EUROPEAN JOURNAL OF CANCER 48, SUPPL. 2 (2012) S1–S11

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.info

Invited Publications

Thursday, 22 March, 08:30−10:30

Session I. Multimodal Approach to Rectal Cancer

PG 1.01 SPEAKER ABSTRACT

Rectal cancer: what is the aim of multimodal therapy?

D. Arnold. *Hubertus Wald Cancer Center, Hamburg, Germany*

No abstract available.

PG 1.02 SPEAKER ABSTRACT

Clinically relevant study end points in rectal cancer

C. Fernandez-Martos. *Oncology, Seccion de Oncologia Gastrointestinal, Fundacion Instituto Valenciano de Oncología, Valencia, Spain*

For multiple reasons, including complexities in anatomy, report in histopathological examination, local staging techniques limitations, and management, locally advanced rectal cancer represent a challenging disease for the design of clinical trials and for reporting of end points. In rectal cancer currently there is no validated any early end point as surrogate for long-term clinical outcome such as local control and survival. However the use of some kind of response rate (i.e. Pathological complete response, downsizing the primary tumor, tumor regression rate, Radiological response . . .) as an endpoint in early (phase II) clinical trials is widespread for the obvious reason that objective response to therapy is a clear early indication of activity. Overall survival is the gold standard primary end point in phase III adjuvant clinical trials. However the long follow up needed to observe reliable results and the increasing number of effective salvage treatments available that may confuse the merits of the experimental treatment, have prompted the search for earlier surrogates end points. In adjuvant colon cancer disease-free survival − defined as the time from randomization to any event, irrespective of cause − have been validated as surrogate for overall survival and is considered to be the most informative endpoint for assessing the effect of treatment and therefore the most relevant to clinical practice. Although never validated in the locally advanced rectal scenario, DFS has been proposed as an appropriate end point in adjuvant rectal cancer trials, and is actually the most frequently used in newer trials. Due to the particularly devastating nature of local recurrence in locally advanced rectal cancer, local control (which is itself a subset of the overall DFS endpoint) is still considered an important endpoint. Recently circumferential resection margin (CRM/R0) has been proposed as novel candidate for early end point because the CRM status can substantially account for effects on disease-free and overall survival after chemoradiation, radiation or surgery alone, but again need a formal validation for long-term outcomes. An effort of consensus is needed among clinicians and methodologists to define the most appropriate end points in both early and phase III trials in LAR cancer.

PG 1.03 SPEAKER ABSTRACT

Neoadjuvant treatment: Do we need radiotherapy?

R. Glynne-Jones. *Gastrointestinal Cancer, Mount Vernon Cancer Centre, Northwood, United Kingdom*

Historically, in locally advanced rectal cancer there has been a high local recurrence rate, but with total mesorectal excision (TME), metastatic disease is now the predominant problem, reflecting the likely presence of micrometastases at diagnosis, rather than inadequate surgery. In resectable rectal cancer, modern randomised studies show chemoradiation (CRT) or short course preoperative radiotherapy (SCPRT) reduce locoregional failure (LRF), without improving disease-free survival (DFS) or overall survival (OS) (Peeters 2007, Sebag-Montefiore 2009, Sauer 2004, Bosset 2006, Gerard 2006, van Gijn 2011) [1−6]. SCPRT and CRT appear equivalent in terms of local recurrence, DFS and OS (Bujko 2006, Ngan 2010) [7,8]. Trials integrating oxaliplatin into CRT have not increased the pathological complete response rate (pCR) but suggest the use of two drugs halves the positive CRM rate (Gerard 2010, Aschele 2011) [9,10]. For unresectable/locally recurrent cases, 5FU-based CRT significantly improves resectability and relapse-free survival compared to RT alone (Braendengen 2008) [11]. In stage III patients with colon cancer, adjuvant oxaliplatin improves 3-year DFS compared to 5-FU/folinic acid alone (Kuebler 2007, André 2009) [12,13]. However, rectal cancers (within 12 cm of the anal verge) have been excluded from these studies, and so the role of adjuvant postoperative chemotherapy in rectal cancer after preoperative CRT is controversial (Bujko 2010) [14]. There is a high risk of metastatic disease in locally advanced rectal cancer, yet systemically active doses of chemotherapy are not delivered in CRT schedules, and compliance to postoperative adjuvant chemotherapy is generally poor. Hence, some groups have added chemotherapy either prior to CRT, when compliance to chemotherapy is high (Fernandez-Martos 2010) [15], or following chemoradiation to increase the response rate (Garcia-Aguilar 2011) [16]. Some groups have suggested this strategy leads to excellent long-term results, but raise concerns for a high early death rate (Chua 2010) [17]. Pelvic radiotherapy causes permanent morbidity in about 5−10% of patients, and impacts on small bowel function, sexual functioning, urinary incontinence, bowel function (Peeters 2005) [18], and an increase in faecal incontinence (Lange 2007) [19]. There is an increased risk of a second malignancy (Birgisson 2005, Van Gijn 2011) [20,6]. These complications are likely to be similar after preoperative CRT (Ngan 2010) [8]. In contrast to radiotherapy, the side effects of chemotherapy are usually short-term, although the neuropathy from oxaliplatin may be permanent. Several groups have explored omitting radiotherapy when MRI suggests the tumour is easily resectable. This omission does not appear to have increased the local recurrence rate (Taylor 2011, Frasson 2011, Mathis 2012) [21−23]. Three feasibility/retrospective studies of neoadjuvant chemotherapy (NACT) alone without radiation (Cercek 2010, Schrag 2010, Ishii 2010) [24−26] used FOLFOX plus/minus bevacizumab. The pCR rate after chemotherapy alone varied from to 7%-35%, but as small non-randomised studies are unableto show an impact on metastatic disease. Chemotherapy at systemically-effective doses aims to reduce the risk of metastases. For unresectable cancers or where MRI shows a threatened/breached CRM (10−15% of cases), radiation as a component of CRT is clearly required. Chemotherapy prior to CRT or SCPRT does not compromise the delivery CRT, but has not increased pCR rates, R0-resection rate, improved DFS or reduced metastases. There is significant late morbidity from pelvic radiotherapy and a doubling of the risk of second malignancy. Hence NACT alone without radiotherapy could be explored compared with SCPRT or CRT in selected patients with resectable rectal cancer showing adverse features (extramural vascular invasion etc.) in a future research programme. In the UK, current NICE clinical guidelines have set NACT strategies as a priority of future research in rectal cancer, http://guidance.nice.org.uk/CG131 However, large well-conducted carefully imaged randomised phase III trials comparing chemotherapy alone with the current standard of SCPRT or CRT will be required if we are to provide definitive answers.

Reference(s)

[1] Peeters KC, Marijnen CA, Nagtegaal ID, et al., for the Dutch Colorectal Cancer Group. The TME Trial after a Median Follow-up of 6 Years: Increased local control but no survival benefit in irradiated patients with resectable rectal Carcinoma. Ann Surg 2007; 246(5): 693–701.

[2] Sebag-Montefiore D, Stephens RJ, Steele R, et al., Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373(9666):811−20.

[3] Sauer R, Becker H, Hohenberger W, et al., German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351:1731–1740.

[4] Bosset JF, Collette L, Calais G, et al., Chemoradiotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355: 1114–1123.