Editorial

Should cT2 esophageal cancer get neoadjuvant treatment before surgery?

Peter Thuss-Patience[1], Loredana Vecchione[2], Ulrich Keilholz[2]

[1]Department of Hematology, Medical Oncology and Tumor Immunology, Augustenburger Platz 1, Charité Universitätsmedizin Berlin, 13353 Berlin, Germany; [2]Charité Comprehensive Cancer Center, Charitéplatz 1, 10117 Berlin, Germany

Correspondence to: Ulrich Keilholz, Professor. Charité Comprehensive Cancer Center, Charitéplatz 1, 10117 Berlin, Germany.
Email: ulrich.keilholz@charite.de.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Hongcheng Zhu (Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Markar SR, Gronnier C, Pasquer A, *et al.* Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study. Eur J Cancer 2016;56:59-68.

Submitted Jul 28, 2017. Accepted for publication Aug 21, 2017.
doi: 10.21037/jtd.2017.08.143
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.143

In recent years treatment options for esophageal cancer were expanding as randomized trials have shown a beneficial effect of preoperative chemotherapy and of chemoradiotherapy (1-7). However, it is unclear whether early stage cancers also benefit from preoperative therapy since the number of patients included in such randomized trials is small (8-10). In a more recently published randomized trial, Mariette *et al.* (11) investigated the benefit of preoperative chemoradiotherapy in stage I and II esophageal carcinomas. A total of 195 patients were randomized between primary surgery and preoperative chemoradiotherapy (cisplatin/5-FU +45 Gy), followed by surgery. Despite of a significant downstaging and a pathologic complete remission (pCR) in 33.3% of cases in the chemoradiotherapy group, no improvement of neither R0 resection rate nor overall survival were observed. Moreover, there was no difference in postoperative complications but there was an increase in hospital mortality in the chemoradiotherapy group (11.1% *vs.* 3.4%), which may have affected the overall outcome of the trial. Due to these results neoadjuvant treatment for T2 esophageal cancer remains highly controversial.

A multi-center European retrospective study investigated the role of neoadjuvant treatment in clinical T2N0 oesophageal cancer (12). A total of 355 patients with cT2N0 disease were identified, of whom 285 received primary surgery and 70 received preoperative treatment (chemotherapy or chemoradiotherapy). Again, a significant downstaging with 18.6% of pCR was achieved by preoperative treatment but no significant survival benefit was observed. No difference in in-hospital mortality could be detected either. Nevertheless, in their concise analysis, giving an excellent overview over the current discussion, the authors conclude that in cT2N0 oesophageal cancer surgery alone can achieve similar outcomes as neoadjuvant therapy plus surgery.

These conclusions are supported by several smaller analyses and two other large retrospective studies. Song *et al.* (13) analyzed 918 patients from the SEER data base (The Surveillance, Epidemiology and End Results) with cT2-3N0 oesophageal cancer and did not find any benefit of preoperative treatment in the 367 cT2N0 patients. Speicher *et al.* (14) analyzed data from the US National Cancer data Base. Among the 1,599 cT2N0 patients induction therapy was used in 688 (44.1%) (chemoradiation 68%, radiation alone 14.9%, chemo alone 3.0%). Patients treated with induction therapy were less likely to have positive margins. Both groups did not differ in postoperative morbidity or mortality. No survival benefit of preoperative induction therapy could be detected.

What shall we do with our next patient? Has the question been solved? Is primary surgery the treatment option for patients with stage cT2 adenocarcinoma or squamous cell carcinoma of the esophagus?

Current guidelines do not give clear advice on this

matter: the German S3 guidelines consider the use of preoperative chemotherapy and or chemoradiotherapy in stage cT2 adenocarcinoma or squamous cell carcinoma of the esophagus (15). In line with this, the current NCCN guidelines also offer the option of preoperative chemoradiotherapy or primary surgery in T1b/T2, N0 low risk lesions (<2 cm, well differentiated) (16). On the contrary, the ESMO guidelines (17) consider surgery as the treatment option for limited disease and for patients unable/unwilling to undergo surgery, a combined approach of chemotherapy and radiotherapy is suggested.

Why don't we get a clear treatment recommendation from guidelines? The matter is complex and not so straightforward.

In all these trials, squamous cell carcinoma and adenocarcinoma were analyzed together. Only Markar *et al.* tried to separate these groups, but numbers were getting too small for definite conclusions (12).

In the Cross trial which established the preoperative chemoradiotherapy standard for locally advanced operable esophageal cancer (4,5) the benefit of chemoradiotherapy (41.4 Gy + Paclitaxel/Carboplatin) was much more pronounced in squamous cell carcinoma rather than in adenocarcinoma. Locally advanced operable adenocarcinomas of the lower oesophagus may also be treated by perioperative chemotherapy without radiation. This approach was established by large randomized phase III trials (2,3,6,7). In the most recently presented randomized phase III trial (3) 716 patients with adenocarcinoma of the stomach or gastroesophageal junction (Siewert I-III) were treated with either ECF (Epirubicin, Cisplatin, Fluoropyrimidine), the standard established by the MAGIC trial (6) or with FLOT (5 FU Leukovorin, Oxaliplatin and Docetaxel). With a hazard ratio of 0.77 (P=0.012) overall survival could be further improved by integration of docetaxel. All these trials included lower esophageal cancer and included T2 stages and are therefore relevant for the question how to treat cT2 disease. In the Forrest plot of the FLOT study, also T1/2 had a benefit with an HR of 0.66 (although not significant due to small numbers).

Staging in esophageal cancer is another important problem that could contribute to this dilemma how to treat cT2 and it is not sufficiently addressed within trials and in trial comparisons. As pointed out by Markar *et al.* (12), understaging of cT2N0 was a big problem, which became obvious when comparing clinical and pathological staging results. Indeed, many of the clinically staged cT2N0 patients had characteristics qualifying for preoperative treatment. While 18.9% were overstaged, 34.7% of patients were clinically understaged in their pT stage and 48.1% were clinically understaged in their pN stage. Speicher *et al.* (14) found only 26.7% of cT2N0 patients to have had accurate pre-treatment staging: 31.7% of patients were downstaged but 41.6% were upstaged based on their pathologic T or N stage. Crabtree *et al.* (18) analyzed the reliability of clinical staging of T2N0 in oesophageal cancer. Of 482 patients staged cT2N0 who went directly to surgery 27.4% were confirmed as pathologic T2N0. Twenty-nine point nine percent were downstaged while 46.7% were upstaged (T3-4, N0 or Tany, N1-3). Based on these data, we can easily imagine that half of the cT2N0 patients are understaged, both in the T and in the N stage, thus meaning that they are undertreated since they should be candidate for a preoperative approach.

What is the real role of the lymph nodes (LNs) involvement? LN positivity has been reported as a very poor prognostic marker in gastroesophageal cancer (19), also for cT2 oesophageal disease with 5-year survival rates of 35% for LN positive tumors and 72% for LN negatives (20). Indeed, it seems that LN positive patients benefit from neoadjuvant treatment with an HR of 0.81 (although not significant due to subgroup analysis) (5). The same has been observed in the FLOT trial (3). The HR for LN positive patients was 0.80 (in favor of FLOT), also not significant. The benefit seems to be there but is not significant. Shall we consider the LN involvement as a parameter to decide which approach to follow? Most probably yes but only if we are sure that we are currently staging our patient in the right way.

There is an obvious dilemma interpreting cT2N0 data. Neoadjuvant treatment induces high rates of pCR even in cT2N0 patients, which predicts favorable survival. Many of the cT2N0 patients were not accurately staged and have had a stage, which would qualify for preoperative treatment.

How to deal with this dilemma? We think that there could be several approaches.

(I) The fatalistic approach may accept that survival in the cT2N0 group remains poor with only about 40% of patients alive at 5 years (12). In this group of clinically staged cT2N0 preoperative treatment would not improve this dismal prognosis, although half of the patients could be understaged, thus meaning that they should have benefitted from preoperative treatment.

(II) The pragmatic approach may be to recommend postoperative treatment to those patients upstaged

by surgery. In the analysis reported by Speicher *et al.* (14) 50.2% of the patients found at surgery to have node positive disease received adjuvant treatment. However, adjuvant treatment for oesophageal cancer is not justified by randomized phase III data. Indeed, for adenocarcinoma, the American and Asian approach used postoperative treatment (21,22), while in European patients, postoperative treatment could only be administered to less than 50% of patients (2,3,6).

(III) The aggressive approach advocates preoperative treatment to all patients staged T2N0 by considering that a high number of patients is upstaged to T3 or N+. Neoadjuvant treatment does not increase morbidity or mortality in the overwhelming majority of studies (2-4,6,12,14) and the postoperative quality of life is not worse in patients who have received neoadjuvant therapy (23). Moreover, preoperative treatment may induce pathologic complete response of up to 30% of patients and this seems to be an independent predictor for improved survival following neoadjuvant chemoradiotherapy (24) or chemotherapy (19). All in all these data represent a good argument to choose for an aggressive approach. Nevertheless, using this approach it is accepted that in essence about 50% of patients will be overtreated.

(IV) Last but not the least, there is the scientific approach, which may be the way for the future. The scientific based approach should be based on a systematic evaluation of more accurate staging methodology and a better understanding of the biology of the tumor. Higher sensitive and specific methodologies should help in identifying the group of patients who may benefit from neoadjuvant treatment. Endoscopic ultrasound may be improved by high resolution probes and miniprobes (25) and the use of fine needle aspiration of suspected LNs may further improve its accuracy. Furthermore, PET CT may help detecting lymphatic spread and could be potentially used to early identify the group of patients who benefit from neoadjuvant.

We need to launch large programs to identify predictive biomarkers. Microsatellite instability (MSI high) recently emerged as a potential marker for patients with a favorable prognosis both in the gastric and colon cancer setting, which was not further improved by neoadjuvant or adjuvant treatment. The survival of 303 patients included in the MAGIC trial was analyzed according to their MSI status (26). Of 19 patients identified with MSI-high, those without chemotherapy had a much better survival than those MSI-high patients who received perioperative chemotherapy. An analysis regarding der MSI status of the Korean adjuvant CLASSIC trial, in which patients were randomized between observation and adjuvant Capecitabine + Oxaliplatin after resection of gastric adenocarcinoma were recently presented (27). Again MSI high patients (n=38) had a favorable prognosis which could not be improved by adjuvant chemotherapy. MSI is an interesting future marker although it may be less relevant in esophageal than in gastric cancer (28). The intracellular amount of beta tubulin is involved in the cytotoxic action of taxanes. Class III Beta tubulin (TUBB3) was recently presented as a potential marker for docetaxel efficacy in the adjuvant setting (29).

With the knowledge of prognostic and predictive markers, we have to find better treatments. HER 2 positivity defined a subgroup of patients with metastatic and or locally advanced gastric adenocarcinoma with benefit from trastuzumab; an anti HER 2 antibody, in the palliative setting (30). Trials in the perioperative setting are currently being performed (NCT02205047).

Most importantly, it is the knowledge of the tumor biology that should drive our decision in the future. In some cases, like in colorectal cancer, the molecular landscape of the tumor has shown to be more sensitive than the TNM stage to define the patients who are at risk of relapse (31) and to predict the metastatic spread (32).

The molecular landscape of esophageal cancer is not yet completely known as the molecular landscape of colon cancer. Several questions are still open but we are moving forward. One of the main problems of all the studies that have evaluated the role of surgery or chemoradiotherapy in esophageal cancer are that squamous cell carcinoma of the esophagus was combined with esophageal adenocarcinoma. The different clinical behavior seen in the neoadjuvant trials corresponds to different tumor biology. As recently published by the TCGA group (28), squamous cell carcinoma of the esophagus are different at their molecular levels as compared to esophageal adenocarcinoma. Most importantly esophageal squamous carcinoma are more similar to squamous tumorous of the head and neck and lung. Esophageal adenocarcinoma is similar to chromosomal unstable (CIN) gastric cancers thus meaning that they could be considered as a single disease entity and could be treated

with the same approach.

No esophageal adenocarcinoma was found in this study to be either MSI or EBV positive, in contrast with gastric cancer. MSI high or EBV positive tumors preferentially respond to immune—checkpoint inhibition. Nevertheless PD1 and PD-L1 antibodies are currently being tested in esophageal cancer in clinical trials for perioperative treatment together with chemotherapy (trial in preparation) or chemoradiotherapy (NCT03087864) and for postoperative treatment in patients after chemoradiotherapy and surgery NCT02743494 of esophageal cancers. Translational research will show whether chemoradiotherapy may synergize with PD-1 inhibition to understand changes in tumor biology under treatment.

In summary, treatment recommendations for patients presenting with cT2 oesophageal cancer remain difficult. A survival benefit from neoadjuvant treatment cannot be proven although we know that a subset of these patients is understaged and would in principle benefit from preoperative treatment. We have to put our efforts into preoperatively identifying subsets of patients likely to respond to stratified treatment approaches in order to improve treatment efficacy. We have to improve our staging methods and our understanding of tumor biology prior to treatment and changes under treatment to develop individualized approaches. Meanwhile, an open discussion with the patient about possible over-treatment and possible treatment benefits should guide the shared decision process.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Lagergren J, Smyth E, Cunningham D, et al. Oesophageal cancer. Lancet 2017. [Epub ahead of print].
2. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
3. 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;35:4004.
4. 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.
5. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090-1098.
6. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
7. 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.
8. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681-92.
9. Kranzfelder M, Schuster T, Geinitz H, et al. Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer. Br J Surg 2011;98:768-83.
10. Ronellenfitsch U, Schwarzbach M, Hofheinz R, et al. Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data. Eur J Cancer 2013;49:3149-58.
11. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 2014;32:2416-22.
12. Markar SR, Gronnier C, Pasquer A, et al. Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study. Eur J Cancer 2016;56:59-68.
13. Song Y, Tao G, Guo Q, et al. Survival benefit of surgery with radiotherapy vs surgery alone to patients with T2-3N0M0 stage esophageal adenocarcinoma.

Oncotarget 2016;7:21347-52.
14. Speicher PJ, Ganapathi AM, Englum BR, et al. Induction therapy does not improve survival for clinical stage T2N0 esophageal cancer. J Thorac Oncol 2014;9:1195-201.
15. Porschen R, Buck A, Fischbach W, et al. S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus (Langversion 1.0 - September 2015, AWMF-Registernummer: 021/023OL). Z Gastroenterol 2015;53:1288-347.
16. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Esophageal and Esophagogastric Junction Cancers 2017.
17. Lordick F, Mariette C, Hvaustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50-v57.
18. Crabtree TD, Kosinski AS, Puri V, et al. Evaluation of the reliability of clinical staging of T2 N0 esophageal cancer: a review of the Society of Thoracic Surgeons database. Ann Thorac Surg 2013;96:382-90.
19. Smyth EC, Fassan M, Cunningham D, et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. J Clin Oncol 2016;34:2721-7.
20. Stiles BM, Mirza F, Coppolino A, et al. Clinical T2-T3N0M0 esophageal cancer: the risk of node positive disease. Ann Thorac Surg 2011;92:491-6; discussion 496-8.
21. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725-30.
22. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.
23. Hauser C, Patett C, von Schoenfels W, et al. Does neoadjuvant treatment before oncologic esophagectomy affect the postoperative quality of life? A prospective, longitudinal outcome study. Dis Esophagus 2015;28:652-59.
24. Alnaji RM, Du W, Gabriel E, et al. Pathologic Complete Response Is an Independent Predictor of Improved Survival Following Neoadjuvant Chemoradiation for Esophageal Adenocarcinoma. J Gastrointest Surg 2016;20:1541-6.
25. Meister T, Heinzow HS, Osterkamp R, et al. Miniprobe endoscopic ultrasound accurately stages esophageal cancer and guides therapeutic decisions in the era of neoadjuvant therapy: results of a multicenter cohort analysis. Surg Endosc 2013;27:2813-9.
26. Smyth EC, Wotherspoon A, Peckitt C, et al. Mismatch Repair Deficiency, Microsatellite Instability, and Survival : An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. JAMA Oncol 2017. [Epub ahead of print].
27. Choi YY, Kim H, Yang HK, et al. Clinical impact of microsatellite instability in patients with stage II and III gastric cancer: Results from the CLASSIC trial. J Clin Oncol 2017;35:4002.
28. Cancer Genome Atlas Research Network; Analysis Working Group: Asan University; BC Cancer Agency, et al. Integrated genomic characterization of oesophageal carcinoma. Nature 2017;541:169-175.
29. Cecchi F, Catenacci DV, Schwartz S, et al. Predicting survival in gastric cancer patients randomized to docetaxel with mass spectrometric quantitation of TUBB3. J Clin Oncol 2017;35:4068.
30. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
31. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-6.
32. Naxerova K, Reiter JG, Brachtel E, et al. Origins of lymphatic and distant metastases in human colorectal cancer. Science 2017;357:55-60.

Cite this article as: Thuss-Patience P, Vecchione L, Keilholz U. Should cT2 esophageal cancer get neoadjuvant treatment before surgery? J Thorac Dis 2017;9(9):2819-2823. doi: 10.21037/jtd.2017.08.143

