New approaches to treating gastro-oesophageal cancer

Robust evidence on the value of neoadjuvant chemotherapy, together with more effective imaging modalities, are opening up new options for diagnosis, staging, treatment and patient selection in gastro-oesophageal cancer. Andrés Cervantes looks at the implications for the management of this challenging disease.

The challenges of managing gastro-oesophageal cancer are illustrated by the case of a 50-year-old man with locally advanced oesophageal cancer. His main presenting symptom was dysphagia when eating solid foods. He had weight loss, no pain in the thorax or abdomen, no dysphonia or cough, no dyspepsia or gastro-oesophageal reflux. His performance status was considered to be 1.

Looking at his risk factors, the patient was a heavy smoker, he had significant – though moderate – alcohol consumption, and was obese, with a body mass index of 32.5 kg/m^2.

Physical examination revealed no lymph nodes in the patient's neck nor in the supraclavicular area; there were also no thoracic alterations, no hepatomegaly or ascitis, and no signs of pleural effusion. All these physical examination data indicate that the patient had localised disease. Having dysphagia only when eating solid foods indicated that the invasion of the oesophagus was not completed because the patient could swallow liquids without any difficulty.

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Andrés Cervantes of the Hospital Clinico Universitario, Valencia, Spain, provides an update on the challenges of treating gastro-oesophageal cancer. He highlights the new treatment options and techniques for predicting tumour response that are changing the treatment of patients with this cancer. Florian Lordick of the Braunschweig Clinic, Germany, poses the wide range of questions sent in by participants during the e-grandround live presentation, which is summarised here by Susan Mayor.

The recorded version of this and other e-grandrounds is available at www.e-eso.net

Diagnostic tests

An oesophagoscopy indicated an ulcerated neoplastic lesion in the lower third of the oesophagus at 38 cm from the teeth, situated over an ectopic area of gastric mucosa, 3 cm long, without involving the gastro-oesophageal junction. This oesophagitis was related to gastro-oesophageal reflux. This description is very clearly a Barrett's oesophagus area transforming into a lower third oesophageal cancer.

The stomach and the duodenum were also explored because the tumour could have passed through the stenotic lesion, but they did not show any change. During the procedure, a biopsy was performed and this showed poorly differentiated and infiltrating diffuse adenocarcinoma of the oesophagus over Barrett's oesophagus.

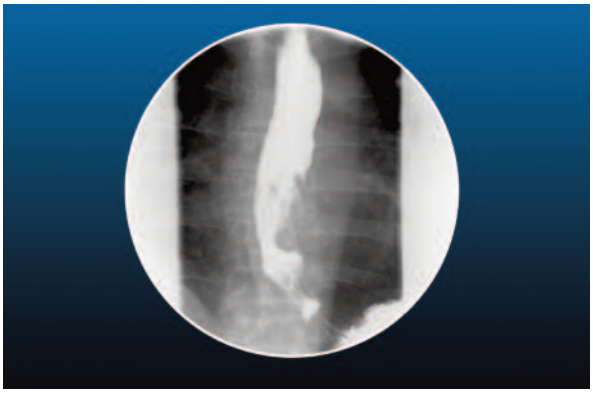
The oesophagogram was one of the most common diagnostic techniques performed some years ago, and we still perform this type of imaging. The image (see figure) shows some alteration of the mucosa of the lower third of the oesophagus, with irregular areas indicating a malignant tumour of the oesophagus.

A CT scan of the thorax, abdomen and pelvis showed no distant metastases; the lungs and liver were clear, and the only two findings were related to local regions. First, in the oesophagus, there was a thickness of the whole oesophageal wall at the lower third of the oesophagus. This was without any anatomical relation to the trachea or left bronchus. There was also enlargement of lymph nodes in the para-oesophageal area and in the upper mediastinum.

After doing the oesophagoscopy, the oesophagogram and a complete body CT scan, the clinical staging is considered cT3cN1cM0 stage 3a (where 'c' indicates clinical assessment), because the tumour has completely thickened the whole wall of the oesophagus. It is N1 because the enlarged lymph nodes are observed in the CT scan and cM0 because, clinically, there is no evidence of metastatic disease. We considered this patient to be at clinical stage 3a.

To summarise this, I would like to consider what was the classical approach to oesophageal cancer. First, the patient underwent surgical resection. After surgical resection, pathology assessment helped in the estimation of the risks. Postoperative treatment was based on the classical TNM stage. Postoperative chemotherapy was of either doubtful or no value, and postoperative chemoradiation was recommended by some experts.

DIAGNOSTIC OESOPHAGOGRAM



Oesophagrams should be used strictly for diagnosis and not for staging. The irregular dark area shows the malignancy

Source: Courtesy of Andrés Cervantes

Question: *What do you consider the standard procedures in staging oesophageal cancer today? Which examinations can be recommended as standard?*

Answer: *I think that oesophagoscopy is the main procedure for diagnosis, although this does not help to stage the patient. We would use a CT scan and then a PET scan, especially for a tumour located in the lower third of the oesophagus and at the gastro-oesophageal junction. I think CT and PET scanning are the critical tests. We do not use ultrasonographic endoscopy very often, except for patients with very small tumours – patients with T1 and T2 involving only the mucosa or muscular layer – but they are uncommon. In a patient at such an early stage, perhaps endoscopic ultrasonography could be of benefit in diagnosis.*

Lordick: *We use endoscopic ultrasonography to define the T stage. Would you say it is also good when you combine endoscopy and PET-CT scans? Would this be your standard approach?*

Answer: *That is right.*

Question: *In your case presentation, the patient had no major dysphagia. If the patient presents with dysphagia, do you insert stents or do you dilate the oesophagus before you start with any other treatment?*

Answer: *Assessing the nutritional status of a patient with oesophageal cancer is very important. This patient was presenting with no weight loss, indicating that although dysphagia was the main symptom, it was not presenting any problems. In patients presenting with major dysphagia we would try to do staging procedures very quickly because, when the disease is localised, improvement is common when you start chemotherapy. However, when we see a patient with disseminated disease, we try to start by implanting a stent first, because treatment is unlikely to be very successful and we prefer to focus on improving their nutritional status.*

Question: *What about the use of proton pump inhibitors with prokinetic drugs in order to prevent carcinoma of the oesophagus in patients with gastro-oesophageal reflux disease? Are you aware of data that show that oesophageal cancer can be*

prevented by the long-term use of proton pump inhibitors?

Answer: *I am not aware of any data that show that those pumps may prevent patients from developing oesophageal cancer.*

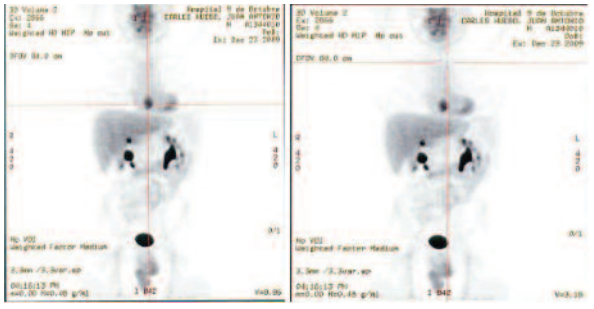
Current approaches to localised gastro-oesophageal cancer

A multidisciplinary approach should be adopted in the care of patients with localised gastro-oesophageal cancer. Clinical staging should include PET scanning for tumours located in the lower oesophagus or in the gastro-oesophageal junction.

The patient in our case study had a PET scan performed with labelled fludeoxyglucose (^{18}F), which confirmed the absence of distant metastases. This is a very important point because PET scanning is more sensitive even than current helical CT scans in detecting dissemination of the tumour. Approximately 18%–20% of patients without metastasis in the conventional workup are diagnosed as stage IV with a PET-CT.

The ^{18}FdG PET-CT scan showed a hypermetabolic area at the lower third of the oesophagus, with a maximum standardised uptake value (SUV) of 8.9 g/ml. Another metabolic area was observed at the upper mediastinum (SUV max: 3.4 g/ml), associated with the lymph glands (see below). This confirmed that this patient had locoregional disease involving the oesophagus and also locoregional lymph nodes.

^{18}FdG PET-CT SCAN FOR STAGING



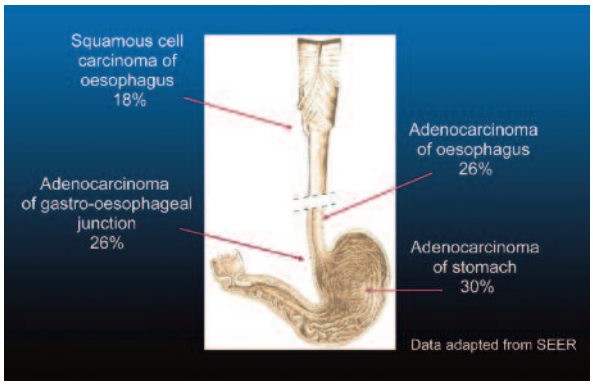
Areas of very high uptake of the ^{18}FdG show the tumour in the lower third of the oesophagus and reveal the involvement of lymph nodes in the mediastinal area

Source: Courtesy of Andrés Cervantes

Distribution of gastro-oesophageal tumours

Squamous cell carcinoma of the oesophagus is mainly located in the upper two-thirds of the oesophagus, and accounts for approximately 18% of cases. Adenocarcinoma of the lower oesophagus affects 26% of patients, while adenocarcinoma of the gastro-oesophageal junction accounts for a further 26%. Gastro-oesophageal tumours at these two sites are increasing in incidence and are common in developed countries – the US and Europe – where gastric cancer is not so common. Traditionally, gastric cancer was more common in Mediterranean countries, but its incidence is now decreasing, while tumours located around the junction and the lower section of the stomach are increasing. In this clinical case, smoking, alcohol and obesity are all related to the reflux disease, which could be the cause of the tumour.

DISTRIBUTION OF GASTRO-OESOPHAGEAL TUMOURS



These relative incidence data were adapted from the US Surveillance, Epidemiology, and End Results programme (SEER), and are likely to be different in other parts of the world

The Siewert classification of gastro-oesophageal junction adenocarcinomas is a surgical one: type I is when the tumour is located in the distal oesophagus (36% of patients); type II is true junctional disease (27%); and type III is when the bulk of the tumour is below or at the subcardial area (37%) (*Br J Surg* 85:1457).

Preoperative chemotherapy

Several studies have helped us in understanding that preoperative chemotherapy should be considered the standard of care.

A meta-analysis of randomised clinical trials of preoperative chemotherapy for oesophageal cancer by Gebski et al. (*Lancet Oncol* 8:226) showed clear, although limited, benefits (see p 16). Many of the studies were underpowered, with a very limited number of patients, and are now relatively old.

The MRC trial OE02 is important because it included 800 patients, making it the largest trial published so far in gastro-oesophageal cancer. It is also the most recent trial, published in the *Lancet* in 2002 (vol 350, p1727). The study included patients with all types of resectable oesophageal or cardia carcinoma,

including squamous carcinomas, adenocarcinomas and undifferentiated carcinomas (*n*=802). The patients were randomised to surgery alone or to the experimental arm of two courses of cisplatin (80 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 continuous infusion days 1–4), given in a very conventional way and repeated after 21 days, with surgery performed immediately after the second course. It is important to note that two-thirds of patients had adenocarcinoma histology (66%) and one-third had squamous histology (31%).

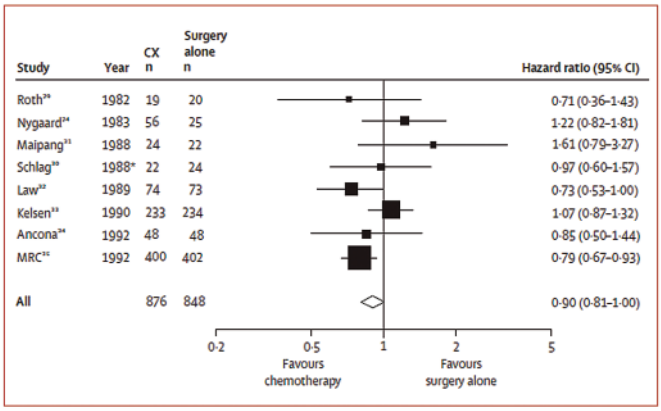
Results (see below) showed that median survival was improved by 3.5 months (13.3 vs 16.8 months), and overall survival after two years was improved by 9% (34 vs 43 months). Most types of histology benefited from the experimental approach (*Lancet* 350:1727). Long-term results – after 10 years of follow-up – have recently been published, indicating that the benefits of preoperative chemotherapy continued over the longer term (*JCO* 27:5062–5067).

The next trial I would like to discuss is the MAGIC trial. Although many people consider this trial as a gastric cancer trial, a group of patients with oesophagus and junction cancer were included. Patients were randomised to surgery only, or to preoperative chemotherapy with the classical British ECF combination of fluorouracil, cisplatin and epirubicin. Patients were given three courses of preoperative chemotherapy followed by three further courses after surgery. The quality of the trial is well established, and it has been published in the *New England Journal of Medicine* (vol 355, p11).

Final results indicate that median survival was improved by four months (24 vs 20 months) and two-year survival increased by 9% (50% vs 41%). The key finding was a 13% increase in five-year survival (36% vs 23%). Both progression-free survival and overall survival were significantly improved. This benefit applied to all patients, including those with stomach tumours, junction tumours and oesophagus tumours.

A further study of perioperative chemotherapy for localised gastro-oesophageal cancer, the French trial FNLCC 94012-FFCD 9703, has not yet been published in full (Boige et al, Abstract 4510, ASCO 2007). It randomised 224 patients to surgery alone or to three courses of platinum and fluorouracil (5FU 800 mg/m^2 on days 1–5), and did not include epirubicin, making it different to the British

META-ANALYSIS OF NEOADJUVANT CHEMO TRIALS

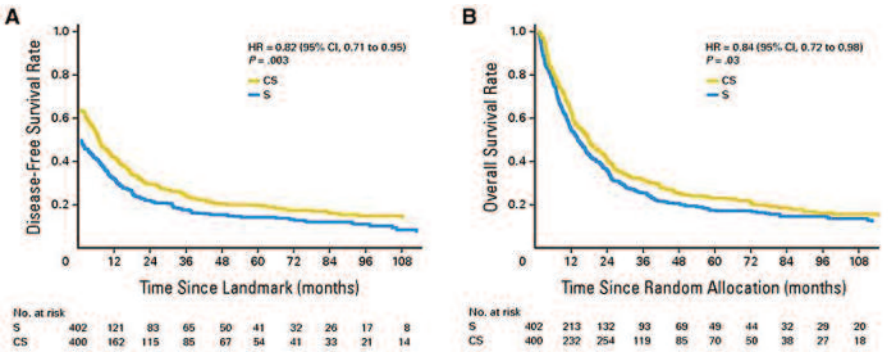


All-cause mortality estimates for neoadjuvant chemotherapy compared with surgery alone

Preoperative chemotherapy was shown to offer a slight advantage in this meta-analysis, which included studies dating back to 1982

Source: Reprinted from Gebski et al (2007) *Lancet Oncology* 8:226-234, with permission from Elsevier

UK MRC OE02 TRIAL



Ten-year results showed a sustained improvement in both disease-free and overall survival with preoperative chemotherapy

CS – neoadjuvant chemotherapy plus surgery arm, S – surgery alone

Source: WH Allum et al (2008) *JCO* 27:5062–5067. Reprinted with permission. ©2008 American Society of Clinical Oncology.

trial. Another difference is that two-thirds of the patients had gastro-oesophageal junction tumours, and only one-third had gastric tumours.

Results showed that perioperative chemotherapy improved progression-free survival and overall survival. Median survival increased by nine months and three-year survival by 10%, while five-year survival increased by 14%.

These three trials of perioperative chemotherapy for localised gastro-oesophageal cancer are all leading us in the same direction. They show the reduction in the risk of death at five years was 25% (in the Cunningham trial; *NEJM* 355:11) to 31% (in the French trial; Boige, ASCO 2007), indicating that perioperative chemotherapy may improve survival when given to patients with localised and resectable oesophageal or gastro-oesophageal cancer.

A meta-analysis of randomised clinical trials of preoperative chemoradiotherapy for oesophageal cancer (*Lancet Oncol* 8:226) indicates potential benefits, but also flags up some issues. There is a trend to higher mortality in patients treated with a combination of chemotherapy and radiation after surgery. Although this is now a commonly used approach in the US, my personal opinion, which is shared with others, is that in Europe chemotherapy without radiation could be the standard care for patients with lower-third, junction and gastric cancers, before surgical resection.

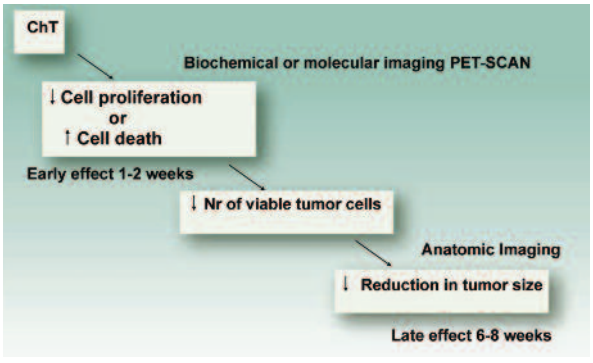
Question: *In which patients do you consider using neoadjuvant chemotherapy?*
Answer: *In all resectable patients except those clinically staged as cT1.*
Question: *Would you use neoadjuvant chemotherapy in T3 tumours and also when you see lymph nodes involved?*
Answer: *Yes, for any node-positive tumours, including T3 and T4, we would use preoperative chemotherapy.*
Question: *Do you use, or is it possible to use, capecitabine and oxaliplatin as part of the neoadjuvant chemotherapy?*
Answer: *Several trials performed in advanced disease have shown that oxaliplatin can be used safely and with good efficacy, substituting for cisplatin. Capecitabine could also substitute for fluorouracil. Going back to the clinical case we were reviewing, we recommended preoperative chemotherapy, and a combination of oxaliplatin and capecitabine was started. After the first course, the patient had complete resolution of dysphagia and a reassessment with PET-CT was performed after two weeks to assess the metabolic response.*
Question: *Do you think that chemoradiation is the preferred approach over chemotherapy alone, in neoadjuvant indications?*
Answer: *The only place in which chemoradiation could be better than chemotherapy is in patients with squamous tumours of the two upper-thirds of the oesophagus. Definitive chemoradiation can cure about 25% of these patients. Apart from this group of patients, as far as I know, there are no good randomised trials comparing chemotherapy with chemoradiation. The data we have from the meta-analysis compared chemoradiation with surgery alone. There are also some toxicity concerns. For this reason, I prefer to start with chemotherapy alone in patients with tumours that are resectable, and not use chemoradiation. There are several studies showing that chemoradiation is effective, and can result in an even higher proportion of patients with pathological complete remission than using chemotherapy alone. However, I think this strategy should be considered experimental, and should be explored in future phase III trials.*

Assessing tumour response to treatment

The classical way of assessing response to chemotherapy is anatomic imaging. After several weeks, or even months, of therapy we expect to see a reduction in tumour size. This could be seen as a very late effect, six to eight weeks after starting treatment. This is what we do at the moment, but we have to improve on this. We have to make the most of the opportunities we have now to include biochemical or molecular imaging. PET scanning is useful because it can detect an effect of therapy in reducing cell proliferation or in stimulating cell death. This effect can be seen as early as one to two weeks after treatment, so it can guide treatment decision making. Several groups have published data on this, and more work is ongoing.

A study by Ott and colleagues, looking at tailoring treatments based on metabolic response (Ott et al *JCO* 24:4692) included 65 patients with locally advanced adenocarcinomas of the gastro-oesophageal union who received preoperative cisplatin-based chemotherapy. They were assessed before the start of treatment and on day 14. Results show a clear difference in PET response, based

ASSESSING TUMOUR RESPONSE



New imaging modalities offer the potential to identify responders much sooner than relying on tumour shrinkage

on a reduction of at least 35% in the maximum standard uptake value. These patients do better than those not showing a significant response on PET. I think this is an important finding, although it is based only on retrospective studies.

In the patient in our case study, early reassessment with a PET scan performed two weeks after starting treatment showed a complete response, with no uptake of ^{18}FdG. Knowing that this patient was so chemosensitive, we decided to go on and give four more courses of the combination of capecitabine and oxaliplatin.

Results from the MUNICON phase II trial looking at the value of PET to assess early metabolic response and guide treatment of adenocarcinoma of the gastro-oesophageal junction confirmed the finding that patients with an early PET response that leads to several courses of chemotherapy do much better than those not showing a PET response, who go directly to surgery (*Lancet Oncol* 8:797–805). These data confirm the prognostic value of PET scanning in the assessment of response to treatment.

Surgical resection

The patient in our case study underwent thoracoabdominal surgery with a total oesophagectomy. An oesophago-gastrostomy was performed using Akiyama's technique, with extensive mediastinal and perigastric lymphadenectomy. During reconstruction using Akiyama's technique, an omentectomy was also performed.

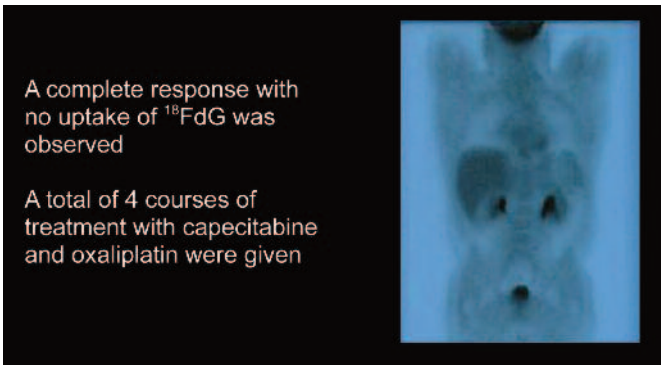
Pathology assessment and estimation of risk

It is very important to assess pathology to be able to estimate the risk for a particular patient. The main data from the case study's pathology report showed the patient had a moderately differentiated adenocarcinoma of the lower oesophagus. The tumour was infiltrated to the peri-oesophageal fat, so we considered this patient to have a ypT3 tumour (where 'yp' indicates pathological assessment after preoperative therapy). Perineural invasion was present, although none of the nine mediastinal nodes and none of the 13 perigastric nodes were involved. So this patient was ypT3 ypN0/22 M0 out of the 22 resected lymph nodes. In the omentum, no metastatic deposits were detected in the peritoneum. Overall, this patient was considered as a ypT3 ypN0/22 M0 patient.

RECOMMENDED APPROACH FOR LOCALISED OESOPHAGEAL CANCER

- Clinical assessment and staging
- Multidisciplinary team discussion
- Preoperative treatment in all patients with clinical stage II and III disease
- Surgical resection after chemotherapy
- Pathology assessment and the estimation of risk
- Postoperative chemotherapy?
- Participation in trials

PET AS A GUIDE TO TREATMENT



The MUNICON trial showed that metabolic response assessed early on a PET scan can help doctors identify which patients will benefit from preoperative chemotherapy

Source: Courtesy of Andrés Cervantes

Postoperative treatment

Many trials have been designed with pre and postoperative treatment. However, the postsurgery state of patients, including their nutritional status and the presence of surgically related complications, means that almost half of our patients cannot go through this final part of therapy. We decided against continuing chemotherapy to the patient in our case study on account of the changes to his nutritional status.

The patient is being followed up with clinical visits every three to four months for two years. He has no dysphagia, his trachea is working well and he can eat properly without any difficulties in swallowing. No postoperative chemotherapy was given due to the patient's poor nutritional adaptation and slow recovery after surgery. He lost around 20 kg in weight after surgery, although no steatorrhea or other signs of malnutrition were observed. There is no standard of care for follow-up, and this should be based on clinical signs and symptoms reported by the patient. We repeated a CT scan every six months for two years, and this patient has not shown any evidence of metastatic disease or signs of local relapse so far.

Conclusions

In conclusion, the patient in our case study was diagnosed with a locally advanced lower third oesophageal adenocarcinoma. Clinically, there was a T3 node-positive tumour with absence of metastatic disease. I would like to stress that a multidisciplinary discussion is essential for all cases. This case is a good example of the benefits of multimodality treatment. The surgical approach allowed an R0 resection, which is essential to offer the patient the possibility of long-term survival. A resectable oesophageal cancer should be treated with preoperative chemotherapy in a multidisciplinary team approach.

More, and better designed, clinical trials are needed to refine the optimal approach. I would encourage everyone to consider entering your patients into appropriate multicentre trials to provide more information on the optimal approach for managing oesophageal cancer for the future.

Florian Lordick (FL) of the Braunschweig Clinic, Germany, hosted a question and answer session with Andrés Cervantes.

Q: *When do you consider postoperative radiotherapy?*
A: That is a very difficult question. If the resection is R2 or R1, and there is evidence of microscopic or gross residual disease after surgery, then radiation could be considered as a palliative therapy. But we should balance the benefits of the radiation against the potential of inducing some other toxicities. I would be careful in selecting only those patients with residual disease after therapy for postoperative radiation. In general, it is not my standard of care.
Q: *What type of chemotherapy should be used? Is it necessary to include epirubicin in the treatment regimen?*
A: In the three trials indicating positive effects, two gave positive results for the benefit of chemotherapy without using epirubicin. Most data on epirubicin are from the British group and are well established findings, but we have other trials indicating that, even in the absence of epirubicin, there are benefits with chemotherapy. So the use of epirubicin is not a must in my opinion.
Q: *Given that early PET response is predictive, when the patient responds to chemotherapy can you go with definitive chemoradiation and avoid surgery?*
A: This approach has not been well studied in patients with lower-third adenocarcinoma. In general, it is considered that surgery may be better than radiation as definitive treatment in these patients. I would recommend definitive chemoradiation only for those patients with cancers located in the upper two-thirds of the oesophagus. Even in the presence of a good response on PET scan, I would recommend surgery as standard of care.
FL: I agree that in patients with adenocarcinoma of the distal oesophagus there is not yet a clear role for definitive chemoradiation. The standard approach today is surgery for patients presenting with resectable adenocarcinoma of the distal oesophagus and gastro-oesophageal junction. However, I think the hypothesis is justified and studies should be conducted to see whether there is a role for non-surgical treatment in very good PET responders.
Q: *Do you also use radiation without chemotherapy as preoperative treatment in oesophageal cancer?*
A: No, I think radiation alone should not be used as preoperative treatment in oesophageal cancer. There are data and recommendations in the current ESMO guidelines showing there is no indication for radiation alone, apart from palliative treatment in some advanced and unresectable disease, but not as neoadjuvant therapy.
Q: *Does neoadjuvant chemotherapy in oesophageal cancer improve survival?*
A: I showed a meta-analysis and, more definitively, three trials, that indicate short-term and long-term improved survival in patients with gastro-oesophageal cancer receiving preoperative chemotherapy. These three trials give evidence at level 1 that preoperative chemotherapy does improve survival in patients with oesophageal cancer.
FL: We should consider that this question came from India, where there may be more patients with oesophageal squamous cell cancers than in Europe. Maybe the questions asked in India are not answered by the trials presented and we need more studies in that part of the world.
A: The squamous situation is different. Only the MRC trial included patients with squamous cancer (31% of the total). However, there was a very good trial presented by Kelsen et al. in 1988 (*NEJM* 339:1979–1984) indicating that preoperative chemotherapy in patients with squamous disease is not so beneficial.
Q: *Do you agree that there are differences between the optimal management of patients presenting with squamous cell cancer and those presenting with adeno-*

carcinoma of the oesophagus?

A: Yes, I agree. For patients presenting with squamous cell cancer, the aetiology and biology are different, and the type of patient is different – it is more related to smoking. So, palliative care for these patients would be definitive chemoradiation and I would resort to surgery only if they do not respond or if the patient's tumour is still resectable. These types of disease are complicated.

Q: *Do you think there is enough evidence to use oxaliplatin instead of cisplatin in the preoperative setting?*

A: The data we have on oxaliplatin are very limited, so I do not think that this could be considered a standard of care. However, data from many trials show its advantages when oxaliplatin is substituted for cisplatin in the treatment of metastatic disease. Low-dose oxaliplatin is now easily accessible, and not as expensive as it was some years ago. Overall, I would not consider there is level I evidence to substitute oxaliplatin in locoregional disease, but for practical reasons I think we could use it.

Q: *After surgical treatment, do you always administer postoperative chemotherapy even in cases of yPT1 N0 and no more risk factors, after complete resection?*

A: I do not have the definitive answer to this question, but if a patient has a complete resection and is chemosensitive I do not see any reason not to use it, so long as the patient has adapted well after surgery and is keeping their weight stable without treatment. I try to treat all patients, if their pathology reports are good, with three more courses of postoperative chemotherapy. However, only half of patients are in a good enough condition to receive this type of treatment.

Q: *How many lymph nodes are required to consider that surgery was successful, and what do you do if there are only a few lymph nodes in the specimen. What is your approach?*

A: I am not aware of any guidelines indicating the number of lymph nodes we have to have in the resected specimen. But for the junction we should have more than 14 in order to get the right staging. When there is residual disease after chemotherapy and after surgery, the use of postoperative chemotherapy is indicated whatever the number of lymph nodes present.

Q: *Is it possible to insert a stent preoperatively if necessary?*

A: We never do that. This would only be considered in a patient with rapid worsening of dysphagia. I would try a nasogastric tube or just change therapy if a patient is sensitive to other drugs. But, in general, most patients improve after just a few days of chemotherapy.