



Optimal postoperative surveillance strategy in patients undergoing neoadjuvant chemoradiotherapy followed by surgery for esophageal carcinoma

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Provenance: This is an invited article commissioned by the Academic Editor Chun-Dong Zhang (Department of Gastrointestinal Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan).

Comment on: Steffen T, Dietrich D, Schnider A, *et al.* Recurrence patterns and long-term results after induction chemotherapy, chemoradiotherapy, and curative surgery in patients with locally advanced esophageal cancer. *Ann Surg* 2019;269:83-7.

Submitted Aug 01, 2019. Accepted for publication Aug 19, 2019.

doi: 10.21037/jtd.2019.08.89

View this article at: <http://dx.doi.org/10.21037/jtd.2019.08.89>

Neoadjuvant chemoradiotherapy (NACRT) followed by esophagectomy is a well-established standard of care for patients with locally advanced esophageal carcinoma (EC) (1). Although trimodal therapy provides significantly better survival outcomes than surgery alone, the long-term outcomes of patients with locally advanced EC remain unsatisfactory with 5-year overall survival rates ranging from 25% to 47% (2,3). Postoperative managements based on convincing evidence are crucial to optimize clinical outcomes of such patients. In particular, an appropriate surveillance strategy allows early detection of recurrence, prompting salvage therapy and thereby achieving improved survival outcomes (4,5). On the other hand, long-term follow-up is often inadequate due to the complex backgrounds of patients receiving multimodal therapy, which prevents clinicians from establishing a clear consensus on the most suitable surveillance scheme for this population (1).

A response to NACRT is apparently the most powerful prognostic determinant in patients undergoing multimodal therapy. In fact, patients who achieve pathological complete response (pCR) with NACRT have a lower incidence of both locoregional recurrences (LRRs) and distant metastases (4), longer times until recurrence (2,5), and better survival outcomes (6,7) than those with non-pCR disease. In addition, patients with squamous cell carcinoma (SCC) reportedly achieved higher pCR rates than those with

adenocarcinoma (AC) (2,8) and recurrence patterns differ markedly between these two histopathological subtypes, especially in non-pCR diseases (8). These observations allow us to speculate that postoperative managements should be tailored according to histopathological subtypes and pathological responses to NACRT in EC patients after surgery.

A recent study by Steffen and colleagues revealed two clinical variables, histopathological subtypes and responses to NACRT, to be very important for determining the time frame of relapse after surgery (9). They investigated long-term outcomes of two independent cohorts of prospective multicenter phase II trials, evaluating the efficacy of multimodal therapy for patients with locally advanced EC, clinically staged as T3N0, T1-3N+, or T4N0-3. Their cohorts were comprised of both patients with AC (n=45) and those with SCC (n=37). Despite the small number of patients included in their investigation, the findings are highly reliable because of the prospective study design, low mortality and high curability rates, and good survival outcomes, which were comparable to those of the CROSS trial (3). The follow-up exceeding 6 years was sufficiently long in both trials to understand and demonstrate the long-term recurrence patterns of these populations.

In the non-pCR patients in their study, almost all tumor relapse events occurred within the first 2 years after surgery, a finding in line with some prior results (8,9). Interestingly,

patients with SCC remained at risk for tumor relapse even 4 years after esophagectomy, while those with AC rarely relapsed after a 3-year event-free survival. These observations suggest that all patients should be followed up carefully for the initial 3 years after surgery, regardless of tumor histology, and that further long-term surveillance is advisable for patients with SCC. Given that nearly all LRRs reportedly occurred within 3 years after surgery in non-pCR patients (4,10), periodic endoscopic surveillance can be omitted from the follow-up regimen after 3 years.

It is noteworthy that, in their study, some of the SCC patients achieving pCR experienced late relapses (4 years postoperatively). This pattern of relapse has not, to our knowledge, been documented previously. The relapse rates of patients who achieve pCR after NACRT reportedly range from 14% to 39% (4,11,12). Distant metastasis is the major mode of recurrence and is associated with dismal survival outcomes (4,8), while LRRs are reportedly rare in patients with pCR (4,10). Although Xi *et al.* found no significant histopathological differences regarding recurrence patterns and time to recurrence, one patient with SCC experienced late relapse 5 years after surgery in their pCR group (8). These results raise the possibility that continued follow-up beyond 4 years should be recommended for pCR patients with SCC. Periodic endoscopic examination is presumably not necessary for this population unless LRRs are clinically suspected (4).

Steffen *et al.* also revealed patients with tumor regression grade (TRG) 2 of Mandard classification system, which was defined as rare residual tumor cells, to show markedly poorer survival outcomes than those with TRG1, i.e., complete regression (9). This finding implies that even a very small number of residual tumor cells adversely affect long-term survival outcomes (13). Further investigations are warranted to assess this possibility since another study showed no significant survival difference between TRG1 and TRG2 after chemoradiotherapy (CRT) (14) and another no difference after chemotherapy alone (15). Furthermore, other variables, such as clinical tumor staging (4), pathological nodal status (4,6) and lymph node down-staging (15), have been reported to be useful for stratifying survival outcomes as well as the treatment responses of primary lesions. Further studies designed to establish a comprehensive stratification system for recurrence risk are awaited.

Collectively, postoperative surveillance strategies should be individualized according to histopathological subtypes and pathological responses to NACRT. In addition, even

a microscopic population of residual tumor cells might negatively influence long-term survival outcomes. These findings by Steffen and colleagues are both rational and useful for optimizing and standardizing follow-up strategies in patients undergoing NACRT followed by surgery for locally advanced EC, although further multicenter studies with a larger cohort are warranted to confirm and support the current results.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Sugawara K, Yamashita H, Seto Y. Optimal postoperative surveillance strategy in patients undergoing neoadjuvant chemoradiotherapy followed by surgery for esophageal carcinoma. *J Thorac Dis* 2019;11(Suppl 15):S1874-S1876. doi: 10.21037/jtd.2019.08.89