

# Neoadjuvant DCF vs. ACF for resectable oesophageal squamous cell carcinoma

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*Comment on:* Yamasaki M, Yasuda T, Yano M, *et al.* Multicenter randomized phase II study of cisplatin and fluorouracil plus docetaxel (DCF) compared with cisplatin and fluorouracil plus Adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003). *Ann Oncol* 2017;28:116-20.

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Despite falling incidence rates, squamous cell carcinoma of the oesophagus (OSCC) remains a common cancer globally; in 2012 an estimated 398,000 OSCC diagnoses were made worldwide (1-3). Whereas patients with very early OSCC ( $\leq$  cT2N0) may benefit from endoscopic or surgical resection without adjunctive therapies, patients diagnosed with OSCC which is  $\geq$  cT3 or has clinically involved lymph nodes are recommended to undergo chemotherapy Japanese Esophageal Society Guidelines or chemoradiotherapy (ESMO, NCCN Guidelines) in addition to surgery to increase the chance of cure (4-6). Data supports both neoadjuvant chemotherapy and chemoradiotherapy in OSCC, therefore regional preferences are also important in selection of neoadjuvant therapy (7-9). Additionally, as OSCC is a radiosensitive tumour, OSCC patients may alternatively be treated with definitive chemoradiotherapy without resection which results in comparable overall survival (OS) to neoadjuvant chemoradiotherapy followed by surgery (10,11). To add to this complexity, historically most oesophageal cancer trials have included both oesophageal adenocarcinoma and OSCC patients, and there are biological differences between these tumours which impact on response to therapy and prognosis (12,13). In order to define the best treatment approach for OSCC, more high quality trials containing only OSCC patients are required. Therefore, the results presented by Yamasaki *et al.*

in *Annals of Oncology* provide a welcome addition to the literature (14).

In the phase II randomised trial reported by Yamasaki *et al.*, 162 patients with localised OSCC were treated with either 2 cycles of neoadjuvant cisplatin and 5-fluorouracil chemotherapy plus either adriamycin (ACF) or docetaxel (DCF). Recurrence free survival (RFS), the primary endpoint of the trial, was significantly improved for patients treated with DCF [2-year RFS DCF *vs.* ACF were 64.1% and 42.9% respectively (HR 0.53, 95% CI 0.33–0.83,  $P=0.0057$ )]. DCF chemotherapy also appeared to have a better downstaging effect; pathological T stage was earlier in the DCF treated patients ( $P=0.008$ ), although rates of lymph node involvement remained comparable between DCF and ACF groups. With regard to survival outcomes, a trend was demonstrated towards improved OS for DCF treated patients (2-year OS 65.4% *vs.* 78.6% for ACF *vs.* DCF respectively), however this did not reach statistical significance ( $P=0.08$ ). The authors suggest that neoadjuvant DCF chemotherapy should be compared with neoadjuvant chemoradiotherapy in order to determine the best neoadjuvant treatment for localised OSCC.

The strength of this trial is that in contrast to many other oesophageal cancer studies which also include patients with oesophageal adenocarcinoma, it recruited a homogenous population entirely composed of OSCC patients. The trial population is also relatively large compared to many other

studies in this context. These strengths allow for a well powered comparison of study endpoints without the need for subgroup analysis which challenges the interpretation of many other oesophageal cancer clinical trials. The surgical outcomes described are excellent, independent of the neoadjuvant chemotherapy used; R0 resection rates were high in both ACF and DCF arms of the trial (95.9% *vs.* 96.2% respectively,  $P=0.93$ ). These R0 resection rates are encouraging; however may reflect not only chemotherapy efficacy, but also patient selection for surgery and the quality of surgery. Survival rates were also promising; 2-year survival in the DCF arm of 78.8%, which is comparable to that seen in the updated CROSS study for OSCC patients (15). The results of this study highlight the superiority of taxane chemotherapy compared with anthracyclines when used in combination with a platinum-fluoropyrimidine backbone for patients with resectable oesophageal cancer. In particular, these results are similar to those of the FLOT4-AIO study where perioperative FLOT (5-fluorouracil, oxaliplatin and docetaxel) chemotherapy was associated with superior OS compared to anthracycline based perioperative ECX (epirubicin, cisplatin and capecitabine) for patients with resectable gastric adenocarcinoma (HR 0.77; 95% CI 0.63–0.94;  $P=0.012$ ) (16). The results of OGS1003 and FLOT4-AIO, taken together with the negative results of the OE05 study which showed no benefit for the addition of epirubicin to neoadjuvant cisplatin and capecitabine in operable oesophageal adenocarcinoma (HR 0.90; 95% CI 0.77–1.05;  $P=0.19$ ), suggest that anthracyclines do not have a future role in the perioperative management of gastroesophageal cancer, independent of histological subtype (17).

Despite the encouraging survival outcomes demonstrated for DCF treated patients by Yamasaki *et al.*, there are a number of issues which may limit the applicability of these trial results. Generally speaking, these data must be viewed in the context of the standard of care neoadjuvant treatment which in European and NCCN guidelines is chemoradiotherapy, whereas in Japan neoadjuvant chemotherapy may be preferred. Firstly, although toxicity data for this regimen are not described in the current manuscript, they are reported in a separate publication (18). As observed in other trials using the DCF regimen, enhanced efficacy comes at a cost of increased toxicity (19). Patients treated with DCF had higher rates of grade 3/4 neutropenia and febrile neutropenia compared with patients treated with ACF (90% *vs.* 69% and 39% *vs.* 17% respectively) (18). Although toxicity in the DCF arm of the trial did not appear to impact on the proportion of patients completing neoadjuvant chemotherapy or undergoing

surgery, the relatively high incidence of potentially serious complications such as febrile neutropenia is a concern. This compares with the low rate of neutropenia and febrile neutropenia associated with carboplatin and paclitaxel chemoradiotherapy regimens (e.g., 2% incidence of  $\geq$  grade 3 neutropenia in the CROSS study) (9). Also absent are data on rates of local versus distant recurrence which are of key interest in any discussion surrounding chemotherapy and chemoradiotherapy in oesophageal cancer. A final issue affecting the likelihood of adoption of neoadjuvant chemotherapy as a standard treatment for OSCC is that definitive chemoradiotherapy is considered a reasonable alternative to surgery for patients with localised OSCC. As two clinical trials demonstrate similar OS for OSCC patients treated with definitive chemoradiotherapy compared with chemoradiotherapy plus surgery, albeit with higher rates of local recurrence compared with surgery alone, there is clinical equipoise in this situation (10,11). On-going clinical trials are addressing the question of whether salvage surgery on relapse following chemoradiotherapy is equivalent to neoadjuvant chemoradiotherapy followed by immediate surgery. Pending these trial results, definitive chemoradiotherapy remains a validated and widely endorsed treatment for resectable OSCC (4,5). For oncologists who prefer definitive chemoradiotherapy rather than neoadjuvant treatment followed by surgery for their patients, the question of whether neoadjuvant chemotherapy rather than chemoradiotherapy is superior before resection is of less importance. However as surgical resection is still the preferred treatment for a substantial proportion of the population, defining the best neoadjuvant treatment is still relevant for those patients.

In conclusion, the data presented by Yamasaki *et al.* are provocative in view of the excellent R0 resection rates and survival demonstrated for patients with resectable OSCC treated with neoadjuvant DCF chemotherapy. Exploring whether the toxicity of DCF can be mitigated by the use of prophylactic growth factors or alternative dosing schedules without compromising efficacy may be of value. Finally, these data also provide corroborative evidence in support of a reduction of the use of anthracycline chemotherapy in oesophageal cancer, with taxanes emerging as the optimal first choice for most patients.

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## Footnote

**Conflicts of Interest:** EC Smyth declares honoraria for advisory role from Five Prime Therapeutics, Bristol Meier-Squibb, Gritstone Oncology and Servier. The other author has no conflicts of interest to declare.

## References

1. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015;64:381-7.
2. Trivers KF, Sabatino SA, Stewart SL. Trends in esophageal cancer incidence by histology, United States, 1998-2003. *Int J Cancer* 2008;123:1422-8.
3. Zhao J, He YT, Zheng RS, et al. Analysis of esophageal cancer time trends in China, 1989- 2008. *Asian Pac J Cancer Prev* 2012;13:4613-7.
4. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27:v50-v7.
5. National Comprehensive Cancer Network. NCCN Esophageal Cancer Guidelines. 2016. Available online: <https://www.nccn.org/patients/guidelines/esophageal/files/assets/common/downloads/files/esophageal.pdf>
6. Kuwano H, Nishimura Y, Oyama T, et al. Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. *Esophagus* 2015;12:1-30.
7. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *The Lancet* 2002;359:1727-33.
8. Allum WH, Stenning SP, Bancewicz J, et al. Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer. *J Clin Oncol* 2009;27:5062-7.
9. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med* 2012;366:2074-84.
10. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;23:2310-7.
11. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007;25:1160-8.
12. Smyth EC, Lagergren J, Fitzgerald RC, et al. Oesophageal cancer. *Nat Rev Dis Primers* 2017;3:17048.
13. Cancer Genome Atlas Research Network; Analysis Working Group; Asan University; BC Cancer Agency; et al. Integrated genomic characterization of oesophageal carcinoma. *Nature* 2017;541:169-75.
14. Yamasaki M, Yasuda T, Yano M, et al. Multicenter randomized phase II study of cisplatin and fluorouracil plus docetaxel (DCF) compared with cisplatin and fluorouracil plus Adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003). *Ann Oncol* 2017;28:116-20.
15. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *The Lancet Oncology* 2015;16:1090-8.
16. Al-Batran SE, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. *J Clin Oncol* 2017;suppl 35: abstr 4004.
17. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. *Lancet Oncol* 2017. [Epub ahead of print].
18. Shiraishi O, Yamasaki M, Makino T, et al. Feasibility of Preoperative Chemotherapy with Docetaxel, Cisplatin, and 5-Fluorouracil versus Adriamycin, Cisplatin, and 5-Fluorouracil for Resectable Advanced Esophageal Cancer. *Oncology* 2017;92:101-8.
19. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-7.

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