2021 NCC/CATS/CSTCVS/STM expert consensus on perioperative immunotherapy for esophageal cancer

Xiaozheng Kang[1#], Jianjun Qin[1#], Ruixiang Zhang[1], Zhen Wang[1], Qingfeng Zheng[1], Yong Li[1], Jianping Xu[2], Jing Huang[2], Xin Wang[3], Zhouguang Hui[3,4], Liyan Xue[5], Yousheng Mao[1], Yin Li[1], Jie He[1], Chun Chen[6,7], Haiquan Chen[8], Ke-Neng Chen[9], Long-Qi Chen[10], Maoyong Fu[11], Junke Fu[12], Qing Geng[13], Taiqian Gong[14], Shiping Guo[15], Yongtao Han[16], Yi He[17], Jian Hu[18], Hongjing Jiang[19], Jie Jiang[20], Yuequan Jiang[21], Mingqiang Kang[6,7], Jianqun Ma[22], Shaohua Ma[23], Yongde Liao[24], Hecheng Li[25], Shanqing Li[26], Zhigang Li[27,28], Shuoyan Liu[29], Yang Liu[30], Guibin Qiao[31], Lijie Tan[32], Hui Tian[33], Gaofeng Zhao[34], Jun Zhao[35,36], Shiying Zheng[35,36], Yongan Zhou[37], Magnus Nilsson[38], Francisco Schlottmann[39], Riccardo Rosati[40], Cascinu Stefano[40], Philip Wai-yan Chiu[41], Neil B. Newman[42], Noriyuki Hirahara[43], Dae Joon Kim[44], Rutika Mehta[45], Kimberly L. Johung[46], Michael Cecchini[47], Shane Lloyd[48], Kenneth Meredith[49]

[1]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [4]Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [6]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fujian Medical University, Fuzhou, China; [7]Key Laboratory of Cardio-Thoracic Surgery, Fujian Medical University, Fujian Province University, Fuzhou, China; [8]Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; [9]Department of Thoracic Surgery, Peking University Cancer Hospital and Institute, Beijing, China; [10]Department of Thoracic Surgery, West China Hospital of Sichuan University, Chengdu, China; [11]Department of Thoracic Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, China; [12]Department of Thoracic Surgery, The First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, China; [13]Department of Thoracic Surgery, Renmin Hospital of Wuhan University, Wuhan, China; [14]Department of Thoracic Surgery, Sixth Medical Center, Chinese People's Liberation Army General Hospital, Second Clinical College of Southern Medical University, Beijing, China; [15]Department of Thoracic Surgery, Shanxi Cancer Hospital, Taiyuan, China; [16]Department of Thoracic Surgery, Sichuan Cancer Hospital and Institution, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; [17]Department of Thoracic Surgery, Henan Provincial People's Hospital, Zhengzhou, China; [18]Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [19]Department of Esophageal Minimally Invasive Surgery, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [20]Department of Thoracic Surgery, The First Affiliated Hospital of Xiamen University, Medical College of Xiamen University, Xiamen, China; [21]Department of Thoracic Surgery, Chongqing University Cancer Hospital, Chongqing Cancer Institute, Chongqing Cancer Hospital, Chongqing, China; [22]Department of Thoracic Surgery, Harbin Medical University Cancer Hospital, Harbin, China; [23]Department of Thoracic Surgery, Peking University Third Hospital, Beijing, China; [24]Department of Thoracic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [25]Department of Thoracic Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [26]Department of Thoracic Surgery, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China; [27]Department of Thoracic Surgery, Section of Esophageal Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [28]Institute for Thoracic Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [29]Department of Thoracic Surgery, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, Fuzhou, China; [30]Department of Thoracic Surgery, Chinese People's Liberation Army General Hospital, Beijing, China; [31]Department of Thoracic Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; [32]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China; [33]Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China; [34]Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [35]Department of Thoracic Surgery,

The First Affiliated Hospital of Soochow University, Medical College of Soochow University, Suzhou, China; [36]Institute of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Suzhou, China; [37]Department of Thoracic Surgery, Tangdu Hospital, Air Force Medical University, Xi'an, China; [38]Division of Surgery, Department of Clinical Science, Intervention and Technology, Karolinska Institutet and Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden; [39]Department of Surgery, Hospital Alemán of Buenos Aires, Buenos Aires, Argentina; [40]Gastrointestinal Surgery Division, Vita-Salute University-San Raffaele Hospital, Milan, Italy; [41]Division of Upper Gastrointestinal and Metabolic Surgery, Department of Surgery, Prince of Wales Hospital, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China; [42]Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [43]Department of Digestive and General Surgery, Shimane University Faculty of Medicine, Izumo, Shimane, Japan; [44]Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; [45]Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA; [46]Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut, USA; [47]Department of Internal Medicine (Medical Oncology), Yale School of Medicine, New Haven, Connecticut, USA; [48]Radiation Oncology Department, University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah, USA; [49]Gastrointestinal Oncology, Sarasota Memorial Institute for Cancer Care, Sarasota, Florida, USA

[#]These authors contributed equally to this work.

Correspondence to: Yin Li. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. Email: liyin@cicams.ac.cn; Jie He. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. Email: hejie@cicams.ac.cn.

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Introduction

Esophageal cancer is one of the most prevalent malignancies in China, and nearly 50% of the global burden occurs in this country (1,2). Furthermore, esophageal cancer is a highly lethal disease with a poor long-term survival rate for locally advanced and metastatic patients. Therefore, more effective treatment regimens to improve outcomes are essential in China and around the world. By means of perioperative multimodal therapy, the 3-year and 5-year overall survival (OS) rates after surgery in well-equipped centers with experienced surgical staff have increased to 61.6% and 52.9%, respectively (3). Despite this success, the postoperative recurrence rate is still 33.7% after a median follow-up time of nearly 52 months (4). The critical question remains to overcome these hurdles in improving long-term disease-free survival (DFS).

In 2020, four landmark trials established immune checkpoint inhibitor (ICI) therapy as a new standard of care for adjuvant and first-line systemic treatment in select esophageal cancer patients. The CheckMate 577 trial has provided proof-of-concept, as adjuvant nivolumab administration in patients not achieving a pathologic complete response (pCR) after resection in esophageal cancer patients following trimodality treatment was found to markedly improve DFS (5). In addition, the KEYNOTE-590 study demonstrated drastically improved survival when pembrolizumab was added to cisplatin-fluoropyrimidine chemotherapy in esophageal squamous cell carcinoma (ESCC) programmed death ligand 1 (PD-L1) positive patients with a combined positive score (CPS) of ≥10 tumors (6) in the palliative setting. Meanwhile, the CheckMate 649 trial reported that treatment with oxaliplatin-fluoropyrimidine chemotherapy plus nivolumab in patients with unresectable tumors and CPS ≥5 gastroesophageal adenocarcinoma (GEA) tumors provided a statistically significant 2-month improvement in OS (7). In comparison, the ATTRACTION-4 trial did not yield a similar OS benefit despite a noticeable improvement in progression-free survival (8).

The latest phase I/II trials on neoadjuvant immunochemoradiotherapy for esophageal cancer (PALACE-1 and PERFECT) showed that the pCR rate was up to 55.6% and increased immune cell infiltration (9,10). This impressive pCR rate achieved by neoadjuvant immunochemoradiotherapy may warrant phase III clinical trials on neoadjuvant immunotherapy for resectable locally advanced esophageal cancer patients. Therefore, more and

more pharmaceutical-sponsored or investigator-initiated studies on ICIs have been designed and conducted around China to obtain further real-world evidence. A recent cross-sectional survey of 69 major centers for esophageal cancer in China reported that 82.6% of these centers had implemented perioperative immunotherapy combined with chemoradiation or chemotherapy (data unpublished) with or without the participation of clinical trials.

Until present, there have been no guidelines or expert consensus regarding perioperative immunotherapy for resectable locally advanced esophageal cancers. To respond to the changing trends in this field, facilitate better clinical decision-making, and limit the number of potential ethical issues, the National Cancer Center (NCC), Chinese Association of Thoracic Surgeons (CATS), Chinese Society for Thoracic and Cardiovascular Surgery (CSTCVS), and Esophageal Disease Panelists of Society for Translational Medicine (STM) jointly developed an intersociety consensus statement.

Methods of review

Chinese experts in the subject under consideration were selected from the NCC, CATS, and CSTCVS organizations to examine subject-specific areas and write consensus statements. The NCC writing committee members were tasked with performing comprehensive literature searches and developing recommendations based on literature review. The CATS Esophageal Surgery Committee members/CSTCVS Esophageal Disease Panelists graded the evidence supporting the recommendations and assessed the risk-benefit profile for each recommendation. A scheduled teleconference was used to organize the topics covered by the consensus and review the proposed recommendations, and two subsequent teleconferences were then held to vote on the final recommendations formally. All recommendations were subjected to a vote. Acceptance for the final recommendations required greater than 75% approval of each of the recommendations. The consensus process incorporated a modified Delphi method (11). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to appraise evidence's certainty and formulate and grade recommendations (12). The following recommendations are based on the best available evidence. When high-quality evidence was lacking, we presented the best expert opinion based on best practices. The STM Esophageal Disease Panelists reviewed the statement and commented on a series of closed predefined questions.

Consensus recommendations

Recommendation 1

For resectable locally advanced esophageal cancer, preoperative immunotherapy currently still has no sufficient evidence for efficacy and safety in clinical practice. Therefore, preoperative immunotherapy should be limited to the framework of clinical trials. The potential benefits and risks must be balanced carefully before a physician can recommend for or against preoperative immunotherapy, and patients should be well-informed before making decisions (quality of evidence: medium; consensus level: 100%).

Rationale: According to the Guidelines of Chinese Society of Clinical Oncology (CSCO): Esophageal Cancer [2020] (13), resectable esophageal cancer in the setting of locally advanced disease is defined as stage cT1–2N+ or cT3–4a in accordance with the eighth edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM classification for esophageal cancer (14). Solitary bulky or multiple enlarged lymph nodes are considered to be a relative contraindication to surgery depending on the patient's age and performance status.

Trimodality therapy, a mainstay in contemporary preoperative management of locally advanced esophageal cancer, is well tolerated and extensively used. However, the optimal preoperative immunotherapy for esophageal cancer remains elusive. In the PALACE-1 trial, 20 resectable ESCC patients, regardless of PD-L1 status, received preoperative chemoradiotherapy (CRT) according to the CROSS regimen combined with two cycles of pembrolizumab (2 mg/kg). Within 4–6 weeks after preoperative therapy, patients underwent surgery. The pCR rate was 55.6% (10/18). ≥ Grade 3 toxicity was observed in 13 patients (13/20, 65%), and one patient experienced grade 4 toxicity (9). In contrast, the PERFECT trial enrolled only patients with resectable esophageal adenocarcinoma (EAC): 40 patients received neoadjuvant CRT according to the CROSS regimen combined with five cycles of atezolizumab (1,200 mg). The pCR rate was 25% (10/40). No statistically significant difference in response or survival was found between the PERFECT and a propensity-matched neoadjuvant CRT cohort (10).

The NICE study (15) enrolled 11 patients diagnosed

with locally advanced thoracic ESCC who received two cycles of preoperative chemotherapy (albumin-bound paclitaxel + carboplatin) and camrelizumab (200 mg). A pCR (ypT0N0M0) was achieved in 45.4% (5/11) of the cases, while ypT0 occurred in 54.5% (6/11) of patients. Grade 3/4 toxicities included neutropenia (8/11) and thrombocytopenia (2/11). Meanwhile, the KEEP-G 03 study evaluated the safety of preoperative triple-agent chemotherapy (liposomal paclitaxel + cisplatin + tegafur) combined with sintilimab (200 mg) for the treatment of resectable ESCC (16). The pCR rate was 26.7% (4/15), and the incidence of common grade 3/4 toxicities was 35.3% (6/15). The additional study results were summarized in *Table 1*.

Growing but still limited evidence indicates that preoperative immunotherapy for esophageal cancer is feasible and may be meaningful, given that efficacy is proven. The pCR rates for ESCC or EAC in the studies mentioned above are similar to those in the CROSS trial (25). Preoperative immunotherapy cannot be recommended as standard care under the current regulatory framework due to the lack of evidence from phase III clinical trials. Robust information is integral to any good decision-making process, and this novel modality should be viewed with cautious optimism by clinicians and patients. Finally, all relevant practices should be conducted under well-informed consent in the framework of clinical trials.

Recommendation 2

In order to support more accurate clinical information for physicians to conduct preoperative immunotherapy evaluation, especially pseudoprogression and hyperprogression, multimodal medical images are needed. Computed tomography (CT), endoscopic ultrasonography (EUS), and positron emission tomography (PET)-CT are recommended as complementary modalities for initial staging and restaging after preoperative immunotherapy; meanwhile, the combined use of EUS fine-needle aspiration (FNA) can improve the assessment of lymph node involvement, while endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) may be performed, if necessary, to confirm pathological node (N) staging. The modified Response Evaluation Criteria in Solid Tumors (RECIST) in cancer immunotherapy trials (iRECIST) criteria may be helpful in restaging after preoperative immunotherapy (quality of evidence: low; consensus level: 97.3%).

Rationale: Each imaging modality has its advantages and disadvantages; therefore, the thin-section, contrast-enhanced, and multiplanar reformation options in CT; endoscopic US; and PET-CT should be considered complementary modalities for preoperative staging and therapeutic monitoring patients with esophageal cancer (26). When needed, magnetic resonance imaging (MRI) can provide additional information for efficacy evaluations (13). In addition, it is essential to evaluate the baseline status of regional lymph node metastasis and perform pathological restaging. Therefore, EUS-FNA and/or EBUS-TBNA are recommended to obtain more accurate preoperative pathological N staging.

No widely recognized criteria have been established for efficacy evaluations of preoperative therapy for esophageal cancer. Three evaluation systems, iRC, iRECIST, and immune-related RECIST (irRECIST), are currently in use in the field of immunotherapy for advanced solid tumors (27-29). However, their application value in the evaluation of esophageal cancer is unknown. After discussion, the experts recommend the iRECIST criteria developed by the RECIST expert panel and based on RECIST 1.1 (29) as the standard reference in clinical studies and clinical practice. With the recent publication of results from the CALGB 80803 trial, which assessed the utility of interim PET after induction chemotherapy, there is value in using this imaging modality to differentiate responders from nonresponders and tailor chemoradiation to obtain better outcomes (30).

Recommendation 3

There have been no accurate predictive biomarkers available in esophageal cancer patients for perioperative immunotherapy until the present. PD-L1 expression, as measured by CPS, may be helpful in clinical decision-making (quality of evidence: low; consensus level: 75.7%).

Rationale: Except for a small proportion of human epidermal growth factor receptor 2 (HER-2) amplified EAC patients, there are currently no specific predictive biomarkers, such as epidermal growth factor receptor (EGFR) in non-small cell lung carcinoma, or Kirsten rat sarcoma viral oncogene (KRAS) in colorectal carcinoma, which would allow for a more individualized therapeutic strategy. Immunotherapy trials for metastatic esophageal cancer, including the KEYNOTE-590 (6), CheckMate 649 (7), ATTRACTION-4 (8), KEYNOTE-181 (31), ATTRACTION-3 (32), and ESCORT (33) trials, show that

Table 1 Summary of the outcomes of perioperative immunotherapy for esophageal cancer

Name/author	Country	Year	Trial design	Histology	Regimen	Outcomes
Preoperative chemoradiotherapy plus immunotherapy						
PALACE1 (9)	China	2020	Phase I, single-arm, single-center	ESCC	Paclitaxel (50 mg/m^2 qw) + carboplatin (AUC 2 qw); PTV 41.4 Gy/23f; pembrolizumab 2 mg/kg q3w; surgery at 4–6 weeks after treatment	The overall pCR rate was 56% (10/18), the MPR for the primary lesion was 89% (16/18), the R0 resection rate was 94% (17/18), and the incidence of grade 3 or above AEs was 65%. AEs were mainly lymphopenia, and 1 patient died of esophageal bleeding
Lee *et al.* (17)	Korea	2019	Phase II, single-arm, single-center	ESCC	Paclitaxel + carboplatin qw, PTV 44.1 Gy/21f; pembrolizumab 2 mg/kg q3w; surgery at 5 weeks after treatment; postoperative pembrolizumab 2 mg/kg q3w adjuvant treatment for 2 years or until disease progression	The pCR rate for the primary lesion was 46.1% (95% CI: 28.8–64.6%), the postoperative mortality rate was 7.7% (2/26), and the primary cause of death was acute lung injury. AEs were mainly neutropenia (50.0%) and liver dysfunction (30.8%), and the 6-, 12-, 18-month OS rates were 89.3%, 80.8%, and 73.1%, respectively
PERFECT (10)	Netherlands	2019	Phase II, single-arm, single-center	GEA	Paclitaxel (50 mg/m^2 qw) + carboplatin (AUC 2 qw); PTV 41.4 Gy/23f; atezolizumab (1200 mg/kg q3w); surgery at 4 weeks after treatment	The overall pCR rate was 30% (10/33), the R0 resection rate was 100% (33/33), and the perioperative 30-day and 90-day mortality rates were 0%. AEs were mainly fatigue (95%), mucositis (60%), nausea (53%), and anorexia (43%). Serious AEs included allergic reaction (5%), maculopapular rash (5%), febrile neutropenia (3%), pneumonia (3%), suspected sepsis (3%), and hypotension with fever (3%)
Kelly *et al.* (18)	United States	2019	Phase Ib, double-arm, multicenter	GEA	Standard concurrent radiotherapy and chemotherapy (paclitaxel + carboplatin qw); PTV 41.4 Gy/23f; nivolumab (240 mg or 1 mg/kg q2w) +/- LAG-3 targeted drugs (relatlimab 80 mg q2w)	The overall pCR rate was 40% (4/10). The AEs were mainly dermatitis (6.3%) and hepatitis (6.3%)
Preoperative chemotherapy plus immunotherapy						
Cheng *et al.* (19)	China	2021	Phase I, single-arm, single-center	ESCC	Albumin-bound paclitaxel (260 mg/m^2 q3w) + carboplatin (AUC 5 q3w); camrelizumab (200 mg q3w)	The overall pCR rate was 27.8% (5/18), the MPR for the primary lesion was 44.4% (8/18), and the R0 resection rate was 100%. Serious AEs were neutropenia (10%), with no perioperative mortality

Table 1 (*continued*)

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Name/author	Country	Year	Trial design	Histology	Regimen	Outcomes
Wang *et al.* (20)	China	2021	Phase II, single-arm, single-center	ESCC	Docetaxel (75 mg/m^2 q3w) + nedaplatin (75 mg/m^2 q3w); camrelizumab (200 mg q3w); surgery at 4–6 weeks after treatment	The overall pCR rate was 25% (3/12), and the MPR was 42% (5/12). No grade 3 immunotherapy related AEs were observed, no surgery related mortality. The AEs (grade ≥3) were anemia (3%)
NICE (15)	China	2020	Phase II, single-arm, single-center	ESCC	Albumin-bound paclitaxel (100 mg/m^2 qw) + carboplatin (AUC 5 q3w); camrelizumab (200 mg/kg q3w); surgery at 4 weeks after treatment	The overall pCR rate was 45.4% (5/11), the pCR rate for the primary lesion was 54.5% (6/11), and the R0 resection rate was 100% (11/11). Grade 3 and above AEs were mainly neutropenia (72.7%) and thrombocytopenia (18.2%)
KEEP-G 03 (16)	China	2020	Phase Ib/II, single-arm, multicenter	ESCC	Liposome paclitaxel (135 mg/m^2 q3w) + cisplatin (75 mg/m^2 q3w) + tegafur (40mg bid d1–d14 q3w); sintilimab (200 mg q3w)	The overall pCR rate was 26.7% (4/15), the MPR for the primary lesion was 53.3% (8/15), and the R0 resection rate was 100% (15/15). Grade 3 and above AEs were mainly lymphopenia (29.4%) and leukopenia (11.8%)
Zhang *et al.* (21)	China	2020	Phase II, single-arm, single-center	ESCC	Albumin-bound paclitaxel + tegafur; toripalimab (200 mg q3w)	The overall pCR rate was 16.7% (3/18), the MPR for the primary lesion was 50% (9/18), and the ORR and DCR were 79.17% and 100%, respectively
Li *et al.* (22)	China	2020	Phase II, single-arm, single-center	ESCC	Albumin-bound paclitaxel (260 mg/m^2 q3w) + carboplatin (AUC 5 q3w); toripalimab (240 mg q3w); 2–3 cycles; surgery at 4 weeks after treatment	The overall pCR rate was 16.7% (2/12), the MPR for the primary lesion was 58.3% (7/12), and the incidence of serious AEs was 11.8%
FRONTiER (23)	Japan	2019	Phase I, multiarm, multicenter	ESCC	Fluorouracil (800 mg/m^2 d1-d5 q3w) + cisplatin (80 mg/m^2 q3w) + nivolumab (group A: 360 mg q3w; Group B 240 mg q3w); docetaxel (70 mg/m^2 q3w) + fluorouracil (750 mg/m^2 d1–d5 q3w) + cisplatin (80 mg/m^2 q3w) + nivolumab (group C: 360 mg q3w; group D 240 mg q3w)	In group A, the pCR rate was 33.3% (2/6), and the R0 resection rate was 92.3%. No dose-limiting AEs were observed

Table 1 (*continued*)

Table 1 (*continued*)

Name/author	Country	Year	Trial design	Histology	Regimen	Outcomes
Postoperative immunotherapy						
CheckMate 577 (5)	Global	2020	Phase III, double-arm, multicenter	ESCC /GEA	Standard concurrent radiotherapy and chemotherapy (paclitaxel + carboplatin qw); PTV 41.4 Gy/23f; postoperative adjuvant nivolumab (480 mg q4w), 13 cycles	The median DFS was 22.4 months in the study group and 11.0 months in the control group (HR 0.69; 96.4% CI 0.56–0.86; P=0.0003). The incidence of immunotherapy-related AEs was ≤9% in the study group
BTCRC-ESO14 -012 (24)	United States	2018	Phase II, single-arm, multicenter	GEA	Standard concurrent radiotherapy and chemotherapy (paclitaxel + carboplatin; fluorouracil + cisplatin); PTV 41.4 Gy/23f; postoperative adjuvant durvalumab (1500 mg q4w), 13 cycles	AEs were mainly fatigue (33.3%) and nausea (25%). Serious immunotherapy-related AEs were pneumonia (1/12), hepatitis (1/12), and colitis (1/12). The 1-year RFS and OS rates were 79.2% and 95.5%, respectively

AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; AST, alanine aminotransferase; CATS, Chinese Association of Thoracic Surgeons; CI, confidence interval; CRT, chemoradiotherapy; CSCO, Chinese Society of Clinical Oncology; CSTCVS, Chinese Society for Thoracic and Cardiovascular Surgery; CT, computed tomography; ctDNA, biomarkers in circulating tumor DNA; CPS, combined positive score; DFS, disease-free survival; EAC, esophageal adenocarcinoma; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EGFR, epidermal growth factor receptor; EGJ, esophagogastric junction; EUS, endoscopic ultrasonography; ESCC, esophageal squamous cell carcinoma; FNA, fine-needle aspiration; GEA, gastroesophageal adenocarcinoma; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immunotherapy-related adverse event; KRAS, Kirsten rat sarcoma viral oncogene; MRI, magnetic resonance imaging; MPR, major pathological response; MSI, microsatellite instability; NCC, National Cancer Center; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; pCR, pathologic complete response; PET, positron emission tomography; PD-L1, Programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; STM, Society for Translational Medicine; TMB, tumor mutational burden; TRG, tumor regression grade; UICC, Union for International Cancer Control.

patients can benefit from immunotherapy, especially those positive for PD-L1, as measured by CPS. They suggest that PD-L1 expression, while not a definitive biomarker, may be used to screen patient populations for immunotherapy. Alternative biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI), along with HER2, and neurotrophic tyrosine receptor kinase (NTRK), in addition to testing for the above biomarkers in circulating tumor DNA (ctDNA) to potentially acquire a wider variety of tumor clones than in tissue biopsies, still require clinical validation to confirm for their role in screening GEA patients for perioperative immunotherapy (26). In the CheckMate 577 trial, the updated results presented at the 2021 American Society of Clinical Oncology Annual Meeting showed that PD-L1 positive patients with a CPS score of 5 or more on their surgical specimen had better DFS (29.4 *vs.* 1.2 months) with nivolumab compared to placebo-treated controls (34).

Recommendation 4

When neoadjuvant immunotherapy is being considered for esophageal cancer, it is recommended to combine 2–4 cycles of preoperative immunotherapy with chemotherapy or chemoradiotherapy (quality of evidence: low; consensus level: 91.9%).

Rationale: Schedules of preoperative immunotherapy in some recent clinical trials that included 2–4 cycles of sequential immunotherapy with chemotherapy or chemoradiotherapy attained improved rates of R0 resection and pCR. Randomized data addressing survival are however still awaited. The optimum cycles and sequence of immunotherapy and other modalities remain under investigation. Moreover, based on the results from previous studies of preoperative radiotherapy and chemotherapy, the radiotherapy dose should not exceed 50 Gy (35,36).

Recommendation 5

Immunotherapy-related adverse events (irAEs) should be monitored vigilantly. Severe irAEs are rare, but it is essential to recognize and intervene on symptoms even if irAEs are solely graded 1 or 2. The decision to resume or rechallenge immunotherapy after irAEs have been resolved should be discussed in a multidisciplinary team consisting of all the relevant specialists (quality of evidence: low; consensus level: 100%).

Rationale: The irAEs may be different from those associated with conventional cancer treatments because they result from an overstimulated or misdirected immune response rather than the direct effect of a chemical or radiological therapy on cancer and healthy tissues. The incidence of fatal irAEs is approximately 0.3–1.3% (37). For any ICIs, fatal irAEs show early-onset and rapid progression, especially in patients receiving combination therapy. The mean time to fatal irAEs is approximately 14.5 days in patients receiving immunotherapy combined with other treatment and 40 days in patients receiving ICIs alone ($P<0.001$) (38). The monitoring of irAEs is essential to making perioperative immunotherapy available to esophageal cancer patients. When educating patients, the focus should be placed on the 3 or 4 potential irAEs that, although rare, can be the most severe.

In most cases, potential irAEs can be managed safely with immunosuppressive drugs, such as steroids, as long as the potential irAEs are recognized and addressed early. Patients should be advised to tell each physician they see that they are undergoing or have undergone immunotherapy, as this can affect how a symptom is treated and whether the immunotherapy should be continued or stalled. Patients with mild noncardiovascular, nonneurological, or nonhematological irAEs (grade 1) may continue to receive initial treatment (no adjustment). Patients with moderate to severe irAEs (grade 2–3) must stop immunotherapy and receive immunosuppressive drugs until their irAE has been reduced to a mild irAE. Patients with grade 4 irAEs should permanently desist from immunotherapy (39).

The management of irAEs is changing quickly and is an issue at the forefront of multidisciplinary science. The involvement of relevant subspecialties is essential when addressing a new symptom. It is vital to gather insights into evaluating the irAE toxicity and make others aware of all the potential irAEs. Including a medical oncologist with sufficient experience in irAEs is critical in any multidisciplinary consultation on ICI use.

Recommendation 6

Evaluation, education, and monitoring of irAE risk should be initiated in esophageal cancer patients before and within 3–12 months after perioperative immunotherapy (quality of evidence: low; consensus level: 86.5%).

Rationale: Although the blockade of the immune cell checkpoint PD-1 and PD-L1 has become a primary therapeutic option for advanced esophageal cancer that is effective across various solid cancer types and hematologic malignancies, the related irAEs can theoretically affect any tissue or organ in the body and range from mild to life-threatening under certain circumstances. In general, the incidence of irAEs from ICIs is closely associated with the primary tumor site, the type of ICI, and the composition of combination therapy. For monotherapy, the incidence of irAEs of any grade is 15% to 90%, and the incidence of severe irAEs is 0.5% to 13% (37). According to literature reports, these irAEs usually occur within a few weeks after dosing and may occur within 3–12 months after treatment (37).

Most severe irAEs are linked to inflammation, and may include but are not limited to pneumonitis, myocarditis, colitis, hepatitis, nephritis, primary hypothyroidism, hyperthyroidism, primary adrenal insufficiency, hypophysitis, diabetes, inflammatory arthritis, myositis, myasthenia gravis, Guillain-Barre syndrome, aseptic meningitis, encephalitis, autoimmune hemolytic anemia, aplastic anemia, immune thrombocytopenia, or venous thromboembolism (39).

Accordingly, the following general laboratory data have been associated with an increased risk of irAE and should be investigated: complete blood count, prothrombin time, electrolytes, fasting glucose, alanine aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, serum creatinine, creatine kinase, lactate dehydrogenase, thyroid-stimulating hormone, erythrocyte sedimentation rate, and C-reactive protein (39).

Recommendation 7

McKeown or Ivor Lewis esophagectomy performed in a conventional open or minimally invasive fashion with 2-field or 3-field lymph node dissection should be the first-line approach in all esophageal cancer patients after neoadjuvant immunotherapy (quality of evidence: high; consensus level: 97.3%).

Rationale: According to the CSCO Guidelines on Esophageal Cancer [2020] (13), extended 2-field lymph

node dissection (thoracic and abdominal 2-field + upper mediastinal lymph node dissection, especially around the bilateral recurrent laryngeal nerves) is recommended for patients with middle or lower one-third thoracic esophageal cancer and without supraclavicular lymphadenopathy; the 3-field lymph node dissection (bilateral lower cervical and supraclavicular area + extended thoracic and abdominal 2-field lymph node dissection) is recommended for patients with upper one-third thoracic esophageal cancer or supraclavicular lymphadenopathy.

Examining at least 15 lymph nodes has been recommended during esophagectomy for treatment-naive esophageal cancer patients to optimize staging, but the impact of this strategy on survival is uncertain. The post hoc analysis of the NEOCRTEC5010 trial showed that at least 20 lymph nodes should be dissected from locally advanced ESCC patients after preoperative chemoradiotherapy (40). A recent global, multicenter, retrospective study analyzed the surgical data of 3,859 resected locally advanced GEA patients. The results indicated that patients with ypN0 after preoperative chemoradiotherapy followed by esophagectomy could obtain survival benefits if at least 25 lymph nodes were dissected; for patients with ypN+, the optimal number was more than 30 (41).

Recommendation 8

Following preoperative immunotherapy, the transthoracic surgical approach is recommended for Siewert type I esophagogastric junction (EGJ) cancer patients, while the transabdominal surgical approach is recommended for type III EGJ cancer patients. Surgical approaches to Siewert type II EGJ cancer remain controversial and may be determined by the preferences of thoracic or gastrointestinal surgeons (quality of evidence: high; consensus level: 94.6%).

Rationale: Most of the controversy surrounding EGJ cancer management derives from the fact that these tumors share epidemiologic, histologic, and anatomic characteristics with both esophageal and gastric cancers. According to the CSCO Guidelines on Esophageal Cancer [2020] (13), Siewert type I EGJ cancer should be treated using lower thoracic esophageal cancer principles, while Siewert type III EGJ cancer should be treated with the principles of gastric cancer. The surgical options to be considered for Siewert type II EGJ cancers include transthoracic esophagectomy, transhiatal esophagectomy, a left thoracoabdominal esophagogastrectomy, or total gastrectomy with extended distal esophageal resection based on the thoracic or gastrointestinal surgeons' preferences. The Chinese expert consensus on the surgical treatment for adenocarcinoma of esophagogastric junction (2018 edition) can be referred to for more details (42).

Recommendation 9

There is a need to explore pathological response evaluation criteria in the preoperative immunotherapy setting, including primary tumors and metastatic lymph nodes (quality of evidence: low; consensus level: 91.9%.

Rationale: Presently, there is no established guidance on how to process and evaluate resected esophageal cancer specimens after preoperative therapy in the setting of clinical trials and clinical practice. There is also a lack of precise definitions on the degree of pathologic response, including major pathological response (MPR) or pCR. In addition, new treatment modalities, including immunotherapy, may change the tumor microenvironment and how specimens are scored pathologically.

pCR is defined as the absence of residual invasive and *in situ* cancer on hematoxylin and eosin evaluation of the completely resected esophagus specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current UICC/AJCC classification). We recommend using the phrase sampled regional lymph nodes, as indicated in our standard definitions of pCR. These definitions permit flexibility in terms of the surgical approach to regional lymph nodes. Still, they indicate that the presence of any residual invasive cancer following neoadjuvant therapy portends a poorer prognosis.

Mandard *et al.* (43) first evaluated the guiding value of tumor regression grade (TRG) for patient prognosis after neoadjuvant chemoradiotherapy for esophageal cancer. Since then, several TRG systems have been established to classify TRG after neoadjuvant therapy and provide more reliable patient prognosis information (44,45). However, no unified international scoring system has been developed (46).

Even though MPR has been recognized as a predictor of survival in patients with esophageal cancer treated with preoperative immunotherapy and thus a potential surrogate endpoint in clinical trials (47), few studies have described approaches for gross and microscopic assessment of the esophageal resection specimens, which has imposed challenges in reporting and interpreting data from preoperative trials.

In contrast, when immunotherapy is administered in the

preoperative setting, pCR can be assessed within several months of initiating an investigational drug. The use of pCR as an endpoint to support accelerated approval in the neoadjuvant setting may help address unmet medical needs in high-risk populations in a far shorter time frame.

Recommendation 10

Adjuvant immunotherapy should be offered to trimodality-treated esophageal cancer patients who do not achieve pCR (quality of evidence: high; consensus level: 94.6%).

Rationale: Preoperative CRT followed by surgery (trimodality therapy) for locally advanced esophageal cancer is a guideline-recommended standard of care. However, the prognosis of patients who do not achieve pCR after chemoradiotherapy is poor, with a higher risk of recurrence.

CheckMate 577 is a global, double-blind, phase III trial that enrolled stage II or III esophageal or EGJ cancer patients with residual pathological diseases such as ≥ ypT1 or ≥ ypN1 following trimodality therapy. Patients were randomized 2:1 to receive nivolumab (at a dose of 240 mg every 2 weeks for 16 weeks, followed by nivolumab at a dose of 480 mg every 4 weeks) or a matching placebo. The maximum duration of the trial intervention period was one year. The primary endpoint was DFS. At 24 months of follow-up, median DFS was substantially improved in patients treated with adjuvant nivolumab [22.4 months for nivolumab-treated patients versus 11.0 in the placebo arm; hazard ratio (HR) 0.69; 95% confidence interval (CI): 0.56–0.86; P=0.0003]. Nivolumab was well tolerated, with most patients experiencing only grade 1 or 2 toxicities (48). Pending further follow-up, this may result in a survival benefit.

While the results of the CheckMate 577 trial are likely to herald a change in the standard of care for esophageal cancer patients after trimodality therapy and have been accepted by the National Comprehensive Cancer Network guidelines (26), fewer than 30% of participants were ESCC patients, and fewer than 15% were from Asia. Moreover, chemoradiotherapy does not represent the standard of care for locally advanced esophageal or EGJ cancer patients in many parts of the world, where perioperative chemotherapy is preferred. Therefore, further research is needed to determine the optimal treatment strategy for Chinese patients.

Recommendation 11

During perioperative immunotherapy, antibiotic use to treat infectious events may affect the efficacy of immunotherapy. It is recommended that multidisciplinary evaluations be performed after antibiotic discontinuation for 1–2 months to determine whether immunotherapy should be terminated or resumed (quality of evidence: medium; consensus level: 91.9%).

Rationale: The outcome of immunotherapy could be dictated by both the tumor microenvironment and microbial environment (49,50). Current data indicate that antibiotics may affect the efficacy of immunotherapy in patients with advanced solid tumors (51,52). Therefore, antibiotics should be used with caution during perioperative immunotherapy for esophageal cancer. If antibiotics are used to treat infectious complications, immunotherapy should not be resumed until antibiotics have been discontinued for 1–2 months.

Key questions and perspectives

Do you agree that perioperative immunotherapy or chemoimmunotherapy is the new standard of care for resectable esophageal cancer in the future? Why?

Magnus Nilsson: I definitely do believe so, although I think we need some OS data from the CheckMate 577 trial before we can definitely declare adjuvant nivolumab to be standard of care after nCRT and esophagectomy. We also need results from trials combining immunotherapy with perioperative chemotherapy [FLOT (docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil)] for adenocarcinoma.

Francisco Schlottmann: I would not yet affirm that immunotherapy is the standard of care. Although several trials have shown promising results for both neoadjuvant and adjuvant ICI therapy, real-world data are still needed. I believe that patients who do not achieve pCR after trimodality therapy or chemotherapy + surgery are ideal candidates for the use of novel therapies. Other scenarios should be further investigated.

Riccardo Rosati & Cascinu Stefano: No, it could be, but the lack of randomized trials suggests caution in adopting this approach in clinical practice. There are strong suggestions from trials in the advanced disease and the adjuvant setting, but it is not the first time that positive results in advanced disease do not translate to the perioperative setting. Furthermore, a crucial point could be histology. While preoperative chemoradiotherapy is a standard of care for ESCC, there is a debate about the optimal treatment strategy for esophageal adenocarcinoma.

This is due to the CROSS and the FLOT trial results, where adenocarcinoma histology could benefit much more from chemotherapy alone. Finally, the lack of information on the toxicity of immunotherapy combined with chemoradiotherapy is another matter of concern for its use in clinical practice. While waiting for results from clinical trials, we could probably suggest that patients with resectable esophageal cancer undergo chemoradiotherapy and receive adjuvant nivolumab after radical surgery.

Philip Wai-yan Chiu: Yes, I agree because recent data on neoadjuvant immunotherapy to treat ESCC has demonstrated a good response.

Neil B. Newman: This is currently not the standard of care for esophageal cancer. We will need to obtain further in-depth clinical trials to answer this question better. In the USA, the ECOG 2174 trial is assessing whether the administration of preoperative immunotherapy will lead to improvements in pCR and DFS. At this point, we only have small phase I trials (discussed in the manuscript) and retrospective reviews. The utility in the neoadjuvant or perioperative setting will need to be proven with large randomized controlled trials.

Noriyuki Hirahara: I am afraid I have to disagree. The results of the CheckMate study indicate that nivolumab should be given after salvage surgery after definitive CRT. Based on the results of this study, it will be used in a limited number of cases at present. For patients with resectable esophageal cancer patients, docetaxel, cisplatin, plus 5-fluorouracil (DCF) have been shown to have favorable results in Japan at the ASCO. Given the risk of irAEs, it is unnecessary for resectable esophageal cancer patients. However, there is a possibility that the combination of immuno-oncology and chemotherapy may be better than CRT so that perioperative use may increase the survival benefit.

Dae Joon Kim: Currently, there has been no definite evidence on the superiority of immunotherapy for resectable ESCC, and we need more solid evidence going forward. Also, other issues remain to be solved, such as the developing resistance to immunotherapy or cost-effectiveness in some countries. However, given the result of the CheckMate-577 study, nivolumab for 1 year in patients with non-ypT0N0 after neoadjuvant concurrent CRT is a standard of care.

Rutika Mehta: In the United States, at this current time, there are no completed large-scale phase 3 randomized trials looking at perioperative immunotherapy or chemoimmunotherapy for resectable esophageal cancer. The only case scenario where I would use immunotherapy in the locally advanced stage setting would be adjuvant therapy after completion of neoadjuvant chemoradiation, followed by surgery for those patients who did not achieve pCR.

Kimberly L. Johung & Michael Cecchini: At this time, adjuvant treatment with nivolumab should be the standard of care for all patients with residual disease after induction chemoradiotherapy and resection. This recommendation is based on the data from CheckMate 577, which revealed a median DFS with adjuvant nivolumab compared to placebo (22.4 *vs.* 11.0 months; HR 0.69; P<0.001). Due to the impressive activity of nivolumab in the adjuvant setting, it is likely to also be active in the neoadjuvant/perioperative setting in the future, although at this time, there is no phase 3 data to support its use prior to surgical resection. Moreover, in the USA, it is going to be challenging to show the superiority of perioperative nivolumab over adjuvant nivolumab.

Shane Lloyd: I think perioperative immunotherapy alone lacks sufficient evidence to be a standard of care at this time. In the preoperative space, I think adding immunotherapy to chemoradiotherapy or chemotherapy has tremendous potential. I note that the pCR rates for preoperative chemoradiation therapy plus immunotherapy are excellent and among the best we have ever seen. I have a suspicion that this will become a standard of care. In the postoperative space, the CheckMate 577 trial showed that nivolumab improved DFS from 11.0 to 22.4 months, and it should be the standard of care for patients who do not have a pCR after neoadjuvant chemoradiation therapy.

Kenneth Meredith: Yes, it is the new standard of care, at least for patients with residual disease after neoadjuvant therapy and surgery. In the recent *NEJM* article by Kelly *et al.*, DFS was 22.4 months in those who received adjuvant nivolumab compared to 11 months in those who received placebo (48).

How many cycles of preoperative immunotherapy or chemoimmunotherapy do you think is optimal in your practice or trial design? Why?

Magnus Nilsson: So far, I have not seen any robust data on preoperative immunotherapy, only adjuvant (postoperative).

Francisco Schlottmann: Based on the current evidence available, 2–4 cycles of treatment seem reasonable.

Riccardo Rosati & Cascinu Stefano: Generally, patients achieve clinical response after two months of treatment, but it is in the advanced disease. We do not know the number of

cycles able to increase a complete pathological response in preoperative treatment.

Philip Wai-yan Chiu: I trust it can be 2–4 cycles as a preoperative treatment before surgery so that surgical treatment will be timely.

Neil B. Newman: If it is to be given, the amount and best sequence also remain to be determined. Depending on the agent, 2–3 cycles of immunotherapy may be sufficient.

Noriyuki Hirahara: Although there is no secure evidence for the optimal cycles of preoperative treatment, three cycles are considered to be the most appropriate. This is because the onset of hematological toxicities and irAEs is several months after administration.

Dae Joon Kim: I think 2–3 cycles (6–9 weeks) are adequate to avoid a delay in surgical treatment.

Rutika Mehta: I would adopt the optimal number from trials such as KEYNOTE-975 and KUNLUN.

Kimberly L. Johung & Michael Cecchini: At this time, immunotherapy is not approved and therefore not used in the neoadjuvant setting for gastroesophageal cancers. I would limit the number of cycles of preoperative therapy to 6 cycles of FOLFOX for most patients (3 cycles of induction and three cycles of chemoradiotherapy), similar to the regimen in the CALGB 80803 trial. Thus, if adding ICIs, this would be 4–6 cycles of immune therapy. A trial design for how to incorporate immunotherapy preoperative is challenging at this time, given the recent approval of nivolumab in the adjuvant setting. Any neoadjuvant trial will need to show superiority of the survival outcomes when treating patients as in CheckMate 577, which will be challenging. Even if outcomes are improved, it will take a very large study to demonstrate this, given the excellent outcomes reported in CheckMate 577. One strategy may be to enrich a preoperative cohort to include only patients more likely to respond to immunotherapy (i.e., CPS ≥5 or ≥10) and/or use alternative endpoints such as pCR if accepted by regulatory bodies.

Shane Lloyd: I would suggest 3–4 cycles pre-and postoperatively for regimens not containing radiation therapy. This works for about 2 months of immunotherapy, which is a reasonable amount of time to potentially see some response by the time of surgery. For regimens that include radiation therapy, two months is also reasonable as it covers the time of radiation therapy and a little afterward while the patient is awaiting surgery.

Kenneth Meredith: Optimally, three months of chemo/immunotherapy would be ideal. No data supports it for neoadjuvant therapy, but I would do this in a trial setting.

What do you consider to be the optimal timeframe between preoperative immunotherapy or chemoimmunotherapy and surgery? Why?

Magnus Nilsson: I do not know since I am not aware of any data addressing this.

Francisco Schlottmann: Previous trials have shown intervals of 4–9 weeks. A recent study from Memorial Sloan Kettering Cancer Center using neoadjuvant immunotherapy plus chemoradiotherapy reported that the median interval to surgery was 54 days (47–61 days) and showed good postoperative outcomes (53). Overall, a 6- to 8-week interval is reasonable (giving time to patients to fully recover from treatment and get to the OR in optimal conditions).

Riccardo Rosati & Cascinu Stefano: This is really a good question; unfortunately, we cannot provide an equally good answer. Actually, we do not know if immunotherapy requires a longer time to achieve a therapeutic effect if we have to delay the surgical approach.

Philip Wai-yan Chiu: I suggest 4–6 weeks with restaging imaging to demonstrate the response.

Neil B. Newman: This is a new treatment paradigm and will need larger phase III studies to confirm the optimal sequence interval to incorporate surgical management. There are many factors to take into consideration while we await results from the CROSS trial. Clinical trials need to elucidate the ideal period of time from chemoradiotherapy and the amount needed from immunotherapy. Immunotherapy and radiation can work synchronously to allow for immune infiltration and tumor downstaging, increasing R0 and pCR rates. In rectal cancer, with neoadjuvant CRT, we see that waiting for more extended periods of time can increase pCR rates, and perhaps with the addition of immunotherapy, it can do the same in esophageal cancer.

Noriyuki Hirahara: The first symptom that appears as a side effect of immunotherapy or chemoimmunotherapy is usually skin toxicity, which appears on average 6 weeks after administration. Since various subsequent adverse events occur, surgery should be performed as soon as possible after 3 cycles of treatment.

Dae Joon Kim: Surgery 3–4 weeks after immunotherapy will be good because there is no bone marrow suppression at that time.

Rutika Mehta: Without data from large-scale trials, it is not possible to define this accurately.

Kimberly L. Johung & Michael Cecchini: The addition

of immunotherapy to preoperative chemoradiotherapy would not change the optimal timeframe to proceed with surgery (within 8 weeks of chemoradiotherapy). While immunotherapy responses are often delayed compared to chemotherapy in the metastatic setting, this is not necessarily relevant in the preoperative setting. Chemoradiotherapy will result in local tumor control for most patients, and nivolumab's role is primarily to reduce distant relapses, which is less dependent on the timing of surgery. Moreover, nivolumab's use in the adjuvant setting also mitigates the importance of giving prolonged nivolumab in the neoadjuvant setting.

Shane Lloyd: I wait 4–6 weeks after radiation therapy, as was used on the CROSS trial, and would do the same if immunotherapy was involved. I think waiting closer to 4 weeks is sufficient after chemoimmunotherapy. I would not recommend using preoperative immunotherapy only at this time.

Kenneth Meredith: If only chemoimmunotherapy is applied, then the operation could occur anytime within 6–8 weeks or sooner. Clearly, a longer time interval allows for a better assessment of response. An interval PET scan at four weeks to assess response may also be helpful.

Do you believe that adding preoperative immunotherapy increases the risks of surgical difficulty, morbidity, and mortality? Why?

Magnus Nilsson: I do not know since I am not aware of data addressing this.

Francisco Schlottmann: I do not believe preoperative immunotherapy increases the risks of surgical technical difficulty (as opposed to preoperative radiotherapy). Preoperative assessment, however, is key to operating on patients in good condition.

Riccardo Rosati & Cascinu Stefano: In reality, I am not able to define this risk. Neither the KEYNOTE-585 (FLOT +/– pembrolizumab) nor the DANTE trial (FLOT +/– atezolizumab) seemed to raise these concerns. Although both trials are focused on gastric and gastroesophageal cancers, they can help to answer this question.

Philip Wai-yan Chiu: I trust this will not have a major effect on the risks of surgery.

Neil B. Newman: Currently, there is no suggestion that perioperative immunotherapy has this interaction. According to several small phase one studies, there is no suggestion of increased perioperative mortality. However, this will need to be tested in a phase III trial. There is some suggestion in smaller neoadjuvant immunotherapy trials, although this may be an increase in adverse events from the administration of the immunotherapy in itself. As long as the patients are physiologically well enough to tolerate surgery, there is no suggestion of worse outcomes.

Noriyuki Hirahara: The degree of difficulty of the surgery is not expected to change, although the evidence is limited because the tissue changes caused by the preoperative treatment are unknown. However, the risk of pulmonary complications due to irAEs will increase.

Dae Joon Kim: No. Well-known immunotherapy-related complications can be managed successfully in a conservative manner.

Rutika Mehta: If combined with chemoradiation, there can be some presumed increased risks. However, without large-scale data, it is not possible to comment on this.

Kimberly L. Johung & Michael Cecchini: For the majority of patients, preoperative immunotherapy does not impact the difficulty of surgery or perioperative morbidity/mortality. It is not cytotoxic and has no negative impact on wound healing. The data in melanoma with ICIs (anti-PD1/anti-PD-L1 and anti-CTLA4) support the safety of the use of immunotherapy in the perioperative setting.

Shane Lloyd: Generally, no, except in the rare case of radiation-induced pneumonitis or myocarditis. Operating on these rare patients can be avoided with pulmonary function testing and cardiac clearance before surgery. I do not believe there is excess toxicity in patients with normal laboratory findings, including complete blood count (CBC), comprehensive metabolic panel (CMP), and thyroid function tests.

Kenneth Meredith: No, I have had a few patients on whom I have performed robotic esophagectomy after immunotherapy, and I did not see any increase in difficulty compared to chemoradiotherapy. Nevertheless, I also do a significantly high volume of esophageal work.

What are the biomarkers indicating perioperative immunotherapy in esophageal cancer?

Magnus Nilsson: I suggest the PD-L1 expression using CPS and the rare MSI subtype. The CPS can, however, be difficult to establish from preoperative biopsies.

Francisco Schlottmann: I suggest PD-L1 expression, MSI (high), and mismatch repair (MMR; deficient) status.

Riccardo Rosati & Cascinu Stefano: Unfortunately, no biomarkers seem helpful. PD-L1 has been assessed for a long time, but the results are still debatable. From the

available data, we could conclude that in ESCC, we need a threshold of PD-L1 of 1% while it could be 10% for adenocarcinoma. Nevertheless, it depends on personal preference and is subjective.

Philip Wai-yan Chiu: I have no experience in this perspective.

Neil B. Newman: This needs to be further validated. The best biomarkers that could be examined include CD8/CD4 infiltration into the tumor (such as in the PALACE-1 trial). We know that increased ability to infiltrate the tumor leads to better overall clinical outcomes. Furthermore, other biomarkers that could be of use include circulating tumor DNA (ctDNA). We know from lung cancer data that immunotherapy has less utility when there are no ctDNA cells. Also, we are aware of imaging biomarkers that need further validation, such as radiomics, to predict which tumors may be most responsive to immunotherapy.

Noriyuki Hirahara: Possible biomarkers include neutrophil to lymphocyte ratio (NLR), MSI, and PD-L1. Particularly, PD-1 expression on CD8-positive T cells in tumors is important.

Dae Joon Kim: There has been no single biomarker of predictive and prognostic value. PD-L1 expression and CD8+ T cell infiltration are the markers of the PD-1 inhibitor. A combination of 2 or 3 biomarkers and/or precision immune profiling might be helpful to predict the outcome.

Rutika Mehta: Currently, the best marker we have is PD-L1 until better biomarkers are identified.

Kimberly L. Johung & Michael Cecchini: In patients with metastatic gastroesophageal cancer, PD-L1 expression has been shown to be an imperfect marker to predict which patients will benefit from ICIs. For these patients, the CPS is the best predictor for benefit with ICIs (54). Moreover, in the CheckMate 577 trial's exploratory analysis, it seemed to be a more accurate tool than was tumor PD-L1 expression for determining those patients who would benefit from adjuvant nivolumab (48). However, at this time, the utility of CPS as a biomarker in the preoperative of perioperative setting is unknown, although there is no reason to believe it would be inaccurate in this setting.

Shane Lloyd: None that I know of. PD-L1 expression using the CPS can help screen patients for immunotherapy. Certain studies like KEYNOTE-590 only examined patients with a threshold CPS. Pembrolizumab is more effective in patients with a higher level of MSI.

Kenneth Meredith: PD-L1 expression (KEYNOTE-012).

How do you detect and manage perioperative immunotherapy-related toxicities for the esophageal patient in your daily practice?

Magnus Nilsson: I have not yet used this in my daily practice.

Francisco Schlottmann: Most of our patients are included in clinical trials, and therefore monitoring of irAEs is rigorous. Although we monitor potential irAEs in our daily practice, the Gastrointestinal Oncology Service's education and evaluation of irAEs are done mainly.

Riccardo Rosati & Cascinu Stefano: We can offer immunotherapy only as a second line for metastatic ESCC patients failing first-line chemotherapy in Italy, based on the KEYNOTE-181 trial. We have not reported on the toxicities related to this specific tumor and histology thus far. We check our patients before each administration of immunotherapy.

Philip Wai-yan Chiu: A routine clinical follow-up to assess the symptoms and complaints as well as checking of blood tests.

Neil B. Newman: This requires at least weekly on-treatment visits and careful attention to the side effects that could be induced from radiation. Most notably, this is inclusive of radiation pneumonitis, hematologic declines, cardiac issues, and colitis.

Noriyuki Hirahara: A multidisciplinary toxicity team for irAEs should be established in the institution because irAEs are diverse, and their symptoms and clinical course are quite different from conventional anticancer agents.

Dae Joon Kim: We are following up with the patients weekly or bi-weekly for close monitoring of immunotherapy-related toxicities.

Rutika Mehta: We have institution-based guidelines that are adopted from NCCN guidelines for managing immunotherapy-related toxicities.

Kimberly L. Johung & Michael Cecchini: Immunotherapy-related toxicities, in general, require prompt and proactive management of toxicities. The NCCN guidelines on managing irAEs are the most comprehensive resource for the workup and treatment for immunotherapy toxicities, and we follow these guidelines. Early identification of irAEs is critical in the perioperative setting to avoid toxicities that could jeopardize curative surgery.

Shane Lloyd: Generally, I agree with the conclusion of Recommendation 5 and the Discussion in the present paper. I would recommend periodic history and physical examination with a mind towards myocarditis, rash,

diabetes, thyroid abnormalities, colitis, arthritis and myalgia, neurological abnormalities, pneumonitis, kidney function, and primary adrenal insufficiency with further testing as needed based on symptoms. CBC and CMP should be monitored before each treatment, with thyroid-stimulating hormone and free thyroxine being monitored every 4–6 weeks. Regular cross-sectional imaging can help detect lung toxicity.

Kenneth Meredith: The side effects vary based on the therapy. However, common effects such as skin reactions, blistering, and dryness are treated based on severity ranging from topical treatments, sunscreen, and sun avoidance. Fatigue and hydration are treated sometimes with increasing fluid intake and intravenous fluids if severe water retention is treated with compression stockings and diuretics as needed.

Comments

Francisco Schlottmann: The consensus is very well-written and offers a thorough review of a relevant topic concisely. Immunotherapy is not yet broadly embraced for esophageal cancer, and in many countries, its use is limited to clinical trials. Therefore, I believe this consensus may serve as a guide for physicians in China and many other interdisciplinary teams worldwide.

Riccardo Rosati: We do not have any comment about the consensus. All the statements can be shared. Lacking data in the perioperative setting from phase III trials may be a potential drawback.

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NCC Writing Committee Members: Xiaozheng Kang, Jianjun Qin, Ruixiang Zhang, Zhen Wang, Qingfeng Zheng, Yong Li, Jianping Xu, Jing Huang, Xin Wang, Zhouguang Hui, Liyan Xue, Yousheng Mao, Yin Li, Jie He. CATS Esophageal Surgery Committee Members/CSTCVS Esophageal Disease Panelists: Chun Chen, Haiquan Chen, Ke-Neng Chen, Long-Qi Chen, Maoyong Fu, Junke Fu, Qing Geng, Taiqian Gong, Shiping Guo, Yongtao Han, Yi He, Jian Hu, Hongjing Jiang, Jie Jiang, Yuequan Jiang, Mingqiang Kang, Jianqun Ma, Shaohua Ma, Yongde Liao, Hecheng Li, Shanqing Li, Zhigang Li, Shuoyan Liu, Yang Liu, Guibin Qiao, Lijie Tan, Hui Tian, Gaofeng Zhao, Jun Zhao, Shiying Zheng, Yongan Zhou. Esophageal Disease Panelists of STM: Magnus Nilsson, Francisco Schlottmann, Riccardo Rosati, Cascinu Stefano, Philip Wai-yan Chiu, Neil B. Newman, Noriyuki Hirahara, Dae Joon Kim, Rutika Mehta, Kimberly L. Johung, Michael Cecchini, Shane Lloyd, Kenneth Meredith.

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Footnote

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