Scientific Article

Clinical outcomes of intensity modulated proton therapy and concurrent chemotherapy in esophageal carcinoma: a single institutional experience

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Received 2 January 2017; received in revised form 6 June 2017; accepted 7 June 2017

Abstract

Purpose: Intensity-modulated proton therapy (IMPT) is an emerging advanced radiation technique. Although dosimetric studies demonstrate the superiority of IMPT for improving target conformity and reducing unnecessary dose to critical normal tissues, clinical experience is limited. We aim to describe our preliminary experience implementing IMPT concurrently with chemotherapy in esophageal carcinoma (EC).

Methods and materials: From May 2011 through February 2016, 19 patients with EC (median age, 73 years) were treated with IMPT using 180 to 250 MV protons with a median dose of 50.4 Gy relative biological effectiveness in 28 fractions concurrently with chemotherapy. Beam arrangement was most commonly in the posteroanterior and bilateral posterior oblique beams. The Kaplan-Meier method was used to assess survival outcomes. Treatment-related toxicities were evaluated using the Common Terminology Criteria for Adverse Events, version 4.0.

Results: Single-field and multifield optimization was performed in 13 and 6 patients, respectively. The average gross tumor volume was 69.1 cm³; mean lung and heart dose delivered were 4.94 and 7.86 Gy, respectively; and the maximal spinal cord dose was 32.81 Gy. Clinical complete response was achieved in 84%. Only 4 patients underwent surgery. The most common grade 3 acute toxicities were esophagitis and fatigue (3 patients). Grade 3 esophageal stricture occurred in 1 patient. With a median follow-up time of 17 months, overall survival was 39.2 months, with 1-year overall survival, locoregional recurrence-free survival, and distant metastasis-free survival rates of 100%, 88.8%, and 72.9%, respectively. Locoregional and distant failures occurred in 3 and 5 patients, respectively.

Conflicts of interest: S.H.L. has received research grants from Elekta Inc., Hitachi Chemical Inc., Genentech, Peregrine Pharmaceuticals, and STCube Pharmaceuticals and an honorarium from AstraZeneca. All other authors have no conflicts of interest to declare.

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http://dx.doi.org/10.1016/j.adro.2017.06.002
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Conclusions: IMPT is an effective treatment for EC, with high tumor response, good local control, and acceptable acute toxicity.

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Introduction

Radiation therapy (RT) is a mainstay treatment modality for esophageal carcinoma (EC), in addition to chemotherapy and/or surgery. For unresectable or medically inoperable cases, RT could be administered with or without chemotherapy as either definitive or palliative treatment. The primary concern of treatment for EC is toxicity resulting from the proximity to adjacent critical structures such as lung, heart, and spinal cord, which affects dose distribution and leads to suboptimal tumor control or substantial risk of treatment-related toxicities, especially in combination with other modalities. Previous clinical studies reported cardiopulmonary toxicities rates of as high as 29% to 33% in EC patients treated with concurrent chemoradiation and postoperative morbidity and mortality rates of 55% and 11% in those treated with trimodality therapy.

Emerging advanced radiation techniques, including intensity modulated RT (IMRT) and more recently proton therapy, have proven to provide both dosimetric and clinical advantages in EC. Proton beam has the physical advantage of the Bragg peak contributing to lower entrance and exit dose than photon beam. Proton therapy can be delivered by the so-called passive scattering approach (passive scattering proton therapy [PSPT]), which uses the range shifter to modulate the beam range and generate a wider Bragg peak for distal tumor coverage and uses scatterers combined with customized collimators and apertures to shape the beam for lateral spreading. The spread-out Bragg peak, however, was uniformly designed according to the maximal depth of tumor in each particular field, which can lead to proximal excessive dose in irregularly shaped tumors. Unlike PSPT, spot-scanning proton therapy (SSPT) allows modulation of the beam at each individual point of the target volume on a layer-by-layer basis, thus delivering greater conformality to the target and superior normal tissue sparing. SSPT can be performed using the single-field optimization (SFO) or the multifield optimization (MFO) technique; these techniques are known as intensity modulated proton therapy (IMPT). Because of its lower sensitivity to proton range uncertainties and organ motion, SSPT using SFO was generally used, and both SFO and MFO were considered IMPT in our study.

Several dosimetric studies have demonstrated the potential advantages of proton therapy in EC treatment. The first clinical study using PSPT and concurrent chemotherapy in 62 EC patients reported promising outcomes. The potential benefit of IMPT in EC has been studied dosimetrically, and Zeng et al recently reported clinical outcomes in 13 patients treated with trimodality therapy using proton scanning beam. Here we report our initial clinical experience of IMPT with concurrent chemoradiation in EC. We describe the technique, dosimetry, and clinical results, including tumor response, survival outcomes, and toxicity.

Methods and materials

Patients

This retrospective analysis was approved by the institutional review board at MD Anderson Cancer Center. Newly diagnosed patients with esophageal carcinoma who were treated with conventional-dose IMPT with a curative aim were included in this study. A total of 32 patients, most of whom were unresectable and received definitive chemoradiation, enrolled in a simultaneous integrated boost dose escalation trial and were treated with IMPT. After excluding those with reirradiation, incomplete follow-up data, and unconventional dose fractionation, 19 patients were included in this analysis. All patients underwent pretreatment and follow-up evaluation, including esophagogastroduodenoscopy (EGD) with endoscopic ultrasound; positron emission tomography/computed tomography (PET/CT) scans; CT scans of the chest with contrast; metastatic workup; pulmonary function test; and hematologic, liver, and renal function studies. Patients were staged according to the American Joint Committee on Cancer Criteria, 7th edition. Chemotherapy was administered as induction treatment and/or concurrent with radiation.

IMPT

Patients were advised to not take anything by mouth for at least 3 hours before simulation and daily radiation treatment. Four-dimensional (4D) CT simulation was performed in all patients to account for respiratory motion with a slice thickness of 2.5 mm while patients were immobilized in the supine position on a body cradle with a T-bar. For carcinoma of the cervical esophagus, a head-shoulder thermoplastic mask was applied with the patient’s arm by his or her side.

The target volume incorporated the fludeoxyglucose-avid tumor identified on PET/CT scan and EGD/endooscopic
The organs at risk were contoured and MFO plans were used to account for treatment setup variability and was only used for evaluation purposes. The organs at risk were contoured and limited the dose constraints following the institutional protocol.

The Eclipse treatment planning system (Varian Medical Systems Inc., Palo Alto, CA) was used to design the IMPT plans using either the SFO or MFO technique with a uniform plan normalization to provide 99% coverage of the CTV by the prescribed dose. Because SFO plans are usually more robust to set up and include range uncertainty, MFO plans were only used when there were dosimetric benefits. A motion-robust IMPT technique was developed for EC patients. In general, 2 to 3 beams were used for EC IMPT plans. Beam angles were chosen based on water equivalent thickness (WET) analysis, as described by Yu et al. For patients with distal EC, 3 posterior/posterior oblique beams with a beam angle ranging between 150 and 210° usually were used to avoid diaphragm motion. Worst-case robustness evaluation was used, in which the dose distribution was evaluated for 9 dose scenarios simultaneously: the isocenter of the CT images was shifted by ±3 mm along the anteroposterior, left-right, and superoinferior directions, and the relative proton stopping power ratios to water were scaled by ±3.5%. The introduced errors are systematic, and the minimum dose to each voxel in the CTV, along with the maximum dose to each voxel outside of the CTV, were calculated and used to evaluate the robustness of the plan. If the plan was found to be not robust (>5% difference between the nominal plan and worst-case plan), then the plan needed to be optimized. Similarly, the plan was also recalculated on the inhale/exhale phases of the 4D-CT, which represents the extremes of tumor motion. The plan needed to be reoptimized if >5% difference was found between the dose distribution on inhale/exhale CT and the nominal plan.

Clinical endpoints

Clinical outcomes include tumor response, acute and late toxicities, locoregional failure-free survival, distant metastasis-free survival, progression-free survival, and overall survival (OS). Survival outcomes were calculated from the date of diagnosis to the date of death or last follow-up. Tumor responses were evaluated using PET/CT and EGD within 4 months after treatment. Complete response was defined as negative pathology from EGD with biopsy (clinical complete response [cCR]) or less than 1% of viable tumor in surgical specimen (pathological complete response [pCR]). Treatment-related toxicities were scored according to the Common Terminology Criteria for Adverse Events, version 4.0. Acute toxicity was assessed weekly during radiation, and late toxicity was defined as events that occurred or persisted more than 2 months after completion of radiation. Dose-volume histogram data were extracted from the treatment planning software.

Statistical analysis

We used descriptive statistics to report patient and treatment characteristics. The Kaplan-Meier method was used to evaluate survival outcomes. Statistical analysis was performed using SPSS, version 22.0.0 (IBM, Armonk, NY).

Results

Patients and treatment

Between May 2011 and February 2016, the medical records of 19 patients with EC were reviewed. The median age was 73 years (range, 51-87). The majority of patients were male (89.5%) and had adenocarcinoma (63.2%) and EC of the lower esophagus or gastroesophageal junction (63.2%). Most patients were stage 3 (52.6%), and 2 patients (10.5%) initially presented with metastatic disease. Total radiation dose varied from 41.4 to 50.4 Gy (relative biological equivalence [RBE]) in 23 to 28 fractions. Four patients received simultaneous integrated boost (SIB) with different GTV/PTV doses, including 41.4/46 Gy in 23 fractions in 1 patient who had prior mediastinal irradiation for seminoma, 45/50 Gy in 25 fractions in 1 patient, and 63/50.4 Gy in 2 patients according to the SIB dose escalation trial. Most patients received 5-flourouracil (5-FU)–based chemotherapy concurrently with radiation treatment. The most common concurrent chemotherapy regimen was docetaxel and 5-FU or capecitabine (73.7%). Other regimens were carboplatin plus paclitaxel (n = 4) or carboplatin plus 5-FU (n = 1). Induction chemotherapy was administered in 8 patients with oxaliplatin and 5-FU or capecitabine with (n = 2) or without (n = 6) docetaxel. Patient demographics, tumor characteristics, and treatment details are listed in Table 1, and a dose-volume histogram analysis of all IMPT plans is given in Table 2. SIB was successfully achieved by both SFO and MFO techniques, as depicted in Fig 1.

Tumor response and patterns of failure

Of the 19 patients, 16 (84.2%) achieved cCR of the primary disease. Among 4 patients who underwent esophagectomy, 2 achieved pCR of the primary disease but 1 had a residual lymph node. One patient had 30%...
residual disease, and the other was deemed unresectable after discovery of peritoneal carcinomatosis intraoperatively.

At last follow-up, there were 7 disease failures: 2 local, 1 locoregional and distant, and 4 distant failures. The 3 locoregional failures (15.8%) were in-field recurrences, and none of these patients had surgery after CRT. Median time to locoregional and distant failures were 7.9 months (range, 1.3-16.3) and 2 months (range, 2-4.1), respectively. Of 2 patients with isolated local recurrence, 1 underwent salvage surgery; the other refused surgery, but the patient’s disease remained stable for 10.3 months. For the total 5 distant failures, chemotherapy was administered in 3 patients for pulmonary and omental metastases. A patient with brain metastasis was treated by tumor resection followed by whole brain radiation.

Survival outcomes

By the time of analysis, there were 5 deaths: 3 patients died from disease progression, 1 died without disease, and the other had an unknown cause of death. With a median follow-up of 17 months from diagnosis, the 1-year OS and estimated 2-year OS rates were 100% and 87.5%, respectively, with a median OS of 39.2 months (95% confidence interval, 29-49.5). Estimated 2-year OS, progression-free survival, LRFS, and distant metastasis-free survival rates were 87.5%, 50.6%, 74%, and 72.9%, respectively.

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**Table 1**  Patient and tumor characteristics (N = 19)

| Characteristics                          | No. of patients (%) |
|------------------------------------------|---------------------|
| Sex                                      |                     |
| Male                                     | 17 (89.5)           |
| Female                                   | 2 (10.5)            |
| Age, median (range)                      | 73 (51-87) y        |
| Race                                     |                     |
| White                                    | 16 (84.2)           |
| African-American                         | 1 (5.3)             |
| Hispanic                                 | 2 (10.5)            |
| ECOG, median (range)                     | 1 (0-1)             |
| Histology                                |                     |
| Adenocarcinoma                           | 12 (63.2)           |
| Squamous cell carcinoma                  | 7 (36.8)            |
| Differentiation                          |                     |
| Moderately differentiated                | 7 (36.8)            |
| Poorly differentiated                    | 11 (57.9)           |
| Unknown                                  | 1 (5.3)             |
| Initial disease stage (AJCC, 7th edition)|                      |
| IA                                       | 1 (5.3)             |
| IB                                       | 1 (5.3)             |
| IIB                                      | 5 (26.3)            |
| IIIA                                     | 3 (15.8)            |
| IIIB                                     | 4 (21)              |
| IIIC                                     | 3 (15.8)            |
| IV                                       | 2 (10.5)            |
| Tumor location                           |                     |
| Upper/cervical                           | 3 (15.8)            |
| Mid                                      | 4 (21)              |
| Distal/GEJ                              | 12 (63.2)           |
| Tumor length, median (range)             | 4.0 (1-9) cm        |
| Treatment                                |                     |
| Definitive RT/CCRT                       | 15 (79)             |
| Preoperative CCRT followed by surgery    | 4 (21)              |
| Induction chemotherapy                   | 8 (42.1)            |
| Proton dose, median (range)              | 50.4 CGE (41.4-50.4)|
| Proton fraction, median (range)          | 28 fractions (23-28)|
| Proton therapy technique                 |                     |
| Single-field optimization                | 13 (61.9)           |
| Multifield optimization                  | 6 (31.6)            |

AJCC, American Joint Committee on Cancer Criteria; CCRT, concurrent chemoradiation; CGE, cobalt Gy equivalence; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; RT, radiation therapy.

**Table 2**  Dosimetric data of intensity modulated proton therapy in esophageal carcinoma treatment

| Parameters                          | All (mean ± SD) |
|-------------------------------------|-----------------|
| Target                              |                 |
| GTV Volume (mL)                     | 69.10 ± 48.59   |
| Mean dose (CGE)                     | 54.28 ± 4.11    |
| Minimal dose (CGE)                  | 51.57 ± 3.70    |
| Maximal dose (CGE)                  | 57.06 ± 4.26    |
| PTV Volume (mL)                     | 570 ± 257.47    |
| Mean dose (CGE)                     | 52.51 ± 2.66    |
| Minimal dose (CGE)                  | 37.80 ± 7.44    |
| Maximal dose (CGE)                  | 57.87 ± 4.13    |
| Organs at risk                      |                 |
| Lung                                |                 |
| Mean dose (CGE)                     | 4.94 ± 2.31     |
| V5 (%)                              | 20.88 ± 9.94    |
| V10 (%)                             | 15.61 ± 7.38    |
| V20 (%)                             | 9.45 ± 4.94     |
| V30 (%)                             | 5.49 ± 2.96     |
| V40 (%)                             | 3.20 ± 2.11     |
| V50 (%)                             | 1.34 ± 1.18     |
| Heart                               |                 |
| Mean dose (CGE)                     | 7.86 ± 5.04     |
| V10 (%)                             | 22.24 ± 13.81   |
| V20 (%)                             | 15.12 ± 9.96    |
| V30 (%)                             | 10.83 ± 7.90    |
| V40 (%)                             | 7.43 ± 5.93     |
| V50 (%)                             | 3.48 ± 3.58     |
| Liver                               |                 |
| Mean dose (CGE)                     | 2.20 ± 2.22     |
| V10 (%)                             | 9.02 ± 4.64     |
| V20 (%)                             | 6.38 ± 3.92     |
| V30 (%)                             | 4.17 ± 3.41     |
| V40 (%)                             | 3.47 ± 2.87     |
| V50 (%)                             | 1.95 ± 1.86     |
| Spinal cord                         |                 |
| Maximal dose (CGE)                  | 32.81 ± 12.64   |

GTV, gross target volume; PTV, planning target volume; SD, standard deviation; V10, V20, V30, V40, V50, percentage of volume receiving 10, 20, 30, 40, 50 CGE, respectively. Other abbreviations as in Table 1.
Treatment-related toxicities

Severe toxicities were limited to no more than grade 3-4, with acute esophagitis (n = 3), fatigue (n = 3), nausea (n = 2), and hematologic toxicity (n = 2) being the most common. There were no cases of radiation pneumonitis. Two patients had more than a 5% weight loss (grade >1). Esophageal stricture requiring dilatation (grade 3) occurred in 1 patient who received an SIB regimen with a dose of 63 Gy to the GTV. One patient developed postoperative complications, including atrial fibrillation and bowel ileus, but fully recovered. Table 3 shows treatment-related toxicities according to Common Terminology Criteria for Adverse Events, version 4.0, criteria.

Discussion

To the best of our knowledge, the present study is the largest reported clinical experience of using IMPT concurrently with chemotherapy in the treatment of EC. High local tumor control and survival outcomes were achieved with acceptable toxicities. The majority of patients (84%) had CCR within 4 months after treatment; 88.8% and 72.9% had locoregional and distant control at 1 year. There were no treatment-related deaths.

Proton therapy in combination with chemotherapy was an encouraging treatment for EC. Several dosimetric studies demonstrated the advantages of proton therapy over photon therapy in EC.6-9,11 Ling et al showed significant benefits for normal tissue sparing of PSPT in comparison to 3-dimensional CRT and IMRT plans, including 10 patients with EC with mean lung, heart, and liver doses of 6.0, 12.6, and 3.6 Gy, respectively, in proton plans.9 Wang et al reported similar mean lung and heart doses of 6.0 and 15.2 Gy, respectively, in the PSPT plan and concluded that advanced radiation techniques such as IMRT and proton therapy significantly reduced postoperative pulmonary complications compared with 3-dimensional CRT.

Table 3 Acute and late treatment-related toxicities according to group of treatment

| Toxicity                        | No. of patients |
|---------------------------------|-----------------|
| Acute toxicity grading          | 1  2  3  4  5   |
| Gastrointestinal complication   |                |
| Esophagitis                     | 4  9  3  0  0   |
| Nausea/vomiting                 | 7  2  2  0  0   |
| Fatigue                         | 5  5  3  0  0   |
| Anorexia                        | 2  1  1  0  0   |
| Weight loss                      | 8  2  0  0  0   |
| Hematologic complication        | 9  5  1  1  0   |
| Radiation dermatitis            | 4  4  1  0  0   |
| Late toxicity grading           | 1  2  3  4  5   |
| Pulmonary complication          |                |
| Radiation pneumonitis           | 0  0  0  0  0   |
| Pleural effusion                 | 3  0  1  0  0   |
| Cardiac complication            |                |
| Cardiac arrhythmia              | 1  1  0  0  0   |
| Pericardial effusion             | 0  1  0  0  0   |
| Esophageal complication         |                |
| Esophageal stricture            | 2  0  1  0  0   |
lower mean lung dose distribution. With more complicated plans using IMPT, Welsh et al demonstrated the potential dose escalation to the tumor with considerable reductions to the normal organs using 2 to 3 fields of IMPT using the SFO technique. The study revealed that the best plan could lead to a mean lung dose of 3.18 Gy and mean heart dose of 11.9 Gy. Our dose-volume histogram data also showed consistent results with mean lung and heart doses of 4.94 and 7.86 Gy, respectively, which emphasized the key benefit of IMPT in normal tissue sparing. Spinal cord maximum dose in our study was similar to that in a study using PSPT in 62 patients with EC with a cord maximum dose of 31.3 Gy and was better than a 44.5 Gy single PA approach using scanning beam. Additionally, IMPT provided a target dose that was comparable to that of PSPT plans. The mean dose to GTV and PTV was 54.3 and 52.5 Gy, respectively, in our study versus 53.3 and 52.9 Gy, respectively, in the PSPT study.

With the standard radiation dose of 50.4 Gy RBE in 28 fractions combined with 5-FU and taxane-based chemotherapy for either definitive or preoperative treatment, a 3-year OS of 51.7% to 70% was reported with PSPT. Hashimoto et al investigated the clinical outcomes of definitive proton therapy with a dose of 60 Gy RBE in 30 fractions concurrently with cisplatin and 5-FU in 14 patients with EC. One-year local control and OS rates were 90% and 93%, respectively, which were comparable with our results of 88.8% and 100%, respectively. Subsequently, Ishikawa et al presented updated results in 40 patients with 2-year locoregional control and OS rates of 66% and 75%, respectively, and a cCR rate by CT and EGD of 50%. Although the majority of our patients received definitive concurrent chemoradiation with a relatively lower dose (50.4 Gy), we demonstrated slightly better outcomes with estimated 2-year LRFS and OS of 74% and 87.5%, respectively, and a cCR of 84%. The differences in tumor histology (100% squamous cell carcinoma in Ishikawa’s study versus 37% SCCA in our study) and location (83% upper/mid-esophagus in Ishikawa’s study vs 37% in our study) should be taken into account, however. Additionally, our study was limited because of the small number of patients and short follow-up duration.

This promising outcome after proton therapy was better than historical data using conventional RT for EC, with a 2-year OS of only 40%, despite dose escalation and was comparable to IMRT data. Nonetheless, avoiding treatment-related toxicity is crucially important in EC treatment in terms of treatment compliance and patients’ quality of life. Retrospective data reported acute grade ≥2 nausea rates of 29% to 34% in patients with EC who were treated with PSPT versus similar or slightly lower (21%) rates in our study, despite a similar chemotherapy regimen. A plausible explanation could be a lower stomach dose from the IMPT. In PSPT, 1 left lateral oblique beam traverses through the stomach at low dose, but this is not seen for the 2 posteriorly placed beams in IMPT. A greater benefit could be observed in a larger study with longer follow-up. Recently, Zeng et al studied the clinical outcomes of 13 patients with EC treated with trimodality therapy using proton therapy (8 uniform scanning and 5 pencil beam scanning with a single PA beam and an SFO plan). They reported a pCR rate of 25% with 30.8% grade 2-3 nausea.

Nevertheless, the proton beam is very sensitive to heterogeneous tissue density along its path; thus, in the thoracic region, the motion interplay effect between the moving tumor and the scanning IMPT beam is of critical concern. Apart from using the 4D-CT simulation to account for respiratory motion, selection of beam direction and robust plan optimization also play an important role. The motion-robust IMPT study demonstrated that the ΔWET caused by the direction of the implemented beam resulted in dose deviation in the treatment of distal esophageal cancer. It was suggested that the ΔWET technique could be used to define the beam angles that were least affected by respiratory motion. Welsh et al revealed that the anteroposterior/posteroanterior field provided the lowest lung dose parameters; the left postero-oblique (LPO)/right postero-oblique RPO field ultimately reduced the cardiac dose; and the anteroposterior/LPO/RPO field offered the benefit for lung, heart, liver, and spinal cord. Unique dosimetric advantages indicated a method to select the optimal beam arrangement based on tumor characteristics and patients’ comorbidities; for example, the anteroposterior/posteroanterior field or LPO/RPO field might be considered in those who had increased risk of pulmonary or cardiac complications, respectively. In our experience, the appropriate beam direction was tailored by tumor location and based on the ΔWET technique. For example, the anterior beams were selected in tumors of the upper esophagus to avoid the spinal cord, whereas posterior oblique beams were more suitable for mid and lower esophagus to avoid the heart anteriorly. After the plan was generated, a robustness evaluation and motion evaluation using a 4D-CT data set could provide valuable information regarding how the plan would behave with different uncertainties, including respiratory motion, range, and setup uncertainties.

A limitation of this study included the small number of patients and a relatively short follow-up period that would not allow study of late toxicities. Additionally, because of its retrospective nature, heterogeneity of treatment modality inevitably existed; thus, we will continue to prospectively conduct confirmatory studies in larger populations with longer-term evaluation to clearly demonstrate the benefit of IMPT in EC.

Conclusions

Our initial experience of using IMPT at a dose level of 41.4 to 50.4 Gy (1.8-2 Gy/fraction) and concurrent chemotherapy indicates that it is feasible and effective in the treatment of EC as either preoperative or definitive treat-
ment with excellent local tumor control and overall survival and acceptable toxicity. The benefit of maximal sparing of surrounding normal organs has translated into few acute and subacute complications and should translate to minimal late-term toxicities as well; however, a larger number of patients and a longer follow-up period are necessary to further evaluate the long-term treatment outcomes.

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