually be associated to a more aggressive course. In the rectum, instead, there is an exception. So, positive margins at the rectal level are negative and they're associated to a higher-risk of local recurrence and death. But what is most important, as I alluded a few slides ago, is to avoid a tumor rupture because a tumor rupture is indeed something very, very strongly associated to a much more aggressive course. So, positive margins are not, save for specific exceptions, so, tumor confined to the wall or tumor originating in the rectum, but instead, tumor rupture is a bad prognosticator for tumors located at all sites: stomach, small bowel, rectum of course, esophagus, everywhere. So, a tumor rupture is associated to a very dismal prognosis. It can be spontaneous. So, it can be just related to the biology. It can be determined by the surgical resection. So, not all tumor ruptures are the same. So, minor defects of tumor integrity, like the one you have when you have a superficial peritoneal rupture, tumor penetration into the peritoneum, or a core needle biopsy, or a microscopically involved resection margin, as I said, are in fact, not associated to a worse outcome. As they are as tumor fracture, tumor spillage, gastrointestinal perforation, or incisional biopsy or instead are and confer to the tumor a much higher recurrence risk. So, this should not be considered tumor rupture, minor defects of tumor integrity, superficial peritoneal rupture, tumor penetration into the peritoneum, core-needle or R1, should not be considered tumor rupture. While all these others, tumor fracture, spillage, gastrointestinal perforation, incisional biopsy should be considered tumor rupture. And this tumor rupture is really bad. There are multiple studies that show how bad it is. And how often is also associated to a more aggressive mutational genotype, but also, a tumor rupture itself may cause spread. However, this spread, this risk varies according to the biology of the tumor. As you can see here, the risk associated to tumor rupture in low-risk GIST, regardless of the use of imatinib. In the high-risk GIST, regardless of the use of imatinib. There's no need of lymphadenectomy in surgery, except for SDH deficient GIST, the so-called syndromic GIST, pediatric GIST, where the risk of lymphoma metastasis is better and therefore, a conventional lymph dissection is performed. So, assess diagnosis preoperatively is important with endoscopic ultrasound of transabdominal and CT-guided procedures. Surgery is the primary therapy. Laparoscopic resection is feasible. Avoid tumor rupture and positive margins especially for rectal GIST whenever possible. When neoadjuvant imatinib is indicated? Neoadjuvant imatinib is indicated, in general, when you have a big mass or when it is poorly located, so when it's close to the EG junction or when it's in the duodenum, or when it is close to the anus in order to preserve organs and function. Why so, because, I mean, imatinib is very effective. When you have large masses like these, patient would receive adjuvant imatinib anyway, and therefore, since the patient will receive adjuvant imatinib anyway, it may be of benefit to start treatment in the preoperative setting to obtain the advantages that you obtain by shrinkage, tumor shrinkage, by downsizing the tumor, and minimizing surgical morbidity. In this case, for example, you perform, you convert an open procedure to a laparoscopic one. Even in this specific case, you calculate the risk and you check mutational status and then, you decide which approach to perform. Also, taking into consideration all the molecular subtype variants. 80, 90% of patients do respond to imatinib, as I said. They would receive imatinib anyway. And this is an example of the conversion of a GIST, which is almost non-resectable, to a GIST which is resectable. And it's much more easily

resectable. Same apply here. You improve the safety or the resectability in a tumor resectable, because for example, in this case, tumor was close to the superior mesenteric vein and the artery and after it downsized, this proximity is improved. So, it's less close to these structures and surgery is easier to perform. Or you improve organ preservation, like in this case where rectal GIST can be treated with much more preserving procedure. Even a local excision, like in this case where the reduction in size allows a local excision of the tumor without resecting the rectum. Sometimes, to obtain the shrinkage the change in tumor density is associated to a change of the tissue with a less, far less risk of tumor rupture as compared to the original resection. How long to treat these patients for? The longer, the better, but you should not exceed the one-year time-point because usually there is no further shrinkage in tumor size while the risk of secondary distant may stop being in place. And so, that usually is the time point when resection is performed. Never before six months, and anytime between the 6th and the 12th month is a good time to perform the resection. And then, after resection, use of imatinib continues. Preoperative imatinib may improve surgical outcomes, there's a potential to increase resectability and there is the potential to reduce preoperative risk. Surgery is performed between the 6th and the 12th month and continue imatinib usually for at least three years, which is, today, the standard treatment for high-risk GIST. What about surgery of metastatic GIST on imatinib? Who, why and when? So, why? Well, it's because tumor bulk does correlate with progression-free survival and overall survival and not with response in metastatic GIST on imatinib. You've all seen, since the very early studies, performed almost 20 years ago now, where basically a tumor with a larger tumor burden were the ones with the shorter disease control. This was true both in the European and American studies. So, aim of surgery would be to reduce tumor burden and by doing so, prevent secondary mutations, prolong time to progression and possibly increase the rate of patients with durable response and possible cure. Overall, the tumor burden is difficult to reduce by just doing surgery. There might be multiple peritoneal implants. And if the tumor is bulky, it should not be taken for granted that just by removing it, the biological complexity that the bulky tumor has is removed by the surgical resection. When surgery should be considered? So, there have been a lot of debates about when to consider surgery. Why is clear, to reduce tumor burden. When? Which are the patients that should be considered, kind of surgical candidates? It has been a matter of many debates over the past years. There have been surgical series showing basically that all the same thing. So, the patients operated on residual disease responding to imatinib, do better than those operated on residual disease progressing on imatinib. And therefore, from the surgical series, the ideal candidates for surgery were patients in response to imatinib. Patients with isolated progression were still considered possible surgical candidates. So, some benefit was also there. While certain patients having generalized progression were the patients not supposed to be operated. So, non-surgical candidates. This was further confirmed by the two largest multi-institutional retrospective studies performed in over the past years. One on 240 patients in Europe, and one on some 300 patients in the United States. All saying the same things. If surgery is complete and patient is responding, the median overall survival is the longest. This is more likely to be the case for patients with liver metastases only. And this is so because it is very rare that you underestimate the liver extent of disease. So, whether it's related to surgery or to a selection of patients with a more localized metastatic disease, is left to be understood. However, when surgery is performed the resection method should be the aim. So, basically, complete microscopic resection. Also, retrospective comparison between resected and non-resected patients that failed to demonstrate a benefit for surgery. So, in spite of the fact that when you resect a responding patient you have the best outcome. Whether this is better than continuing imatinib in responding patients or performing a surgical resection is still a matter of debate. So, it's not completely understood. And possibly, the added value of surgical resection is very limited compared to the value of the efficacy of the medical therapy. It's also the same in many series. And because of this equivalence between the two approaches, because of this lack of evidence, does favor one approach to another, this would have been the ideal scenario to run a randomized study. However, the two randomized studies that were planned, one in Europe, and one in China, both failed. The European one failed, it was stopped early for pure accrual because it took quite a bit to be put in place. And we lost the momentum, motivation, and also the referral patient's initial presentation. So, this study could not be performed. The same occurred to

the Chinese study, which was supposed to include 210 patients. And was published after 41 patients that were all affected by peritoneal disease. And in spite of the fact that there seems to be some benefit for surgery, this benefit is far from being a proof. So, patients affected by metastatic GIST to peritoneum in response to imatinib seem to benefit more from surgery of residual disease, in this randomized study. But again, this is not consistent with what has been observed in respective studies, showing that patients having the best durable control were those affected with liver disease. However, this study do not answer the question whether surgery should be performed in responding patients. It's not yet understood. Also, propensity score analyses are available, trying to compare these, under a suspected fashion, similar groups were also in order to tease out the role of surgery, but this along with case-matched control analysis are not really conclusive in terms when it comes to the role of surgery in responding patients. Again, you see here, what happens to this post-surgery survival in patients treated by surgery and those who are not treated by surgery. This is not to be a major effect. So, there might be a limited overall survival benefit in the first four years after surgery of responding disease. While there's a limited progression-free survival benefit of patients in the first year of patients operated for responding disease. While this benefit is also present in the first two years after surgery for limited progressive disease. So, at the end of the day, what do we do in responding patients? We tend to discuss on a single, on individualized basis, whether or not to undergo surgery. If the patient is very much motivated, we do consider surgery. Otherwise, we reserve surgery for isolated progression. And finally, also the molecular subtypes need to be taken into consideration because there are situations like, for example, syndromic GIST, pediatric GIST, where one may be pushed to use surgery more even in metastatic disease, because these patients have an indolent course, and there are no drugs as there are instead in conventional, actually, in KIT mutated GIST. And same apply to the effort we exert in PDGFRA mutated GIST. This is an example of a case that was operated almost 15 years ago, and it never recurred in spite of the multiple peritoneal implants. Never recurred yet. So, when to consider surgery in metastatic recurring GIST? Of course, in resectable responding disease, and in resectable isolated progressing disease. However, in these days, there's a shift towards the use of surgery in isolated progression compared to the use of surgery in responding disease. This is an argument which will be published soon on Annals of Oncology on the management of metastatic GIST. And you see that surgery is both considered in responding and limited progression as an option to be discussed with the patient. But and so in both these situations, one may use surgery to try to prolong disease control. In responding disease, the aim is to prolong the duration of imatinib activity. In isolated progression the aim is to postpone the switch to a second line treatment, which will possibly occur at some point in order to maintain the patient on the previous line of therapy, which is usually also the most tolerated, and the best tolerated and the most active one. So, thank you very much for your attention and have a nice day again.