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ESPS Peer-review Report
Name of Journal: World Journal of Gastrointestinal Oncology
ESPS Manuscript NO: 7018
Title: Neoadjuvant treatment for esophageal squamous cell carcinoma
Reviewer code: 02567684
Science editor: Wen, Ling-Ling
Date sent for review: 2013-11-02 19:28
Date reviewed: 2014-01-02 22:41

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The review gives an insight at ESCC treatment. It comments on different countries practices on treating esophageal cancer and on ESCC treatment as opposed to adenocarcinoma. Also, some upcoming treatments are cited. Major comments 1. There were a handful of publication on this topic in 2013 but the review cite only two. There were, for instance, japanese (Jpn J Clin Oncol. 2013 Jul;43(7):752-5. doi: 10.1093/jjco/hyt061) and italian trials (Cancer. 2013 Mar 1;119(5):939-45. doi: 10.1002/cncr.27822) about docetaxel. 2. Missed some comments on CRT drawbacks. Minor comments 1. Some minor typos. 2. First seven lines in future directions do not present futures aspects.

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[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The authors have written a comprehensive review of neoadjuvant treatment of squamous cell carcinoma of the esophagus. Overall the review is comprehensive and balances, although some discussion of the pivotal trials should be more critical. The authors need to update references, in particular the comments about EGFr targeted agents, with all recent reports of these agents indicating failure to improve outcome. Specific comments are outlined below: Abstract: The authors repeatedly make the point that completely different therapy strategies are needed for squamous cell and adenocarcinoma of the esophagus. Although these indeed are different diseases, they often behave similarly with outcomes in the chemotherapy for advanced disease, and the neoadjuvant therapy literature, surprisingly similar. Given that this disease is rare in the West studies usually include esophageal adenocarcinoma and squamous cancer with planned subgroup analyses. It is likely that this difference will emerge in the utilization of targeted agents. It is not completely justified to state that these diseases should have different therapy strategies, when outcomes for currently available neoadjuvant and advanced disease therapies are actually quite similar for the two histologies. The authors could make the analogy with non small cell lung and squamous and adenocarcinoma histologies have both overlapping and distinct therapies. Introduction: The authors should qualify the statement that the "rapid" increase in adenocarcinoma is actually starting to level off in the West. The authors should clarify that squamous cancer incidence is not increasing. Strengths of surgical resection: The authors should point out that patients reported in purely surgical series are selected for surgery and do not reflect all patients diagnosed with squamous cancer, therefore survival in surgery only series is likely higher than for all comers diagnosed with locally

advanced disease. This explains the lower survival observed in phase III controlled trials compared to single institution surgical series. Page 4: a comment about survival dropping to 14% when "residual tumor is present" makes no sense, if these series are surgery only patients. I am assuming all patients treated with surgery alone would have tumor present? Page 5 confusing phrasing: patients who are node positive should be called node positive, not 'metastatic." Degrade tumor stage should be downgrade or downstage. The comment about selection of drug resistant clones being "inconclusive" makes no sense. Page 7: More critical discussion is needed here. OEO2 was a positive trial only because rates of R0 resection were improved with preoperative chemotherapy. There was no impact on distant recurrence of disease, which is surprising for an adjuvant chemotherapy trial. These results are contradicted by RTOG 8911 which showed no benefit for any outcome with chemotherapy including no improvement in rates of R0 resection. The benefit observed for OEO2 (6% OS improvement at long term follow up) was marginal at best. The JCOG study is flawed because the design was hampered by observations from subset analyses of prior studies. Nearly half of the post op chemo arm patients on this trial did not receive chemotherapy. The primary endpoint of this trial (disease free survival) was not met, and the benefit of preoperative chemotherapy was limited to clinical N0 patients, in contrast to their prior post op study where a benefit was limited to N+ patients. These inconsistencies and weaknesses of JCOG 9907 need to be reviewed, in particular given Japan's embrace of preoperative chemotherapy based on this highly flawed study. Page 9: The authors underplay the greater impact of preoperative chemoradiotherapy reported on the CROSS trial for squamous cancers, with a path CR rate of nearly 50% and a HR for survival improvement indicating a near doubling of survival for squamous cancer patients. The