PERGAMON

European Journal of Cancer 38 (2002) S65–S70

European Journal of Cancer

www.ejconline.com

The EORTC Gastrointestinal Tract Cancer Group: 40 years of research contributing to improved GI cancer management

Ö. Anak[a,*], E. Van Cutsem[b], B. Nordlinger[c] on behalf of the EORTC Gastrointestinal Tract Cancer Group

[a]*EORTC Data Centre, Av. E. Mounier, 83/11, 1200 Brussels, Belgium*
[b]*Department of Internal Medicine, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[c]*Chu Ambroise Pare, Chirurgie Digestive, 9 avenue Charles de Gaulle, F-92104 Boulogne-Billancourt Cedex, France*

Abstract

The Gastrointestinal (GI) Tract Cancer Group's aims are to develop protocols concerning the different aspects of gastrointestinal tract malignancies, diagnosis, biology and mainly treatment. Prior to approval, new project proposals are discussed within different committees of the group and in the presence of specialists concerned, according to the type of trial. There are three main committees in the GI Group, chemotherapy, surgery and research. All projects of GI tract cancer are discussed first in the relevant committee before being discussed in the multidisciplinary plenary scientific session of the Group meeting. Multidisciplinarity has always been one of the major principles of the Group. This is well illustrated by the fact that the Chairman of the Group has been alternately a medical oncologist and a surgeon and is presently a surgeon. Radiation therapists also participate in the activity of the group. Like other EORTC groups, the GI Group has developed high standards of quality. Officers and members work in close co-operation with the staff of the Data Center in Brussels and in particular medical advisors, statisticians and data managers. Members from 32 different countries participate in the activities of the Group, mostly from European countries, but also from Russia, Egypt, Hong Kong, Israel, Peru, Russia, South Africa and many others through intergroup activities such as Australia, Canada and the USA.

Keywords: EORTC; Gastrointestinal; Research groups; Review

1. Track record of the Clinical Research activities of the Gastrointestinal (GI) Tract Cancer Group

1.1. Colon cancer

1.1.1. Adjuvant treatment

Studies concerning the adjuvant treatment of colorectal cancer have always formed the backbone of the activities of the Group. Adjuvant therapy of poor prognosis colon cancer with levamisole was tested in a double-blind randomised phase III setting: 297 patients were randomised between levamisole versus placebo as adjuvant therapy of Dukes' C carcinoma of colon [1].

This trial was a negative one. The difference in survival between patients undergoing surgical resection alone and patients receiving the immunostimulant drug levamisole did not reach statistical significance. When this trial was initially being prepared, thought had been given as to whether to have a third treatment arm associating levamisole and 5-fluorouracil (5-FU), the association which later proved successful in the *Moertel trial* [2] and was considered a major breakthrough in the treatment of Dukes' C colon cancer, although the clear role of levamisole was never elucidated. Nevertheless, in this domain the GI group of the EORTC fell short of actively participating in an important progress. We also learnt that future trials in this field should have a larger scale and randomise more patients.

The Group ran two trials evaluating the role of intraportal administration of 5-FU. The first was a phase III clinical trial on adjuvant intraportal infusion with Heparin and 5-FU in resectable colon cancer. Patients who did not have any evidence of distant metastases or residual tumour following surgical resection of Dukes' A, B and C colon cancer were immediately entered to this protocol after surgery. The final results of this trial were published in 1997 [3]. No differences were observed between treatment groups and the control group for postoperative complications and hospitalisation days. Based on all randomised patients, the effect of treatment

* Corresponding author. Tel.: +32-2-774-1614; fax: +32-2-772-6197.
E-mail address: oan@eortc.be (Ö. Anak).

0959-8049/02/$ - see front matter
PII: S0959-8049(01)00464-6

was not statistically significant different with respect to any of the endpoints. These results confirmed that intraportal 5-FU infusion is safe and has a tolerable toxicity, but can not be considered standard treatment for patients with resectable colon cancer.

The second trial was a larger phase III randomised trial on adjuvant portal vein infusion of fluorouracil and heparin in colon and also rectal cancer. The patients, with histologically confirmed resectable cancer of colon or rectum, without distant metastasis, were randomly assigned to surgery alone or surgery plus portal vein infusion [4].

With 1235 patients randomised, this study clearly demonstrated that intraportal 5-FU was not sufficient to improve outcome after surgery. Long-term review of the data from National Surgical Adjuvant Breast and Bowel Project (NSABP) (SSO 2001) [5] have also shown that there was no significant advantage in overall survival in the treatment group.

In the next trial (40911), the GI Group continued its interest in loco-regional treatment of colorectal cancer. It took into account the fact that intraportal CT alone did not appear sufficient to improve outcome and got interested in another way of administrating CT, the intraperitoneal (i.p.) route. After i.p. administration, most of the 5-FU is absorbed though the peritoneum and exits the abdominal cavity through the portal vein into the liver. Thus, in theory, i.p. chemotherapy should combine the effects of i.p. administration and a local effect on tumour surface and might be more effective. Considering that loco-regional treatment alone might not be sufficient, it was associated in this trial with systemic chemotherapy using 5- FU/levamisole or 5-FU/leucovorin, which had in time become the standard treatment of Dukes' C colon cancer.

This was a phase III study of adjuvant regional and systemic chemotherapy in high-risk resected colorectal cancer. The patients were randomised on a two-by-two schema aiming to demonstrate that the addition of early regional chemotherapy to long-term systemic chemotherapy could improve survival and reduce the rate of recurrences when compared with systemic chemotherapy for colon and rectum B2 and C cancers. The second endpoint was to compare systemic chemotherapy with 5-FU + leucovorin to 5-FU + levamisole with respect to survival and time to progression.

A total of 1850 patients were randomised in this trial which was an intergroup study run in co-operation with the Fondation Française de Cancérologie Digestive.

It was the largest trial ever completed by the Group and proved the benefit of intergroup co-operation. The procedure appeared to be very safe. Analysis of the results of this trial will be done as soon as enough events have been observed.

The next trial, the Pan European trial for adjuvant treatment of colon cancer (PETACC)-1, was evaluating the benefit of postoperative adjuvant chemotherapy of colon cancer. The PETACC-1 trial was a randomised trial aiming to compare Tomudex (raltitrexed) with the NCCTG/Mayo regimen (bolus 5-FU 370 or 425 mg/m^2 plus leucovorin 20 mg/m^2 for 5 days every 4 weeks for six cycles) as postsurgical adjuvant treatment in patients with Dukes' Stage C colon cancer who have undergone curative radical resection. The primary objectives of the trial were to improve recurrence-free survival and overall survival rates; the secondary objective was to compare the toxicities of the two regimens. This trial was developed through a new structure, PETACC, which is a network allowing different cooperative groups to work together. It appeared that only intergroup collaboration could permit sufficient accrual to complete rapidly trials requiring more than 1000 patients in order to demonstrate absolute treatment benefits of 5–7%.

Accrual was rapid, but the trial was closed prematurely after an interim analysis showed higher toxicity than was expected in the raltitrexed arm.

The PETACC-2 trial is a randomised phase III intergroup trial of high-dose infusional 5-FU/folinic acid versus standard bolus 5-FU/folinic acid in patients with International Union against Cancer (UICC) stage III colon cancer, who have had a curative radical resection. The main endpoints of this protocol are recurrence-free survival and duration of survival. Safety is the secondary endpoint. The study is ongoing.

The PETACC-3 trial is an international phase III open label randomised trial comparing CPT-11 in combination with high-dose 5-FU/folinic acid (infusional regimen) to the same high-dose 5-FU/folinic acid infusional regimen alone as adjuvant treatment of colon cancer in stage III colon cancer.

In the PETACC-2 and PETACC-3 trials, important translational research projects are done. Until now, 903 patients have been entered in PETACC-2 and 1530 in PETACC-3 trial.

1.1.2. Treatment of metastatic colon cancer

The GI Group has a tradition in the development of new trials in advanced colorectal cancer and has done important work in the development of more optimal regimens of 5-FU through biochemical modulation and through the development/use of infusional regimens. The Group has contributed to the demonstration that infusional regimens of 5-FU/FA are the most optimal ways of administering 5-FU/FA.

The GI Group has recently completed trial 40986 in which patients with advanced colorectal cancer were randomised between a weekly 24-h infusional regimen of 5-FU plus folinic acid with this regimen in combination with irinotecan.

The next question the GI Group will try to answer is whether in combination chemotherapy with 5-FU/FA/irinotecan intravenous 5-FU/FA can be replaced by an

oral fluoropyrimidine. Capecitabine will be studied. In this trial, a second question will also be answered: what is the role of selective Cox-2 inhibitors in advanced colorectal cancer. Therefore, patients will also be randomised to placebo or celecoxib in a 2-by-2 design.

The EORTC GI Group is also studying the role of pre- and postoperative chemotherapy in resectable liver metastases from a colorectal origin (LMCRC) (EORTC 40983).

Liver metastases occur in approximately 40% of patients with CRC and are the principal cause of death in these patients. In spite of progress observed in chemotherapy for advanced colorectal cancer, survival rates remain very low in patients with unresectable LMCRC: surgical resection is at present the only treatment currently offering potential cure when liver metastases are resectable, long-term survival following partial resection is in the order of 25–30%. The treatment is now well-accepted and large single and multicentre studies have been published from Europe and the United States [6,7]. Initially, only solitary deposits were considered to be resectable. The concept was progressively extended to multiple, but unilobar, metastases, and later also to bilobar metastases, as long as resection of the primary tumour and liver metastases was technically feasible. The good results that were observed in some patients have encouraged surgeons to develop more aggressive surgical approaches. However, the problem is that recurrences occur after resection in the majority of patients. Some liver recurrences after a first resection of liver metastases can be resected with similar expected benefits [8], concurrent liver and lung metastases can also be resected with a significant survival improvement [9].

EORTC decided to organise an intergroup randomised phase III trial designed to evaluate the efficacy of oxaliplatin combined with the biweekly 5-FU/FA regimen as an adjuvant treatment before and after resection of liver metastasis from colorectal cancer. If the study is positive, the treatment of liver metastases from colorectal cancer will be modified. Preoperative chemotherapy will be used to improve survival after liver resections.

It is based on the assumption that an effective chemotherapy regimen could improve both progression-free survival and overall survival if administered pre- and postoperatively. Patients in whom preoperative chemotherapy appears effective, i.e. with objective reduction or stabilisation of their metastases, and who do not suffer major toxicity receive the same regimen after surgery as adjuvant treatment. Thus, chemotherapy is perioperative in the treatment arm.

Patients in the control arm receive surgical resection alone, which is the treatment considered as standard for patients with resectable liver metastases. The benefits of administering 5-FU/FA after resection of liver metastases have not yet been clearly proven and this type of regimen can not serve as a reference to evaluate pre- and postoperative chemotherapy with 5-FU/FA + oxaliplatin. The study by Kemeny and colleagues [10,11] demonstrated a significant improvement in 3-year recurrence-free survival of hepatic artery infusion + systemic chemotherapy after resection of liver metastases compared with surgery alone. Although those results are encouraging, the morbidity, toxicity, cost, patient and centre selection requirements prohibit this therapy from being considered as standard treatment at the present time.

1.1.3. Radiofrequency ablation of liver metastases

When liver metastases from colorectal cancer are not suitable for resection, chemotherapy is considered the treatment of choice and is administrated to most patients. In recent years, different methods of tumour ablation have been developed. The two most frequently used methods are cryotherapy and radio frequency ablation. Although we know that these procedures can destroy liver metastases efficiently, it has been demonstrated in a well designed phase III clinical trial that they modify patient survival. The EORTC GI Group considered it was its task to organise such a trial. The CLOCC trial (EORTC 40004) aims at demonstrating in patients with unresectable liver metastases from colorectal cancer that tumour ablation with radiofrequency and systemic chemotherapy with 5-FU/FA and oxaliplatin can improve survival when compared with chemotherapy alone. This trial again will be a multicentre, international, intergroup trial. It will require a tight cooperation between surgeons, medical oncologists and also radiologists since radiofrequency ablation can be performed either intra-operatively or percutaneously.

1.2. Rectal cancer

1.2.1. Preoperative radiation therapy

The EORTC GI Group started a very important trial evaluating preoperative radiation therapy at a time when most American groups were evaluating postoperative treatment of rectal cancer. This was a study assessing the effectiveness of radiation therapy administered in a dosage of 34.5 Gy, divided into 15 daily doses of 2.3 Gy before radical surgery for rectal cancer [12]. 466 patients were entered in the trial.

This trial failed to demonstrate a significant benefit of radiation therapy in term of overall survival, probably due to insufficient statistical power. However, it demonstrated that administration of preoperative radiotherapy decreases the risk of developing local recurrence after surgical resection of rectal adenocarcinoma by a factor of 2.

It should be stressed, however, that the local recurrence rate of 30% observed in this trial in the control

group after surgery alone is in the range of that observed in other trials conducted during this period, but is far beyond the rate observed now after Total Mesorectal Excision (TME), which is approximately 10%. It was shown recently in the Dutch trial that preoperative radiotherapy remains beneficial when optimal surgery for rectal cancer (TME) is performed [13]. The GI Group joined this Dutch Colorectal Cancer Group (DCRCG) to evaluate the role of preoperative radiotherapy in patients receiving TME for primary rectal cancer and has to contributed to a small extent to this trial (EORTC trial 40971).

1.2.2. Postoperative radiation therapy

Another older trial has evaluated postoperative radiotherapy.

This was a phase III randomised trial of postoperative radiotherapy in patients who had a potentially curative resection for locally advanced rectal carcinoma. Following complete excision of a Dukes' B or C rectal cancer, 172 patients were randomised to adjuvant radiotherapy or control arm. After a median follow-up of 85 months, no benefit from postoperative radiotherapy had been observed in disease-free survival, overall survival, local recurrence-free interval or number of sites of recurrence [14]. The absence of benefit after postoperative radiation therapy was confirmed by other trials.

1.3. Gastric cancer

1.3.1. Advanced gastric cancer

The GI Group has done several trials in advanced gastric cancer which have contributed to the knowledge of the activity of different regimens in advanced gastric cancer. The GI Group has developed the FAMTX regimen [15] and has shown that the FAMTX is superior to the FAM regimen that was considered as the standard regimen in the 1980s and early 1990s [16]. Therefore, the FAMTX was considered in the mid-1990s as the standard regimen for patients with advanced gastric cancer. Our protocol 40902 has later shown that FAMTX is not better than 5-FU/cisplatin in advanced gastric cancer [17]. More recently, 5-FU- and cisplatin-based regimens are considered as standard regimens in advanced gastric cancer. Our last trial has contributed to the knowledge. We have shown that that 5-FU/FA/cisplatin is better than 5-FU/FA and infusional 5-FU [18].

The Group is planning to add a molecule acting on novel targets to the cytotoxic treatment to improve the results.

1.3.2. Adjuvant treatment of gastric cancer

The GI Group aimed to compare, in a prospective and randomised trial, curative surgery alone versus curative surgery plus adjuvant chemotherapy with FAMTX. Patients randomised to the FAMTX schedule received methotrexate, 5-FU, leucovorin and doxorubicin. Endpoints were recurrence-free survival and overall survival, as well as toxicity from surgery and/or chemotherapy. This study will be analysed together with the FEMTX (E = epirubicin) trial of the International Collaborative Cancer Group (ICCG) when the required number of events is reached.

1.3.3. Neoadjuvant treatment of locally advanced gastric cancer

The Group is running a randomised phase III study of preoperative chemotherapy followed by surgery versus surgery alone in locally advanced gastric cancer (cT3 and cT4NxM0) (EORTC 40954).

The objective of the study is to assess whether or not a preoperative chemotherapy regimen increases the overall survival of patients with locally advanced gastric adenocarcinoma tumour category cT3/4 Nx M0 (including carcinomas of the cardia type II and III). Patients filling out the selection criteria will be randomised at once to: chemotherapy PLF (5-FU + folinic acid + cisplatin) + surgery or to surgery alone.

The trial is confined to centres where there is appropriate oncological experience in support of surgeons with a particular interest in gastric cancer. The trial is currently open for all EORTC GI institutions.

1.4. Pancreatic cancer

1.4.1. Advanced pancreatic cancer

The GI Group has studied the role of cisplatin in this disease in a randomised phase II-III clinical trial of cisplatin + 5-FU versus cisplatin + 5-FU with alpha interferon in metastatic pancreatic cancer the results will be published soon. Recently, the GI Group has done a randomised phase II trial of gemcitabine + docetaxel versus docetaxel + cisplatin. 96 patients have been entered into this trial. The main endpoint was the response to treatment; the secondary objective was toxicity. The results are submitted for the American Society of Clinical Oncologists (ASCO) 2002 meeting.

1.4.2. Adjuvant treatment of pancreatic cancer

A randomised phase III trial of the EORTC Gastrointestinal Tract Cancer Group aimed to test adjuvant radiotherapy and 5-FU after curative resection of cancer of the pancreas and the peri-ampullary region. In this trial, 218 patients with pancreatic head and periampullary cancer were randomised to adjuvant radiotherapy and 5-FU versus observation alone after surgery.

No statistically significant survival difference was found at the end of this study [19]. Although this trial was basically negative, it serves as a background for the preparation of a future trial which should be limited to

pancreatic head cancer, excluding other peri-ampullary tumours, and thus increasing the chance of observing a significant effect. Radiation therapy should be associated with more effective chemotherapy regimens. The GI Group is currently preparing a new protocol for this purpose in collaboration with the Radiotherapy Group. In this trial, surgery will be compared with the surgery plus postoperative gemcitabine followed by chemoradiotherapy with weekly gemcitabine simultaneously with irradiation (50.4 Gy in fractions of 1.8 Gy).

1.5. Oesophageal cancer

1.5.1. Neoadjuvant treatment

The EORTC GI Group participated in a randomised trial comparing preoperative chemoradiotherapy followed by surgery versus surgery alone in patients with stage I and II squamous-cell cancer of the oesophagus [20]. This trial concluded that in patients with squamous-cell oesophageal cancer, preoperative chemoradiotherapy did not improve overall survival, but it prolonged disease-free survival and survival free of local disease by improving control of the tumour. Disease stage, location of the tumour and the surgical resection's being curative were found to be prognostic factors.

Our Group is to participate in a new intergroup randomised trial assessing the effect on survival of preoperative chemoradiotherapy versus surgery alone in resectable thoracic oesophageal cancer.

1.5.2. Metastatic oesophageal cancer

The results of the EORTC trial 40941 with vinorelbine and cisplatin in metastatic squamous cell carcinoma of oesophagus will be published soon in *Annals of Oncology*.

2. Conclusion

A good co-operation between surgeons, medical oncologists, gastroenterologists and radiation oncologists has always been one of the leading principles of the GI Group of EORTC. If multidisciplinarity is a must for a successful given trial, it is also necessary for a good research strategy. Multidisciplinarity also implies participation of biologists. In the near future, treatment of gastrointestinal tract cancer will be tailored to the characteristics of tumours.

Moreover, the EORTC GI Tract Cancer Group will continue to contribute actively to ongoing adjuvant trials in colon cancers through the PETACC network and prepare intergroup studies of the future to test newly developed drugs. Our group is assessing the possibility of doing some translational research. Translational research will be associated with all new trials developed by the Group. It is likely that, in the near future, treatment of patients with GI malignancies will be tailored to biological parameters. To prepare for this, we will now preserve resected specimens in all of the new trials.

References

1. Arnaud JP, Buyse M, Nordlinger B, *et al*. Adjuvant therapy of poor prognosis colon cancer with levamisole: results of an EORTC double-blind randomized clinical trial. *Br J Surg* 1989, **76**, 284–289.
2. Moertel CG, Fleming TR, Macdonald JS, *et al*. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990, **322**, 352–358.
3. Nitti D, Wils J, Sahmoud T, *et al*. Final results of a phase III clinical trial on adjuvant intraportal infusion with heparin and 5-fluorouracil (5-FU) in resectable colon cancer (EORTC GITCCG 1983–1987). European Organization for Research and Treatment of Cancer. Gastrointestinal Tract Cancer Cooperative Group. *Eur J Cancer* 1997, **33**, 1209–1215.
4. Rougier P, Sahmoud T, Nitti D, *et al*. Adjuvant portal-vein infusion of fluorouracil and heparin in colorectal cancer: a randomised trial. European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group, the Gruppo Interdisciplinare Valutazione Interventi in Oncologia, and the Japanese Foundation for Cancer Research. *Lancet* 1998, **351**, 1677–1681.
5. Roh M, Petrelli N, Wieand S, *et al*. *Postoperative Adjuvant Portal Vein Infusion of 5-Fluorouracil Following Colectomy Prolongs Disease-Free Survival*. Washington DC, SSO, 2001.
6. Nordlinger B, Guiguet M, Vaillant JC, *et al*. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996, **77**, 1254–1262.
7. Hughes KS, Simon R, Songhorabodi S, *et al*. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 1986, **100**, 278–284.
8. Nordlinger B, Vaillant JC, Guiguet M, *et al*. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. *J Clin Oncol* 1994, **12**, 1491–1496.
9. DeMatteo R, Minnard E, Kemeny N, *et al*. Outcome after resection of both liver and lung metastasis in patients with colorectal cancer. In *Proceedings of American Society of Clinical Oncology*, Atlanta, 1999, 18, 249a.
10. Kemeny N, Cohen A, Huang Y, *et al*. Randomized study of hepatic arterial infusion (HAI) and systemic chemotherapy (SYS) versus SYS alone as adjuvant therapy after resection of outcome after resection of hepatic metastases from colorectal cancer. *Proc Ame Soc of Clin Oncol* 1999, **18**, 263a.
11. Kemeny N, Huang Y, Cohen AM, *et al*. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999, **341**, 2039–2048.
12. Gerard A, Buyse M, Nordlinger B, *et al*. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Ann Surg* 1988, **208**, 606–614.
13. Klinkenbijl JH, Jeekel J, Sahmoud T, *et al*. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999 **230,** 776–782 (discussion 782–784).

14. Arnaud JP, Nordlinger B, Bosset JF, *et al*. Radical surgery and postoperative radiotherapy as combined treatment in rectal cancer. Final results of a phase III study of the European Organization for Research and Treatment of Cancer. *Br J Surg* 1997, **84**, 352–357.
15. Wils J, Bleiberg H, Dalesio O, *et al*. An EORTC Gastrointestinal Group evaluation of the combination of sequential methotrexate and 5-fluorouracil, combined with adriamycin in advanced measurable gastric cancer. *J Clin Oncol* 1986, **4**, 1799–1803.
16. Wils J, Klein H, Wagener D, *et al*. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991, **9**, 827–831.
17. Vanhoefer U, Rougier P, Wilke H, *et al*. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil and doxorubicin versus etoposide, leucovorin and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000, **18**, 2648–2657.
18. Vanhoefer U, Wagner T, Lutz M, *et al*. Randomized phase II study of weekly 24 h infusion of high dose 5-FU folinic acid (HD-FU FA) versus HD-FU/FA/biweekly cisplatin in advanced gastric cancer. EORTC-trial 40953. *ECCO* 2001, 88 (abstr).
19. Kapiteijn E, Marijnen CA, Nagtegaal ID, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001, **345**, 638–646.
20. Bosset JF, Gignoux M, Triboulet JP, *et al*. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997, **337**, 161–167.