leaving behind adjacent peritumoral tissues and organs. Radical resection, or en bloc esophagectomy, removes all peritumoral tissues in addition to the esophagus. The extent of lymphadenectomy performed during esophagectomy is also highly variable, ranging from minimal to radical. A radical esophagectomy refers to a procedure by which the esophagus and its enveloping tissues are removed as a single specimen (en bloc), combined with either two-field (abdominal and mediastinal), or three-field (abdominal, mediastinal, cervical) lymphadenectomy. Nonrandomized comparative studies evaluating radical lymphadenectomy have reported mixed findings, with a number that have failed to identify a survival benefit, whereas some others have reported a benefit. An indirect evidence supports radical lymphadenectomy with an independent association found between the number of surgically removed lymph nodes and overall survival. Despite these data, the answer to this controversy should ideally come from prospective, randomized trials, since the phenomenon of stage migration may occur in comparison with non-randomized series of patients. In this regard, the only published phase III trial till this date compared non-radical transhiatal esophagectomy with transthoracic esophagectomy with two-field lymphadenectomy for patients with adenocarcinoma of the esophagus. The overall 5-year survival with the radical approach was 39%, compared with 29% for the patients undergoing the non-radical resection. Although not statistically significant due to underpowered study, many esophageal cancer specialists would consider less of an increase in survival to be clinically relevant. For squamous cancer there have been two small randomized controlled trials published. The first one compared 2-field lymphadenectomy to 3-field lymphadenectomy without significant 5-year survival difference (48% vs. 66%, respectively). The second one compared 2-field lymphadenectomy to lymph node sampling with a survival benefit favoring radical resection (36% vs. 25%). To conclude, radical transthoracic esophagectomy with two-field lymphadenectomy appears to offer an optimal balance between benefits and risks to a majority of EC patients, especially in the growing area of neoadjuvant treatments. Non-radical resection should be probably reserved for patients with a poor general status whereas 3-field lymphadenectomy may be reserved to selected patients with loco-regional disease in experienced hands, surely for patients with upper esophageal tumours.

154 INVITED

Neoadjuvant Treatment – Better Than Surgery Alone?

Abstract not received

155 INVITED

Will Centralization Improve Outcome?

R. Mason[1]. [1]*Guy's & St. Thomas Hospital NHS Trust, Gastro Intestinal Surgery, London, United Kingdom*

Oesophageal cancer particularly adenocarcinoma is increasing in incidence in the west. Resection of such tumours has been associated with significant morbidity and mortality and poor long term survival. In recent studies from the UK, Europe and USA improved outcomes for surgical resection have been achieved by centralisation of services to specialist centres. It appears that both surgeon and institution volume are equally important. This has achieved in hospital mortality figures of well under 5%. This may well be a combination of better staging and selection as well as improved technique and postoperative care.

Whether this improvement in short term outcome can be reflected in improvement in long term survival is not clear and there are conflicting results. Such an improvement will undoubtably be the result of better selection and staging, and the recruitment of patients into trials of multimodality treatment. It is suggested that radical surgery with extensive resection and lymphadenectomy will improve long term survival. There is little evidence to support this in oesophageal resection in contrast to radical gastrectomy.

The most important factors for improvement in outcome are a multidiciplinary approach with accurate staging, selection and multimodal therapy of a high standard.

Taking this approach over the last 20 years we have reduced inhospital mortality from 3.5% to 0.9% and 5 year survival from 28% to 48% with no significant change in stage of presentation but an increased use of preoperative chemotherapy from <10% to >90%.

Special Session (Sun, 25 Sep, 13:15–14:15)
Cross-Over in Trials

156 INVITED

Early Approval Versus Late Approval

F. Pignatti[1]. [1]*European Medicines Agency (EMA), Safety and Efficacy Sector, London, United Kingdom*

"Early approval" strategies include the "Conditional Marketing Authorisation" in the E.U. and "Accelerated Approval" in the U.S.A. Both mechanisms aim to license new drugs as early as possible in the development, while ensuring that confirmatory efficacy and safety data are duly submitted post-marketing. Regardless of the approval mechanism, sufficient data need to be available in terms of clinically relevant endpoints, to allow a benefit-risk assessment before an approval can be granted.

Acceptable primary endpoints for phase III studies for licensing include overall survival (OS) and progression-free survival (PFS) [1,2]. From the perspective of drug developers, the interest in PFS is because of the expectation that treatment effect will be numerically larger and quicker to observe compared to OS, making PFS an ideal candidate for "early approval" strategies. However, the general acceptance of PFS as a primary endpoint from a regulatory perspective is frequently debated. This is often due to difficulties in quantifying the clinical benefit of this radiological endpoint in the context of the benefit-risk balance assessment for regulatory decision. Furthermore, EMA guidelines recommend that when PFS is the chosen primary endpoint, sufficient data on OS have to be available at the time of assessment in order to at least rule out a negative effect. The analysis of OS can be done on the basis of planned secondary analyses or planned co-primary analyses.

Where one-way cross-over to the experimental arm after progression is considered appropriate (e.g. studies *v.* best supportive care with the possibility to switch to experimental treatment at time of progression), non-compliance with the randomized treatment is likely to hamper any subsequent comparisons in terms of OS. Currently, there is no general agreement on acceptable methods or modelling assumptions to correct for non-compliance for subjects who cross-over after progression. Thus, when PFS is the primary endpoint, there is a need to define situations and timing when cross-over is appropriate, to ensure adequately powered treatment comparisons, in accordance with the objectives of the study. The lack of well-powered OS analyses may be less of a concern when the treatment in terms of PFS is large or the expected OS after progression is short.

When the clinical relevance of PFS in its own right is questioned, this endpoint may still be used for "early approval" if it is considered to be a reasonably likely surrogate endpoint for OS. However, in these situations, conclusive results to confirm a benefit in terms of OS would be expected from relevant trials to be submitted post-approval. In this case, the timing of the post-marketing studies is critical, since "early approval" may again hamper the conduct of ongoing or subsequent randomized studies in the same indication.

Although at times relevant post-marketing studies can be conducted in related indications or combinations, there needs to be sufficient biological and pharmacological rationale to allow meaningful extrapolation of results across different settings.

In conclusion, when considering "early approval" strategies it is critical to consider the clinical relevance of the primary endpoint to allow a benefit-risk assessment at the time of approval, the appropriateness and timing of cross-over, and the feasibility of completing further studies post-marketing.

Publication disclaimer: The views presented here are personal and should not be understood or quoted as those of the European Medicines Agency.

References

[1] European Medicines Agency. Guideline On The Evaluation Of Anticancer Medicinal Products In Man. 2006; Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500017748.

[2] Food and Drug Administration. Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. [Internet] 2007; Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

157 INVITED

Cross-over in Oncology Clinical Trials – Statistical Issues

D. Sargent[1]. [1]*Mayo Clinic Cancer Center, Health Science Research, Rochester Minnesota, USA*

Background: Cross-over randomized clinical trials, where patients in one arm are allowed (or required) after some predefined time event to receive