Anti-PD-1 therapy with or without local intervention for oligometastatic esophageal squamous cell carcinoma (ESO- Shanghai20): a prospective, multicenter, randomized controlled, Phase III clinical trial

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Abstract

Background

Anti-PD-1 therapy combined with or without chemotherapy is the standard regimen for metastatic esophageal cancer. Oligometastatic carcinoma is an intermediate state of tumor development between locally advanced and widespread metastasis, with potential long-term survival. The value of the addition of local intervention therapy to standard systemic therapy is still controversial for patients with oligometastasis. The ESO-Shanghai 13 trial demonstrated that systemic therapy combined with local intervention improved progression-free survival and overall survival in patients with oligometastatic esophageal squamous cell carcinoma. However, it is a phase II trial and has two systemic treatment regimens including chemotherapy and chemoimmunotherapy. There were only 43 patients treated with immunotherapy with or without local intervention therapy in ESO-Shanghai 13. To further assess the efficacy of Anti-PD-1 therapy with local intervention therapy in oligometastatic esophageal patients, we initiated a multicenter randomized controlled phase III clinical trial, ESO-Shanghai 20.

Methods

The ESO-Shanghai20 trial will recruit histology-proven esophageal squamous cell carcinoma patients with genuine oligometastasis (four or fewer metastatic lesions) and the eligible patients will be randomly assigned in a 2:1 ratio to receive either the combined local intervention therapy and systemic therapy (the combined group) or the systemic therapy only (the systemic group). Both groups receive anti-PD-1 with or without chemotherapy for 4 cycles every 21 days, followed by anti-PD-1 maintenance therapy every 21 days for 2 years. The local intervention therapy in this trial includes radiotherapy, surgery, and ablation, and allowed different metastases in the same patient to receive different local intervention treatment modes according to the characteristics of the metastatic site. The expected enrollment time is 36 months, and the follow-up time is 24 months. The combined treatment group and the systemic treatment group required 236 and 118 samples, respectively, and a total of 354 cases needed to be enrolled. The primary endpoint is progression free survival, and the second endpoint is overall survival and the toxicity and safety of the treatment.

Discussion

If the result of ESO-Shanghai20 shows that the combination of local intervention therapy with anti-PD-1 therapy is safe and promising for patients with oligometastatic esophageal squamous cell carcinoma, this study will provide a basis for the precise stratified treatment of patients with advanced esophageal squamous cell carcinoma.

Trial registration

NCT06190782.

Background

Esophageal cancer (EC) is the sixth leading cause of cancer deaths globally, accounting for more than 500,000 deaths every year, and is more common in men than in women$^{[1]}$. In China, the incidence and death rate account for about half of the world's total, among which more than 90% are squamous cell carcinoma$^{[2]}$. Despite the improvement in the
survival of EC in the past decades, the five-year survival is still unsatisfactory, only less than 20%[3]. In addition to the as high as 30–50% recurrence rate after radical treatment, some patients with esophageal squamous cell carcinoma are diagnosed at an advanced stage and lose the opportunity to receive radical treatment[4].

Several studies have investigated the role of anti-PD-1 immunotherapy with or without chemotherapy for first or second-line metastatic or recurrent esophageal squamous cell carcinoma (ESCC) and have suggested that anti-PD-1 with or without chemotherapy increased the PFS and OS (Table 1). For example, the Checkmate-648[5], JUPITER-06[6], ORIENT-15[7], KEYNOTE-590[8] and ESCORT-1st[9] studies reported that the chemotherapy (PF or TP regimen) combined with anti-PD-1 increased the median PFS from 4.4–6.4 months to 5.7–8.3 months, and the median OS from 9.1–13.6 months to 13.9–17.2 months compared with the PF or TP regimen alone in the first-line treatment of unresectable advanced and metastatic esophageal squamous cell carcinoma and gastric and esophageal contact tumors. The clinical trials of second-line treatments are listed in the table.1, such as KEYNOTE-181[10], RATIONALE-302[11], ORIENT-2[12], ESCORT[13] and ATTRACTION-3[14], also demonstrated that anti-PD-1 immunotherapy alone improved the median OS from 6.2–13.2 months to 7.2–15.3 months compared with chemotherapy alone for advanced and metastatic esophageal squamous cell carcinoma, regardless of different anti-PD-1 drug used. However, in the above studies, patients with metastasis were not divided into oligometastatic or non-oligometastatic patients, and they were treated with anti-PD-1 with or without chemotherapy only, without any local intervention therapy for metastatic lesions.

Oligometastatic carcinoma is considered to be an intermediate state of tumor development between locally advanced and widespread metastasis, with potential long-term survival. In recent years, multiple clinical trials have indicated that combined local and systemic treatments(chemotherapy or TKI) can improve the overall survival of patients with oligometastases, such as those with lung cancer[15,16], prostate cancer[17], and other malignancies[18]. However, limited research has been conducted to investigate the value of combined use of local intervention therapy and anti-PD-1 therapy for oligometastatic carcinoma. The standard treatment is anti-PD-1 with or without chemotherapy for recurrent and metastatic esophageal cancer[19], and the question of whether oligometastatic patients benefit from combined local intervention treatment based on systemic therapy is still under debate. The ESO-shanghai10 study showed that 34 patients with oligometastatic esophageal squamous cell carcinoma treated with SBRT, regardless of whether combination chemotherapy or not, had a median PFS of 13.3 months and a median OS of 24.6 months, and no severe acute or late toxic reactions occurred[20]. Moreover, the ESO-shanghai 13 study from our center, in which patients with ESCC with a well-controlled primary tumor following radical therapy and no more than four metastatic lesions were randomly assigned 1:1 to either systemic therapy or systemic therapy combined with local therapy, showed that local intervention treatment combined with systemic treatment for oligometastatic esophageal squamous cell carcinoma increased PFS from 6.4 months to 15.3 months, without a significant increase in treatment-related adverse events[21]. However, it was a Phase II trial and the systemic treatment regimens were chemotherapy alone, or anti-PD-1 therapy with or without chemotherapy, which suggested that due to the limitations of the era, only 43 patients received anti-PD-1 therapy.

Given these limitations, to further assess the potential efficacy of local intervention therapy in oligometastatic esophageal patients receiving immunotherapy with or without chemotherapy, we initiated a multicenter randomized controlled phase III clinical trial, ESO-Shanghai20. If the result of ESO-Shanghai20 showed that the combination of local intervention therapy with anti-PD-1 therapy was safe and promising for patients with oligometastatic esophageal squamous cell carcinoma, it would provide a basis for the precise stratified treatment of patients with advanced esophageal squamous cell carcinoma.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>No. of cases</th>
<th>Anti-PD-1</th>
<th>Comparison</th>
<th>Median PFS (m)</th>
<th>Median OS (m)</th>
<th>PD-L1 Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td></td>
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</tr>
<tr>
<td>Checkmate 648</td>
<td>III</td>
<td>970</td>
<td>Nivolumab</td>
<td>Anti-PD-1 + PF vs PF</td>
<td>6.9 vs 4.4</td>
<td>15.4 vs 9.1</td>
<td>TPS &gt; 1%</td>
</tr>
<tr>
<td>JUPITER-06</td>
<td>III</td>
<td>514</td>
<td>Toripalimab</td>
<td>Anti-PD-1 + TP vs TP</td>
<td>5.7 vs 5.5</td>
<td>17.0 vs 11.0</td>
<td>No correlation</td>
</tr>
<tr>
<td>ORIENT-15</td>
<td>III</td>
<td>659</td>
<td>Sintilimab</td>
<td>Anti-PD-1 + TP/TP/PF vs TP/PF</td>
<td>8.3 vs 6.4</td>
<td>17.2 vs 13.6</td>
<td>CPS &gt; 10</td>
</tr>
<tr>
<td>KEYNOTE-590</td>
<td>III</td>
<td>749</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1 + PF vs PF</td>
<td>6.3 vs 5.8</td>
<td>13.9 vs 8.8</td>
<td>CPS &gt; 10</td>
</tr>
<tr>
<td>(73% ESCC)</td>
<td></td>
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</tr>
<tr>
<td>ESCORT-1st</td>
<td>III</td>
<td>596</td>
<td>Camrelizumab</td>
<td>Anti-PD-1 + TP vs TP</td>
<td>6.9 vs 5.6</td>
<td>15.3 vs 12.0</td>
<td>No correlation</td>
</tr>
<tr>
<td>2nd line</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>KEYNOTE-181</td>
<td>III</td>
<td>340</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1 vs PTX/DOX/CPT-11</td>
<td>2.2 vs 3.1</td>
<td>10.0 vs 6.5</td>
<td>CPS &gt; 1</td>
</tr>
<tr>
<td>RATIONALE-302</td>
<td>III</td>
<td>512</td>
<td>Tislelizumab</td>
<td>Anti-PD-1 vs PTX/DOX/CPT-11</td>
<td>1.6 vs 2.1</td>
<td>10.3 vs 6.8</td>
<td>TAP &gt; 10%</td>
</tr>
<tr>
<td>ORIENT-2</td>
<td>II</td>
<td>190</td>
<td>Sintilimab</td>
<td>Anti-PD-1 vs CPT-11</td>
<td>1.6 vs 2.9</td>
<td>7.2 vs 6.2</td>
<td>No correlation</td>
</tr>
<tr>
<td>ESCORT</td>
<td>III</td>
<td>457</td>
<td>Camrelizumab</td>
<td>Anti-PD-1 vs DOX/CPT-11</td>
<td>1.9 vs 1.9</td>
<td>8.3 vs 6.2</td>
<td>No correlation</td>
</tr>
<tr>
<td>ATTRACTION-3</td>
<td>III</td>
<td>419</td>
<td>Nivolumab</td>
<td>Anti-PD-1 vs PTX/DOX</td>
<td>1.7 vs 3.4</td>
<td>10.9 vs 8.4</td>
<td>No correlation</td>
</tr>
</tbody>
</table>

Anti-PD-1: Anti-PD-1 therapy; TPS: Tumor cell Proportion Score; CPS: Combined Positive Score; TAP: Tumor Area Positivity Score. PTX: Paclitaxel; DOX: Docetaxel; CPT-11: Irinotecan; PFS: Progression free survival; OS: Overall survival.

**Methods**

**Study design**

ESO-Shanghai20 is a prospective, multicenter, randomized controlled, phase III clinical trial enrolling patients with genuine oligometastatic ESCC (four or fewer metastatic lesions). Furthermore, the number of metastases within a single organ is restricted to three or fewer and the maximum diameter of each metastatic lesion does not exceed 5 cm. Eligible oligometastatic ESCC patients are randomly assigned into the combined treatment group and the systemic group at a ratio of 2:1. The combined treatment group will receive a combination of local intervention therapy and systemic therapy, and the systemic group receives systemic therapy only. The systemic treatment regimen of both groups was anti-PD-1 therapy with or without chemotherapy for 4 cycles, repeated every 21 days, and
then anti-PD-1 maintenance therapy was administered every 21 days for 2 years or until disease progression, development of intolerable toxicity, acceptance of a new antitumor therapy, withdrawal of informed consent, death, or other circumstances in which the investigator determined that treatment should be discontinued, whichever occurred first. The local intervention therapy is recommended as soon as possible at the beginning of the first systemic therapy, and different metastases in the same patient are allowed to receive different local intervention treatment modes according to the characteristics of the metastatic site. The treatment design is shown in Fig. 1.

**Samples and calculation**

Based on the data of the oligometastatic subgroup in the ESO-Shanghai 13 study,[21] it is assumed that the PFS of the systemic treatment group in this study was 7.5 months, and the PFS of the systemic treatment combined with the local intervention treatment group was extended by 3.5 months to 11 months compared with the systemic treatment group. Under the hypothesis of a random ratio of 2:1, HR = 0.68, and \( \alpha = 0.025 \), the stratified log-rank test was used to compare the survival time distribution of PFS among the groups. The expected enrollment time was 36 months, and the follow-up time was 24 months. The combined treatment group and the systemic treatment group required 224 and 112 samples, respectively. Considering the 5% shedding rate, the combined treatment group required 236 cases, the systemic treatment group 118 cases, and a total of 354 cases need to be enrolled. In each randomized group, two additional stratifications will be conducted, including groups based on the control status of the primary lesion (controlled or uncontrolled), the affiliation with Fudan University Shanghai Cancer Center or other cancer centers. The flow chart of ESO-Shanghai20 is shown in Fig. 2.

**Objectives**

**Primary endpoints**

The primary endpoint is progression free survival (PFS), and PFS is defined as the time interval between the date of the first systemic treatment and the date of first confirmed disease progression or death from any cause. If the patient does not have tumor progression or death at the time of data analysis, the time of the last tumor evaluation will be used as the endpoint for PFS.

**Secondary endpoints**

The secondary endpoint is overall survival (OS), which is the interval between the date of first systemic treatment and the date of death from any cause, and for patients who are still alive at the time point of the final analysis, the time of their last contact will be used as the survival time. In addition, we will document the toxicity and safety of the treatment, and record the treatment-related delays, reductions, tolerability, and other conditions in the study. In this trial, disease progression is assessed against RECIST V.1.1, and adverse reactions are assessed against CTCAE V.5.0.

**Patient selection**

**Inclusion criteria**

Patients enrolled in ESO-Shanghai20 must meet all of the following criteria:

1. Aged 18 years or older, and of either sex.
2. An eastern cooperative oncology group (ECOG) score of 0–1.
3. Histologically- or cytologically-confirmed diagnosis of esophageal squamous cell carcinoma.
4. Genuine oligometastasis (without a history of polymetastatic disease).
5. A total of 4 or fewer distant metastases, a maximum of 3 metastases in a single organ, and a maximum diameter of each metastatic lesion not exceeding 5cm.
6. Biopsy of a metastatic lesion, PET/CT scan, and PD-L1 CPS (IHC 22C3) are not required but preferred.
7. No history of anti-PD-1/PD-L1 therapy. However, the following conditions are also eligible for inclusion: the use of anti-PD1/PD-L1 during induction/neoadjuvant/concurrent therapy, or the use of anti-PD1/PD-L1 for maintenance therapy, but not due to toxicity or disease progression interrupting anti-PD1/PD-L1 treatment, and the interruption has lasted for more than 3 months.
8. Adequate hematological, hepatic, renal, and coagulation function. Baseline laboratory tests required to assess eligibility, including ANC ≥ 1.5×10^9/L, PLT ≥ 80×10^9/L, Hb ≥ 85g/L, ALB ≥ 28g/L, TBIL ≤ 1.5×ULN, ALT and AST ≤ 3×ULN, Cr ≤ 1.5×ULN or CrCl ≥ 40mL/min, FEV1 ≥ 1L. (liver metastases ALT and AST ≤ 5×ULN, liver or bone metastases AKP ≤ 5×ULN).
9. Enrolled voluntarily and signed informed consent by the patient himself or his legal representative.

**Exclusion criteria**

1. Pregnant or lactating women.
2. Lung V20 remains over 25%.
3. Confirmed diagnosis or clinical suspicion of esophageal fistula.
4. Recurrence in the irradiated field.
5. Active infection requiring systemic therapy.
6. Active autoimmune disease requiring systemic treatment in the past 2 years.
7. Immunodeficiency diagnosis, systemic steroid therapy, or any immunosuppressive treatment within 7 days before the first study treatment dose.
8. Patients with a known history of grade 3 or higher adverse events, which are unsuitable for Anti-PD-1 therapy, or adverse events that have not recovered to ≤ CTCAE grade 1 (except alopecia).
9. Uncontrolled pleural effusion, pericardial effusion, or pelvic ascites requiring repeated drainage.
10. Unable or rejection to receive Anti-PD-1 therapy or unable to comply with study requirements or follow-up schedule.
11. Inability to provide informed consent.

**Systemic therapy**

All eligible patients received anti-PD-1 therapy combined with or without chemotherapy for 4 cycles, repeated every 21 days, and then anti-PD-1 maintenance therapy every 21 days for up to 2 years. The first-line treatment is anti-PD-1 therapy combined with chemotherapy, while the second-line or later-line treatment is anti-PD-1 monotherapy. However, the second-line or later-line treatment can also be anti-PD-1 therapy combined with chemotherapy, if the attending physician believes the patients can tolerate it. In this study, any anti-PD-1 drugs approved for esophageal cancer in China or other countries can be used, such as Toripalimab\(^6\), Sintilimab\(^7,12\), Pembrolizumab\(^8,10\), Camrelizumab\(^9,13\), Tislelizumab\(^11\), etc. And the recommended dosage for anti-PD-1 is the standard does of the drug guidelines, usually a fixed dose of 200mg.

If the patients need the treatment of a combination of anti-PD-1 and chemotherapy, then the chemotherapy regimens are recommended as follows (Table 2). For the first-line, the recommended chemotherapy regimens are PF and TP via intravenous infusion or continuous intravenous pumping, repeated every 21 days. For the second-line chemotherapy, the recommended regimens are docetaxel or irinotecan or paclitaxel monotherapy via intravenous infusion, repeated every 21 days, however other single or dual drug chemotherapy can also be used by the attending physician according
to the patients' needs, such as Anlotinib, Apatinib, etc. What's more, the recommended platinum drug and taxanes drug for the TP and PF regimens are cisplatin and paclitaxel respectively, but carboplatin\(^{[23]}\), nedaplatin\(^{[24]}\), albumin-bound paclitaxel\(^{[25]}\), paclitaxel liposome\(^{[26]}\), etc. can also be used. It should be noted that for elderly patients over 75 years old, the attending physician adjusts the drug dosage and the chemotherapy regimens based on tolerance levels.

### Table 2

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>cisplatin 25 mg/m(^2) days 1–3 or 75mg/m(^2) day 1 and 5-Fu 600mg/m(^2) day 1–3, q21d</td>
<td>Other platinum can also be used: Carboplatin (AUC = 5, d1), Nedaplatin (80mg/m(^2) day 1), Lobaplatin (50mg/m(^2) day 1) or Oxaliplatin (130mg/m(^2) day 1)</td>
</tr>
<tr>
<td>TP</td>
<td>paclitaxel 135–175 mg/m(^2) day 1 and cisplatin 25 mg/m(^2) days 1–3 or 75mg/m(^2) day 1, q21d</td>
<td>Other taxanes can also be used: Albumin-bound paclitaxel (260mg/m(^2) day 1) or Paclitaxel liposome (135–175 mg/m(^2) day 1). Other platinum mentioned above can also be used.</td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX</td>
<td>Docetaxel 75 mg/m(^2) day 1, q21d</td>
<td>-</td>
</tr>
<tr>
<td>CPT-11</td>
<td>Irinotecan 270mg/m(^2) day 1, q21d</td>
<td>-</td>
</tr>
<tr>
<td>PTX</td>
<td>Paclitaxel 135–175 mg/m(^2) day 1, q21d</td>
<td>Other taxanes can also be used: Albumin-bound paclitaxel (260mg/m(^2) day 1) or Paclitaxel liposome (135–175 mg/m(^2) day 1).</td>
</tr>
</tbody>
</table>

The following patients are defined to be treated with first-line chemotherapy: initially diagnosed as advanced ESCC, recurrent or distant metastatic disease, and those who have not received previous systemic therapy or have progressed ≥ 6 months after neoadjuvant/adjuvant therapy or definitive chemoradiation. The second-line patients are those who have progressed or recurred during previous chemotherapy (including chemoradiation) or within 6 months after the last dose of neoadjuvant/adjuvant therapy associated with first-line chemotherapy.

### Local intervention therapy

In the combined treatment group, the local intervention therapy is recommended to be performed simultaneously with systemic therapy, and if delayed, the latest start time is before the third course of systemic therapy, but the order of treatment is flexibly determined by the attending physician. The local intervention therapy includes radiotherapy, surgery, and ablation, which are executed by different specialists. In the combined treatment group, each distant metastasis necessitates individualized local intervention treatment without rigid constraints on the approach, permitting diverse local intervention treatment modes for different metastases within the same patient, tailored to the specific characteristics of each metastatic site.

### Radiotherapy

If the patient has multiple lesions and the lesions are scattered and cannot be treated in a single radiotherapy course, non-thoracic radiotherapy or SBRT radiotherapy in the thoracic region is administered initially, and the esophageal primary lesion and/or mediastinal regional lymph nodes are treated last. Radiotherapy techniques include IMRT, SBRT, and 2D, and we recommend prioritizing SBRT treatment followed by IMRT and 2D treatments. In thoracic radiotherapy, it is mandated that lung V20 remains below 25%. Recommended radiotherapy techniques and dosages for the oligometastatic lesions are detailed in Table 3. In the event of progression in the baseline lesion during systemic
therapy or radiotherapy, radiotherapy persists while the attending physician determines whether adjustments to systemic therapy are warranted. If new metastases emerge either before initiating radiotherapy or during the radiotherapy course, subsequent treatment decisions are left to the discretion of the attending physician.

**Table 3**

<table>
<thead>
<tr>
<th>Diseased Region</th>
<th>Treatment Modality</th>
<th>Dose of Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>SBRT</td>
<td>Non-peripheral: 48Gy/6Fx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral: 50Gy/10Fx</td>
</tr>
<tr>
<td>Brain</td>
<td>SBRT</td>
<td>Non-brainstem: 24Gy/3Fx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brainstem: 25Gy/5Fx</td>
</tr>
<tr>
<td>Liver</td>
<td>SBRT</td>
<td>48Gy/6Fx</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>SBRT</td>
<td>48Gy/6Fx</td>
</tr>
<tr>
<td>Celiac lymph nodes</td>
<td>SBRT</td>
<td>48Gy/6Fx</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>45Gy/25Fx-50.4Gy/28Fx</td>
</tr>
<tr>
<td>Bone</td>
<td>SBRT</td>
<td>Centrum: 21-27Gy/3Fx or 20-30Gy/5Fx or 12-18Gy/1Fx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-centrum: 30Gy/5Fx or 35Gy/5Fx</td>
</tr>
<tr>
<td></td>
<td>IMRT/2D</td>
<td>30Gy/10Fx</td>
</tr>
<tr>
<td>Oesophagus or regional lymph nodes</td>
<td>IMRT</td>
<td>50.4Gy/28Fx</td>
</tr>
</tbody>
</table>

**Surgery**

The choice of surgical approach rests upon the discretion and skill of the surgeon, adhering to the highest standards of surgical care. While a preference exists for a minimally invasive technique, it is not mandatory. In the context of visceral metastases, the recommended course involves the resection of lesions. In cases of prior extended lymph node dissection or radiotherapy, addressing nodal metastasis involves removing only the suspicious lymph node; otherwise, a salvage extended lymph node dissection is the preferred option when no prior lymph node dissection has been performed. However, for retroperitoneal nodes, only the suspicious node will be excised. In cases where surgical intervention falls short of achieving complete resection, encompassing positive margins or the presence of macroscopic and microscopic residue, subsequent surgery or postoperative radiotherapy becomes imperative.

**Ablation**

Ablation serves as a viable intervention for liver or lung metastases deemed inoperable or when patients opt against surgery or radiotherapy. The criteria stipulate a maximum tumor diameter of \( \leq 5 \) cm for solitary lesions and \( \leq 3 \) cm for multiple lesions within a single organ, limited to a total of three lesions. Notably, tumors positioned close to the esophagus, gastrointestinal tract, or large blood vessels within a distance less than 1 cm, or in the first hepatic hilum, beneath the liver capsule, are not recommended for ablation. Eligibility mandates the exclusion of patients with pacemakers or metal implants, as well as the absence of severe coagulation dysfunction and bleeding tendency. The preferred method entails percutaneous ablation guided by a CT scan, ensuring the radiofrequency electrodes cover both the target tumor and surrounding tissue within 0.5–1 cm of the tumor. It's crucial to recognize that tumors \( \leq 3 \)
cm in diameter can undergo single-session ablation. For tumors ranging from 3 to 5 cm, the recommendation is multipoint radiofrequency ablation or microwave ablation.

**Calculation method of metastatic lesions**

In this study, the genuine oligometastatic population is defined as patients with four or fewer metastatic lesions. The total number of metastatic lesions is the sum of the number of organ metastatic lesions and non-regional lymph node metastatic lesions. For organ metastasis such as in the brain, lungs, liver, bones, etc., each lesion is considered as a separate metastatic lesion. Each non-regional lymph node region is tallied as a metastatic lesion, and esophageal primary lesions and regional lymph nodes are not counted as individual metastatic lesions. However, if an oligometastatic patient presents solely with non-regional lymph node metastasis without any organ metastasis, then, irrespective of the quantity of non-regional lymph node metastases, they are categorized as having genuine oligometastasis. The computation method for the number of lymph node metastases is illustrated below (Fig. 3): Regional lymph nodes are not included in the count of distant metastases, with the upper boundary defined as the entrance of the esophagus and the lower boundary as the trunk of the abdominal artery; Lymph node metastases in the supraclavicular region, upper neck region, and the region below the trunk artery of the abdominal cavity are considered distant metastases; Each non-regional lymph node metastasis is tallied as a metastatic lesion, regardless of the number of lymph nodes within the area.

**Follow up**

Patients will be scheduled for regular clinic follow-ups, occurring every 3 months in the initial 2 years and transitioning to biannual visits for later years. These visits will include imaging, a detailed physical examination, performance status assessment, routine blood work, and the evaluation of treatment-induced toxicity, adhering to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The progression and response of metastatic lesions (excluding bone metastases, unmeasurable disease) will be methodically assessed using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1)\(^{[27]}\), while the progression and response of the esophageal primary lesion will be assessed using the barium examination previously reported\(^{[28]}\).

**Statistical analysis**

The primary efficacy analysis was conducted within the intention-to-treat population, encompassing all randomly assigned participants. Safety evaluation was performed exclusively on randomized subjects who received a minimum of one dose of the investigational treatment. Progression-free survival and overall survival were estimated using the Kaplan-Meier method. Stratified log-rank tests were employed to assess any intergroup disparities in progression-free survival and overall survival. Additionally, an exploratory analysis was undertaken to investigate potential treatment variances among patients classified based on their PD-L1 status.

**Ethics and participating institutions**

This trial has been approved by the Ethics Committee of Fudan University Shanghai Cancer Center and registered in ClinicalTrials.gov with the registration number NCT06190782. Other institutions involved in this clinical trial include (in no particular order): Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine; Changhai Community Healthcare Center; The Second Affiliated Hospital of Guangxi Medical University; Jiangsu Province Cancer Hospital; Xiangtan Central Hospital of Hunan Province; Dongtai People's Hospital of Jiangsu Province; Xiehe Hospital Affiliated to Fujian Medical University; Inner Mongolia Autonomous Region People's Hospital; Jiangyin People's Hospital of Jiangsu Province; The First Hospital of Shanxi Medical University; Anyang Tumor Hospital of Henan Province; Shangxi Province Cancer Hospital; The Affiliated People's Hospital of Ningbo University; Affiliated Hospital of
Jiangnan University; Nantong Cancer Hospital of Jiangsu Province; Guangxi Zhuang Autonomous Region People’s Hospital; Fujian Province Cancer Hospital.

Discussion

The standard treatment for recurrent metastatic esophageal cancer involves chemotherapy combined with immunotherapy or immunotherapy alone[^19], and the question of whether oligometastatic patients benefit from combined local intervention treatment on the basis of anti-PD-1 therapy is still under debate. The ESO-shanghai13 trial[^21] from our team suggested that a combination of local intervention treatment with systemic therapy can be beneficial for selected patients with oligometastatic esophageal squamous cell carcinoma. However, the value of local intervention treatment on the basis of anti-PD-1 therapy for oligometastatic esophageal squamous cell carcinoma still requires larger-scale phase III clinical trials to confirm. Therefore, we designed the ESO-Shanghai20 trial.

In the ESO-Shanghai20 study, some situations need to be explained. When patients require multi-course radiotherapy, non-thoracic radiotherapy and SBRT radiotherapy are conducted initially, instead of IMRT radiotherapy for thoracic lesions. This decision is based on the potential for both immunotherapy and thoracic radiotherapy to induce treatment-related pneumonia, which could impede the execution of subsequent treatment plans and consequently affect patients’ progression-free survival and overall survival. For assessing treatment response, the current gold standard is the image-based Response Evaluation Criteria in Solid Tumors (RECIST v1.1), but the esophageal primary lesion is classified as ‘unmeasurable disease’. However, in ESCC patients, an ‘unmeasurable’ primary tumor is often the largest lesion, and it is necessary to use another method to evaluate the treatment response of the esophageal primary lesion. In this study, the progression and response of the esophageal primary lesion will be assessed using the barium examination[^28,29], regardless of whether or not received radiotherapy. The evaluation criteria are shown below: CR: Disappearance of the mass shadow, no narrowing of the esophageal lumen, and no, or slight, rigidity of the esophageal wall without residual ulceration. PR: Along the longitudinal axis of the esophagus, more than a 50% reduction in the length of the tumor but less than 100% resolution of the disease, a residual shallow ulcer with a diameter of less than 1.5cm, and improvement but not disappearance of the narrowing of the esophageal lumen. SD: Along the longitudinal axis of the esophagus, less than a 50% reduction in the length of the tumor, or regardless of tumor changes, obvious narrowing of esophageal lumen, but no progression. PD: Along the longitudinal axis of the esophagus, more than a 20% increase in the length of the tumor, and a more obvious narrowing of esophageal lumen.

In addition, bone metastases are also considered to be unmeasurable lesions. In this trial, if a patient has only measurable lesions or measurable lesions and bone metastases, only the measurable lesions are evaluated by the RECIST 1.1 standard, and bone metastases are not evaluated. If a patient has only esophageal primary lesion or esophageal primary lesion and bone metastases, only the esophageal primary lesion is evaluated by the barium examination standard, and bone metastases are not evaluated. If a patient has both measurable lesions and esophageal primary lesion, the lesions will be evaluated by the RECIST 1.1 standard and the barium examination respectively, and then the overall response to treatment will be comprehensively evaluated by combining the evaluation results of RECIST and barium examination (Table 4). The Table 4 is organized such that the rows represent the evaluation results of the barium examination, the columns represent the evaluation results of RECIST 1.1, and the intersection cells represent the overall response results. For example, if either the result of barium examination or the result of the RECIST 1.1 is PD, the overall response result is PD. However, only when both the evaluation results of the barium examination and RECIST 1.1 are CR, the overall response result is CR.
Table 4
Results of the overall response to treatment evaluated by combining the results of RECIST1.1 and barium examination.

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>Barium examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
</tr>
<tr>
<td><strong>RECIST 1.1</strong></td>
<td>CR</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>PR</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>SD</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>PD</td>
</tr>
</tbody>
</table>

Furthermore, despite the guidance provided by the ASTRO/ESTRO classification\textsuperscript{[22]}, the definition of oligometastatic esophageal cancer in actual clinical practice remains arbitrary and relies on consensus from expert groups\textsuperscript{[30]}. In this study, a detailed explanation and definition of non-regional lymph node metastatic lesions are presented, which has guiding significance for future researches. If the result of ESO-Shanghai20 shows that the combination of local intervention therapy with anti-PD-1 therapy is safe and promising for patients with oligometastatic esophageal squamous cell carcinoma, this study will provide a basis for the precise stratified treatment of patients with advanced esophageal squamous cell carcinoma.

**Abbreviations**

ESCC
Esophageal squamous cell carcinoma
PFS
Progression free survival
OS
Overall survival
Anti-PD-1
Anti-PD-1 immunotherapy
TPS
Tumor cell Proportion Score
CPS
Combined Positive Score
TAP
Tumor Area Positivity Score
PTX
Paclitaxel
DOX
Docetaxel
CPT-11
Irinotecan
RT
radiotherapy treatment
CR
Complete response
PR
Partial response
SD
Stable disease
PD
Disease progression

**Declarations**

Acknowledgment
Not applicable

Author contributions
KZ and QL conceptualized and designed the study. GM and KZ wrote the main manuscript text, ZX prepared figures 1-2 and QF prepared tables 2-3. HZ, JY, LZ, YH, BX, CC, ZL, XG, XL, XW, JG, ZX, PW, YZ, FZ, CH, QY, JH, SL, JC, YL and QF conducted the study. KZ, QL, GM, ZX, YC, DA, HZ, and SH are responsible for the patient recruitment. All authors reviewed the manuscript.

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Availability of supporting data
Not applicable

Ethics approval and consent to participate
This protocol has been approved by the Ethics Committee of Fudan University Shanghai Cancer Center (2209261-2-2311A) and registered in ClinicalTrials.gov with the registration number NCT06190782.

Consent for publication
Not applicable.

Competing interests
None.

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References


Figures
Figure 1

Treatment design of ESO-Shanghai20. The combined group received a combination of local intervention therapy (radiation, surgery, or ablation) and systemic therapy, and the systemic group received systemic therapy only. R: randomization, RT: radiotherapy treatment, PD-1: anti-PD-1 therapy, anti-PD-1±chemo: anti-PD-1 combined with or without chemotherapy.
Figure 2

The flow chart of ESO-Shanghai20. PFS: progression free survival   OS: overall survival.
Figure 3

Diagram of lymph node metastatic lesions. Each box in the figure represents a non-regional lymph node metastatic lesion, regardless of the number of lymph nodes in the area within the box, and regional lymph nodes do not count as the number of distant metastases.