

Original Article

Survival outcomes and safety of adding high-dose-rate intraluminal brachytherapy (HDR-ILBT) utilizing the novel balloon applicator (BRAXX) following concurrent chemoradiotherapy (CCRT) for non-surgical esophageal cancer: a prospective pilot and real-world comparative study

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Abstract: To investigate the local control and safety of adding high-dose-rate intraluminal brachytherapy (HDR-ILBT) with novel balloon applicator (BRAXX) after concurrent chemoradiation (CCRT) for non-surgery patients with esophageal cancer. The study enrolled 178 patients with esophageal cancer. A total of 13 patients were prospectively recruited to receive HDR-ILBT after CCRT and compared with two standard-of-care cohorts treated between 2022 and 2024. Brachytherapy was delivered via the BRAXX balloon applicator (Taiwan Food and Drug Administration approval No. 006603) using an Iridium-192 Nucletron remote afterloading system (Elekta, Stockholm, Sweden). The primary endpoint was freedom from local tumor recurrence (FFLTR). Secondary endpoints included overall survival (OS), disease progression-free survival (DPFS), and toxicities. Sankey diagrams and swimmer plot were utilized to visualize the longitudinal tumor response dynamics and individual survival trajectories. The median follow-up was 25.2 months. The 1-year and 2-year FFLTR rates were 93.3% and 81.2% (nCCRT + surgery), 84.6% and 67.7% (CCRT + ILBT), and 62.5% and 52.9% (dCCRT alone), respectively ($P < 0.001$). Consistent survival improvements were observed in both OS and DPFS in CCRT + ILBT cohort. Sankey diagrams demonstrated a favorable dynamic evolution in treatment response within the CCRT + ILBT cohort, achieving a clinical complete response (cCR) rate of 61.5% and overall response rate (ORR) of 69.2% at the end of per-protocol 1-year follow-up. Swimmer plot illustrated that response conversion and consolidation translated into long-term survival. The addition of HDR-ILBT did not exacerbate treatment-related esophageal strictures or fistula formations necessitating intervention. The addition of HDR-ILBT utilizing BRAXX applicator following CCRT is a feasible and promising strategy to enhance local control and prolong survival for non-surgical patients with esophageal cancer. By leveraging its distinct dosimetric advantages and streamlined workflow, ILBT holds the potential to consolidate disease-free status and eradicate residual disease. Further validation through large-scale, prospective clinical trials is still warranted to confirm its clinical benefit and long-term safety. If further validated, this strategy could offer a meaningful addition to the current treatment paradigm.

Keywords: BRAXX applicator, concurrent chemoradiotherapy, esophageal cancer, intraluminal brachytherapy, iridium-192, local control, real-world comparative study

Introduction

Esophageal cancer remains a lethal gastrointestinal malignancy globally, with an estimated

511,000 newly diagnosed cases and 445,000 mortalities reported annually [1]. Esophageal squamous cell carcinoma accounts for approximately 85% and adenocarcinoma represents

14% of cases, both pathohistological subtypes posing a formidable burden on public health [2]. For patients with locally advanced disease, neoadjuvant concurrent chemoradiotherapy (nCCRT) followed by radical esophagectomy is widely recognized as an optimal standard therapeutic approach [3, 4]. The CROSS trial, evaluating neoadjuvant carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions) and followed by surgery, demonstrated a significant prolongation of median overall survival (OS) compared to surgery alone (48.6 vs. 24.0 months). Notably, this benefit was particularly outstanding in the squamous cell carcinoma subgroup, which achieved a pathologic complete response (pCR) rate of 49% and a median OS of 81.6 months [5]. Similar findings were corroborated with squamous cell carcinoma population in Asia by the NEOCRTEC5010 trial, which demonstrated a pCR rate of 43.2% and a significant improvement in nCCRT and surgery cohort with superior five-year OS (59.9% versus 49.1%) and five-year disease-free survival (63.6% vs. 43.0%) compared to surgery alone cohort [6]. These landmark trials shape the foundation of the current standard of care for patients with esophageal cancer.

Although esophagectomy provides superior locoregional control and improved survival, invasive surgery is associated with several perioperative morbidity and mortality [7, 8]. One of the most debilitating complications - anastomotic strictures after surgery - afflict approximately 18.4 to 27.2% of patients, with the incidence surging to 49.8% in cervical anastomosis [9, 10]. The permanent anatomical alterations and long-term sequelae will profoundly compromise patients' quality of life [11]. For instance, these patients may suffer from life-long dysphagia, requiring a median of 4 times (in intra-thoracic anastomosis cases) and 7 times (in cervical anastomosis cases) repeated endoscopic dilations for symptom resolution [9]. Alarming, up to 61% of patients undergoing esophagectomy are at risk of developing recurrent and refractory stenosis, trapping these patients in a protracted cycle of repeated endoscopic interventions [12]. From another clinical aspect, surgical management is not always feasible, as evidence indicates that 14.1% to 33.3% of patients failed to undergo planned esophagectomy after nCCRT [13-15]. Several reasons account for the limitation of surgical candidacy, such as older age, poor perfor-

mance status, irresectability of tumor, advanced nodal disease, presence of multiple comorbidities, patient refusal, or interval disease progression or mortality before surgery [13-16]. To address the therapeutic gap, the American Society of Clinical Oncology (ASCO) guidelines recommend definitive concurrent chemoradiotherapy (dCCRT) as the alternative treatment for patients who are medically inoperable or decline surgery [17]. Furthermore, the National Comprehensive Cancer Network (NCCN) guidelines also mandate a radiation dose escalation to 50-50.4 Gy, superseding the standard pre-operative regimen of 41.4 Gy for non-surgical patients [18].

However, sole reliance on dCCRT introduces significant clinical trade-offs. Patients treated with dCCRT alone without surgery experience significantly lower two-year local control rates compared to those undergoing surgery (57.0% vs. 66.4%). Additionally, the deterioration of swallowing function with nearly half (46.2%) of patients underwent dCCRT requiring repeated endoscopic dilations or esophageal stent placements to manage dysphagia [19, 20]. To overcome this clinical dilemma for non-surgical patients, it is imperative to develop a safe and proactive strategy that bridge the locoregional control gap between surgical and non-surgical cohorts while enhancing primary tumor eradication. Intraluminal brachytherapy (ILBT), first introduced for esophageal cancer in the 1920s, has paved a novel therapeutic avenue for this disease [21]. Owing to its dosimetric advantage of a rapid dose fall-off beyond the target volume, brachytherapy delivers a highly conformal radiation dose to the esophageal tumor while sparing surrounding critical structures [22, 23]. Building upon this foundation, ILBT has emerged as a promising dose-escalation and consolidative strategy for the non-surgical population, aiming to achieve complete tumor eradication without compounding normal tissue toxicity. However, evidence comparing this approach with the current standard-of-care remains limited. Therefore, this prospective study, incorporating contemporaneous real-world standard-of-care cohorts, aims to evaluate the survival outcomes and safety of adding the high-dose-rate intraluminal brachytherapy (HDR-ILBT) using the novel BRAXX balloon applicator in patients with esophageal cancer who received CCRT and were not candidates for surgery.

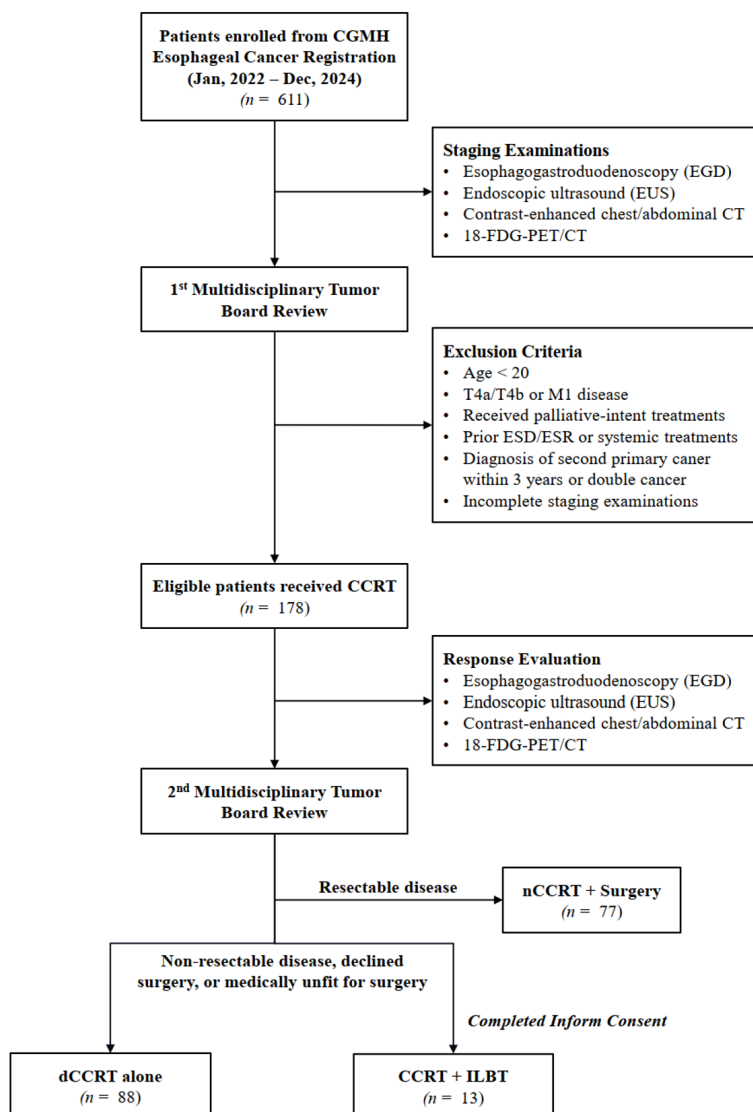


Figure 1. Flow diagram of patient selection and allocation.

Methods

Patient selection

Patient selection and allocation are illustrated in **Figure 1**. We reviewed 611 patients diagnosed with esophageal cancer at Chang Gung Memorial Hospital, Linkou branch, between January 2022 and December 2024. Exclusion criteria included: (1) Age < 20 years, (2) T4a-b or M1 (non-nodal organ involvement) disease or receiving palliative-intent treatment, (3) Prior endoscopic submucosal dissection (ESD) or endoscopic submucosal resection (ESR) or systemic treatment, (4) Second primary cancer within three years or double cancer at diagno-

sis, or (5) Incomplete staging examination. Initial clinical staging was assessed through first review of multidisciplinary tumor board (MTB) by esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), contrast-enhanced chest/abdominal computed tomography (CT), and 18-FDG-PET/CT. Finally, a total of 178 patients were eligible for the study.

Treatment protocol and allocation

Patients' allocation and management adhered strictly to our institutional protocols under the supervision of the multidisciplinary esophageal cancer registry (**Figure 1**). Following the first MTB review, all 178 patients received CCRT as their initial treatment with curative intent. External beam radiotherapy was delivered using Volumetric modulated arc therapy (VMAT) or Intensity modulated proton therapy (IMPT) at a dose ranging from 4500 to 5040 cGy(E) in 25 to 28 fractions. Concurrent chemotherapy regimens consisted predominantly of either carboplatin plus paclitaxel or cisplatin plus 5-fluorouracil (5-FU).

Treatment response was evaluated by a second MTB review to determine surgical candidacy. Response evaluation examinations, including EGD/EUS, contrast-enhanced chest/abdominal CT, and 18-FDG-PET/CT, were performed 5 to 6 weeks after the completion of initial CCRT. Patients were further allocated into surgical and non-surgical cohorts based on tumor resectability, medical fitness, and patient preference after the second MTB consensus. The surgical cohort (n = 77) proceeded to undergo esophagectomy and the resected specimens were examined by experienced pathologists. For the non-surgical cohort (n = 101), a total of 13 patients were prospectively enrolled to receive HDR-ILBT and all of them completed the consolidative CCRT -

comprising RT dose of 1800 to 2000 cGy(E) in 10 fractions with concurrent chemotherapy - to achieve a curative radiation dose prior to brachytherapy since all 13 patients received 45Gy(E)/25fx in the initial CCRT course. The remaining 88 patients, who declined trial enrollment, underwent either consolidative CCRT or observation based on clinical condition, constituting the dCCRT alone cohort.

High-dose-rate intraluminal brachytherapy protocol

The HDR-ILBT procedure was performed within two weeks after the completion of consolidative CCRT. The BRAXX balloon applicator (approved by Taiwan Food and Drug Administration; TFDA; License No. 006603) was utilized to enhance therapeutic efficacy and minimize complications by centering the radiation source within the esophageal lumen. Treatment was delivered using a Nucletron remote afterloading system (Elekta, Stockholm, Sweden) with an Iridium (Ir)-192 radioactive source. The gross tumor volume (GTV) was defined based on the pre-treatment longitudinal length of the primary tumor. The prescribed dose ranged from 5 to 10 Gy delivered in 1 to 2 fractions (12 patients received 5 Gy in 1 fraction; 1 patient received 10 Gy in 2 fractions). Balloon inflation establishes a source-to-surface distance of 6 to 9 mm, ensuring direct mucosal contact. In accordance with our institutional ILBT protocol, a prescribed dose of 5 Gy delivered at a depth of 3 mm from the inflated balloon surface generally provided adequate dosimetric coverage of the esophageal wall. However, due to inter-patient variations in esophageal wall thickness and surrounding anatomical structures, this prescription depth was dynamically tailored by the radiation oncologist. To ensure precise dose delivery, the target volume was re-contoured for every patient based on an on-site planning CT simulation acquired immediately prior to the procedure. To optimize target accuracy, initial staging 18F-FDG PET/CT images were also integrated to better delineate the tumor extent. This real-time adaptive process ensured comprehensive dosimetric coverage of the entire esophageal mucosa while strictly avoiding adjacent organs at risk. All target delineations were independently verified by a second radiation oncologist. Dose-volume histogram (DVH) parameters of the GTV for the 13 patients in the HDR-ILBT cohort are detailed in [Supplementary Table 2](#). Regarding normal

organ dose constraints, our primary safety measure mandated that no hot spots receiving $\geq 100\%$ of the prescribed dose were permitted on the bronchus or aorta to prevent aortic rupture or tracheoesophageal (TE) fistula formation. For other critical structures, including the lungs, spinal cord, and heart, dose limits were not routinely applied. Since Ir-192 exhibits a highly rapid dose fall-off within a few millimeters governed by the inverse square law, the dosimetric contribution to these structures from radioactive source was clinically negligible given their relatively greater anatomical distances. The protection of these structures and the minimization of additional dose were achieved through spatial avoidance, careful optimization of applicator positioning, and precise target delineation. Finally, concurrent chemotherapy was not allowed on the week of brachytherapy.

The entire procedure was performed by an experienced multidisciplinary team - comprising at least two radiation oncologists, a specialized oncology nurse, and a senior radiation therapist - to coordinate applicator placement, treatment planning, dose delivery, and the management of acute adverse effects. To ensure procedural success, patient tolerance was pre-assessed via a test placement using a nasogastric tube, and patient was required to remain fasted for 6 to 8 hours prior to the brachytherapy. To minimize esophageal spasms and patient discomfort, local anesthesia was achieved by spraying lidocaine onto the pharyngeal mucosa before and after applicator insertion. Prior to applicator placement, each balloon was inflated and then fully deflated with a 10-mL syringe to verify structural integrity (**Figure 2A, 2B**). The applicator was straightened and a 5- or 6-Fr Lumencath was carefully inserted into the central source channel to the distal end, followed by the insertion of a dummy source for radiographic localization (**Figure 2C-E**). The applicator was coated with lubricating jelly and gently inserted transnasally to the target depth by the radiation oncologist (**Figure 2F**). At least three balloons (typically balloon No. 2-4) were gently inflated for fixation, ensuring applicator stability and source centralization (**Figure 2G**). A CT simulation was performed to verify the applicator position, and necessary adjustments were allowed using the dummy source as a reference (**Figure 2H**). GTV delineation was performed by the radiation oncologist and treatment planning was conducted by the

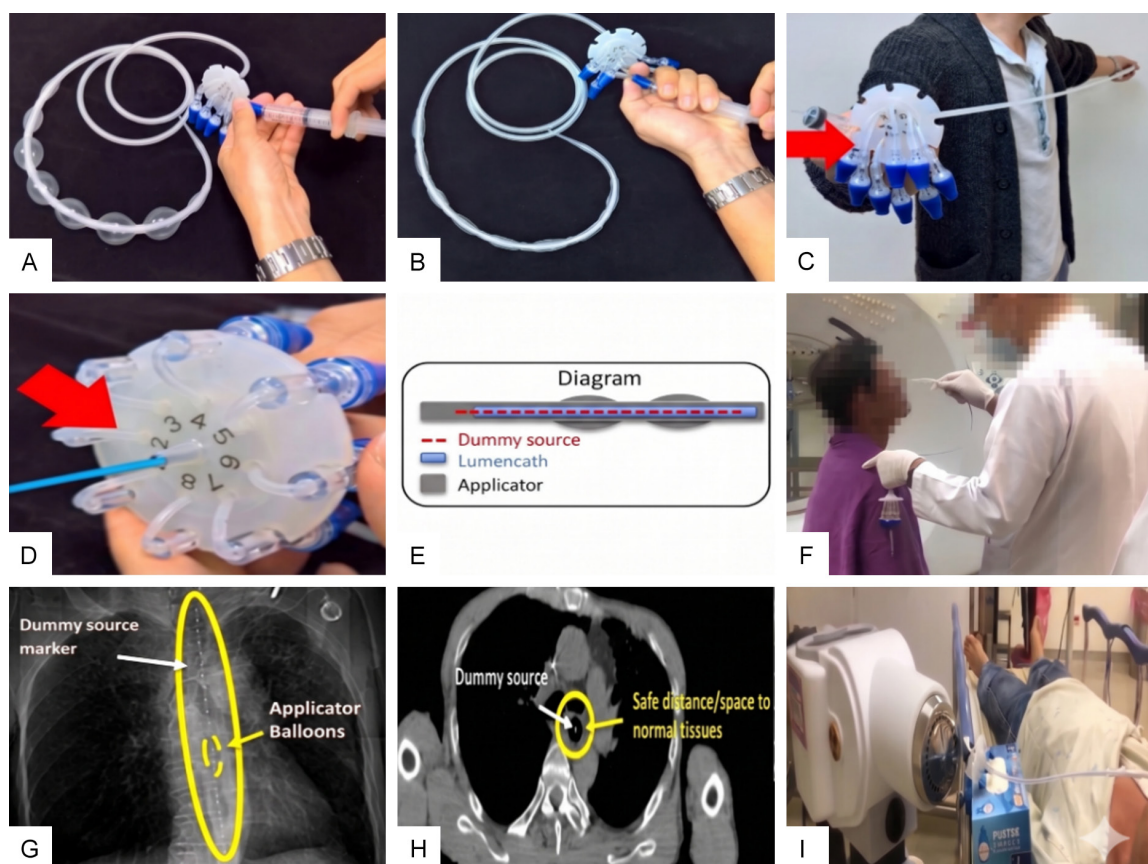


Figure 2. Workflow for HDR-ILBT using the BRAXX applicator. A, B. Applicator Functional Assessment (Inflation & Deflation): Prior to placement, the physician uses a 10-mL syringe to inflate each balloon to verify its structural integrity. All balloons are then fully deflated, returning them to a flattened state. C. Applicator Straightening: The applicator is straightened to avoid bending or kinking during the insertion of the Lumencath and dummy source. D. Lumencath and Dummy Source Insertion: A 5- or 6-Fr Lumencath is carefully inserted into the central channel (indicated by the red arrow) and advanced to the distal end, followed by the insertion of a dummy source for radiographic localization. E. Internal Structure Diagram: A cross-sectional diagram illustrates the dummy source (red dashed line) positioned within the Lumencath (solid blue), housed inside the main applicator (solid gray). F. Transnasal Insertion Maneuver: The prepared applicator (containing Lumencath and Dummy source) is coated with lubricating jelly and gently inserted transnasally to the target depth. G. Balloon Inflation and Fixation: After inflating balloons (typically No. 2-4), a 2D image is obtained to confirm the centralization of the applicator within the esophageal lumen. H. CT Simulation and Treatment Planning: A CT simulation is performed to confirm the accurate position of the applicator. The applicator position can be adjusted accordingly and repeat CT scan to verify. The radiation oncologist then delineated the gross tumor volume (GTV). I. Treatment Delivery: After removing the dummy source and the completion of treatment planning, the applicator is connected to the Nucletron remote afterloading system for treatment delivery.

senior radiation therapist. Patient remained in a supine position and the total treatment time was approximately 10-15 minutes (**Figure 2I**). Upon treatment completion, the balloons were deflated and the applicator was smoothly removed. After an observation period to ensure the absence of acute complications, patients were discharged with a scheduled outpatient follow-up.

Study endpoints

The primary endpoint was freedom from local tumor recurrence (FFLTR), defined as the time

interval from the first day of radiotherapy (RT) to the date of objectively confirmed local recurrence at the primary tumor site. Patients who died without evidence of local primary tumor recurrence or remained alive and recurrence-free were censored at the date of death or last clinical follow-up. Secondary endpoints included overall survival (OS), disease progression-free survival (DPFS), and toxicities. OS was defined as the duration from the initial day of RT until death from any cause, with surviving patients censored at the date of last follow-up. DPFS was defined as the time from the first day of RT to the earliest documented objective

evidence of disease progression (including locoregional, or distant failure) or death from any cause. Patients who remained alive and disease-free were censored at the date of last clinical follow-up. Acute and late toxicities were systematically evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Clinical tumor response was categorized as clinical complete response (cCR), clinical partial response (cPR), clinical stable disease (cSD), or clinical progressive disease (cPD) in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [24]. After the initial CCRT, cCR was objectively confirmed through a formal MTB consensus, based on the comprehensive evaluation of PET/CT, contrast-enhanced CT, and EGD/EUS with biopsy. Following the completion of the intended therapies, a sustained cCR was confirmed at the 1-year follow-up milestone. This required an assessment demonstrating no residual mass on contrast-enhanced CT and/or the complete absence of malignant cells on EGD with biopsy. The overall response rate (ORR) was defined as the proportion of patients who achieved either cCR or cPR at the end of 1-year follow-up.

Post-treatment surveillance

Following the completion of all intended treatments, post-treatment surveillance was conducted according to our institutional protocol. EGD with biopsy was performed at months 3, 6, 9, and 12 at first year post-treatment and these quarterly endoscopic examinations were performed by senior gastroenterologists, who obtained biopsies from any suspicious sites and submitted them for definitive pathological evaluation. Concurrently, contrast-enhanced CT scans were performed at months 6 and 12 during the first-year post-treatment and all CT imaging was systematically reviewed and interpreted by senior radiologists. To ensure the reliability and durability of the observed clinical outcomes, all patients were required to complete a minimum of a 1-year per-protocol follow-up, unless regular surveillance was prematurely terminated due to documented disease progression or mortality. Unscheduled diagnostic workups (e.g., PET/CT, chest radiography, laboratory examinations) based on clinical judgment were initiated for any patient presenting with symptoms suspicious for disease progression or recurrence. Outpatient clinic visits were

scheduled every 3 months during the first two years. Subsequently, the visit frequency was adjusted to 4- to 6-month intervals, gradually transitioning to annual follow-ups thereafter.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQRs), and categorical variables were presented as counts and percentages. Time-to-event analyses were conducted using the Kaplan-Meier method, and comparisons were made using the log-rank test. A pairwise log-rank test was utilized for post-hoc analyses between different groups, with the significance threshold adjusted using the Bonferroni correction to a P -value < 0.0167 . The comparison of toxicities was evaluated using Fisher-Freeman-Halton exact test and baseline characteristics were assessed with Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. For data visualization, Sankey diagrams were constructed to map the dynamic transition of treatment responses for primary tumor across different treatment phases. The swimmer plot was generated to demonstrate individual clinical trajectories of the HDR-ILBT cohort. All calculations and visualizations were performed using MedCalc® Statistical Software, version 23.4.8 (MedCalc Software Ltd., Ostend, Belgium; 2026), and Python, version 3.13 (Python Software Foundation, Wilmington, DE, USA).

Results

Baseline characteristics

The baseline characteristics for the 178 patients are detailed in **Table 1**. The three treatment cohorts were well-balanced across baseline demographic, clinical, and treatment-related characteristics, except for age and clinical T stage. The study population was predominantly male (89.8-93.5%), squamous cell carcinoma (90.9-100%), and good performance status (ECOG 0-1). The epicenter of the tumor was primarily located in the middle (35.2-53.8%) and lower thirds (30.8-42.9%) of the esophagus. Most patients were single-segment involvement (77.3-85.7%). Notably, a significant difference in age was observed across the cohorts, with patients in the dCCRT alone cohort being older than those in the nCCRT + surgery and CCRT + ILBT cohorts (median age:

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Table 1. Baseline characteristics of three cohorts (n = 178)

Variables	nCCRT + Surgery (n = 77)	CCRT + ILBT (n = 13)	dCCRT alone (n = 88)	P Value
Median age, years (IQR)	58.5 (53.9-66.8)	56.2 (50.9-59.3)	61.9 (55.9-71.2)	0.009
Male gender-no. (%)	72 (93.5)	12 (92.3)	79 (89.8)	0.706
Performance status-no. (%)				0.063
0-1	77 (100)	13 (100)	82 (93.2)	
2-3	0 (0)	0 (0)	6 (6.8)	
Pathology type-no. (%)				0.740 ^a
Adenocarcinoma	5 (6.5)	0 (0)	8 (9.1)	
Squamous-cell carcinoma	71 (92.2)	13 (100)	80 (90.9)	
Other*	1 (1.3)	0 (0)	0 (0)	
Median tumor length-cm, (IQR)‡	6.0 (4.9-8.0)	7.0 (5.7-8.2)	6.1 (4.3-8.8)	0.643
Median tumor volume-cm ³ , (IQR)‡	36.8 (21.8-53.2)	30.3 (23.4-43.6)	28.2 (14.8-51.3)	0.193
Tumor location-no. (%)†				0.135
Cervical Esophagus	1 (1.3)	0 (0)	7 (8.0)	
Upper Esophagus	7 (9.1)	2 (15.4)	17 (19.3)	
Middle Esophagus	36 (46.8)	7 (53.8)	31 (35.2)	
Lower Esophagus	33 (42.9)	4 (30.8)	33 (37.5)	
Tumor Extent				0.356
Single segment involvement	66 (85.7)	11 (84.6)	68 (77.3)	
Multi-segment involvement	11 (14.3)	2 (15.4)	20 (22.7)	
AJCC T stage-no. (%)				< 0.001
cT1	0 (0)	0 (0)	3 (3.4)	
cT2	8 (10.4)	1 (7.7)	34 (38.6)	
cT3	69 (89.6)	12 (92.3)	51 (58.0)	
AJCC N stage-no. (%)				0.161
cN0	5 (6.5)	0 (0)	11 (12.5)	
cN1	25 (32.5)	3 (23.1)	33 (37.5)	
cN2	44 (57.1)	8 (61.5)	36 (40.9)	
cN3	3 (3.9)	2 (15.4)	8 (9.1)	
Cigarette smoking no. (%)				0.919
Yes	62 (80.5)	10 (76.9)	70 (79.5)	
No	15 (19.5)	3 (23.1)	18 (20.5)	
Betel quid chewing-no. (%)				0.557
Yes	29 (37.7)	7 (53.8)	35 (39.8)	
No	48 (62.3)	6 (46.2)	53 (60.2)	
Alcohol consumption-no. (%)				0.739
Yes	59 (76.6)	11 (84.6)	65 (73.9)	
No	18 (23.4)	2 (15.4)	23 (26.1)	
Radiotherapy Technique				0.515
VMAT	59 (76.6)	12 (92.3)	69 (78.4)	
IMPT	18 (23.4)	1 (7.7)	19 (21.6)	
Chemotherapy regimen				0.213 ^b
Carboplatin + Paclitaxel	51 (66.2)	11 (84.6)	54 (61.4)	
Cisplatin + 5-FU	20 (26.0)	1 (7.7)	27 (30.7)	
Others	6 (7.8)	1 (7.7)	7 (8.0)	

Data are given as counts and percentages, unless otherwise indicated. Percentages may not sum to 100% due to rounding. *P* values were calculated using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. A two-sided *p* value < 0.05 was considered statistically significant. †Tumor location was classified based on the epicenter of the lesion as determined primarily by PET/CT imaging. Patients with tumors extending across adjacent segments were categorized into the multi-segment involvement category. ‡Tumor length and volume were calculated based on the delineation of the GTV. *There was one patient in the nCCRT + surgery cohort had esophageal melanoma. ^a*P*-value was calculated comparing the squamous cell carcinoma and adenocarcinoma groups. ^b*P*-value was calculated comparing the chemotherapy regimen between Carboplatin + Paclitaxel and Cisplatin + 5-FU. Abbreviations: AJCC, American Joint Committee on Cancer; ILBT, intraluminal brachytherapy; CCRT, concurrent chemoradiation; dCCRT, definitive concurrent chemoradiation; GTV, gross tumor volume; IMPT, intensity modulated proton therapy; IQR, interquartile range; VMAT, volumetric modulated arc therapy; nCCRT, neoadjuvant concurrent chemoradiation; 5-FU: 5-fluorouracil.

61.9 vs. 58.5 and 56.2 years, respectively; *P* = 0.009). At initial staging, most patients presented with clinical T3 (58.0-92.3%) and clinical N2 (40.9-61.5%) disease. However, clinical T stages differed significantly across the three cohorts (*P* < 0.001). Specifically, while the nCCRT + surgery and CCRT + ILBT cohorts consisted predominantly of cT3 disease (89.6% and 92.3%, respectively), the dCCRT alone group presented a notably higher proportion of cT2 disease (38.6%) than nCCRT + surgery (10.4%) or CCRT + ILBT cohorts (7.7%). Though clinical T stage differed, the tumor burdens were highly comparable. There were no significant differences in median tumor lengths (6.0-7.0 cm, *P* = 0.643), median gross tumor volume (28.2-36.8 cm³, *P* = 0.193), tumor location (*P* = 0.135), tumor extent (*P* = 0.356) or clinical N stage (*P* = 0.161). Regarding lifestyle risk factors, the majority of patients presented with a history of cigarette smoking (76.9-80.5%) and alcohol consumption (73.9-84.6%), while betel quid chewing was prevalent in 37.7-53.8% of the cohort. VMAT was the preferred radiotherapy technique (76.6-92.3%) with carboplatin and paclitaxel (61.4-84.6%) as the most frequently prescribed concurrent chemotherapy regimen across the three cohorts.

Survival analysis

The median follow-up was 25.2 months. The 1-year and 2-year FFLTR rates were 93.3% and 81.2% for the nCCRT + surgery cohort, 84.6% and 67.7% for the CCRT + ILBT cohort, and 62.5% and 52.9% for the dCCRT alone cohort, respectively (*P* < 0.001; **Figure 3A**). Post-hoc pairwise analysis demonstrated that radical surgery achieved significantly superior FFLTR compared with dCCRT alone (*P* < 0.001), while no significant differences were observed between the CCRT + ILBT and nCCRT + surgery cohorts (*P* = 0.220) or dCCRT alone cohorts (*P*

= 0.200) (**Supplementary Table 1A**). Notably, the addition of ILBT following CCRT demonstrated a trend toward improved local control with outcomes comparable to those of the surgery group. This finding highlights the potency of the ILBT boost in bridging the therapeutic gap in primary tumor control between dCCRT alone and nCCRT + surgery. Consistent with the findings for local control, both OS and DPFS demonstrated a trend toward improvement when incorporating the ILBT boost compared to dCCRT alone, achieving outcomes comparable to those of the nCCRT + surgery cohort. For OS, the 1-year and 2-year rates were 93.3% and 81.9% for the nCCRT + surgery cohort, 92.3% and 66.6% for the CCRT + ILBT cohort, and 72.4% and 51.5% for the dCCRT alone cohort (*P* < 0.001; **Figure 3B**). For DPFS, the 1-year and 2-year rates were 84.3% and 62.5% for the nCCRT + surgery cohort, 69.3% and 53.8% for CCRT + ILBT cohort, and 43.1% and 36.0% for the dCCRT alone cohort (*P* < 0.001; **Figure 3C**). Post-hoc pairwise analyses of both OS and DPFS showed no statistically significant differences between the CCRT + ILBT cohort and either the nCCRT + surgery or dCCRT alone cohort (**Supplementary Table 1B, 1C**).

Safety profiles and toxicities

The toxicities among the three cohorts are detailed in **Table 2**. While the incidences of any-grade early and late toxicities were comparable across all cohorts, significant differences were observed in severe (grade ≥ 3) early and late toxicities. In the early toxicities (developed within 6 months after treatment), the CCRT + ILBT cohort experienced the highest rate of grade ≥ 3 acute esophagitis (46.2%, *P* = 0.008), which is directly attributed to the higher cumulative radiation dose delivered to the esophageal mucosa by the ILBT. These acute inflammatory events were generally transient and clinically

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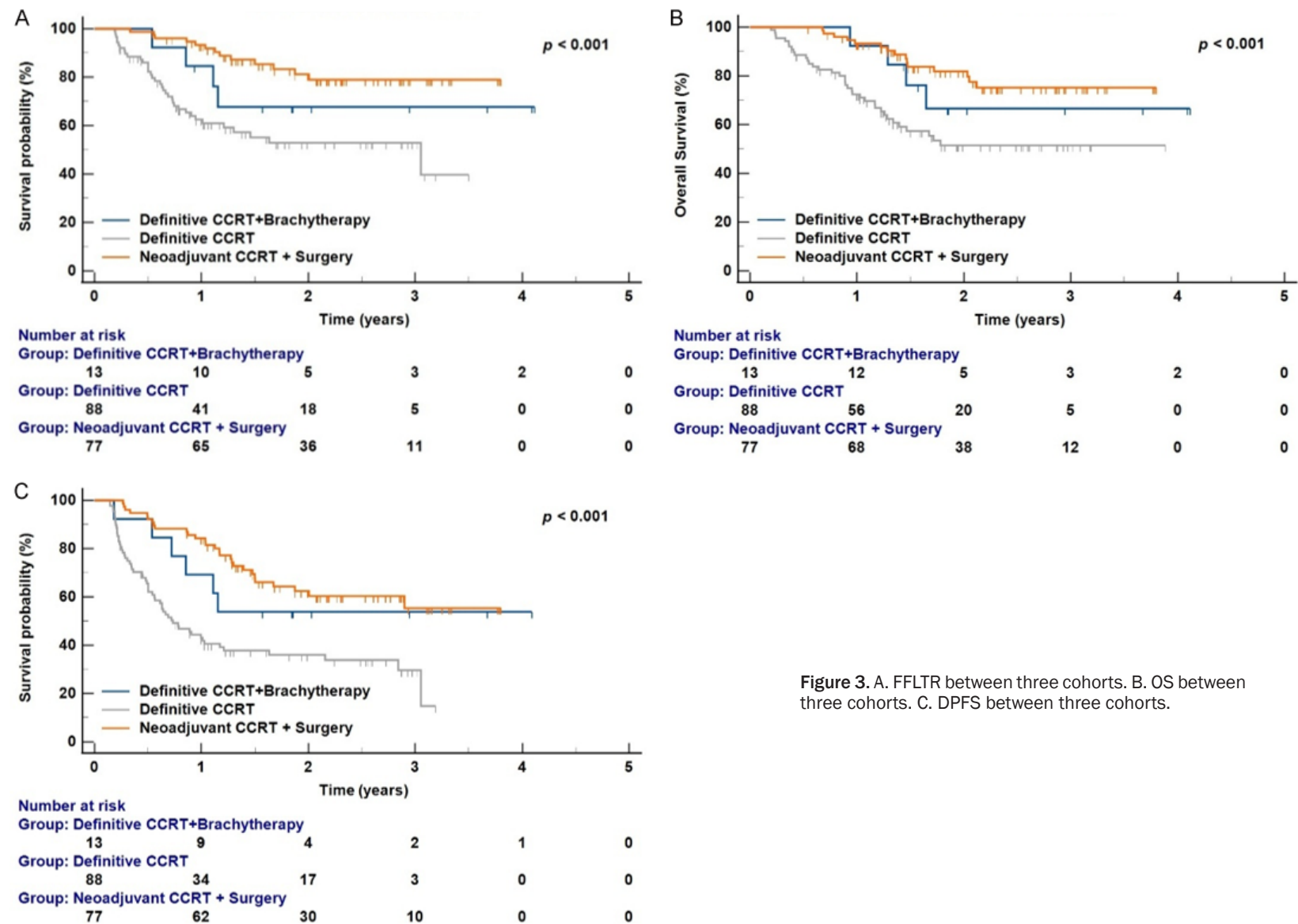


Figure 3. A. FFLTR between three cohorts. B. OS between three cohorts. C. DPFS between three cohorts.

Table 2. Safety profiles and toxicities among three cohorts ($n = 178$)

Toxicities	nCCRT + Surgery ($n = 77$)	CCRT + ILBT ($n = 13$)	dCCRT alone ($n = 88$)	<i>P</i> Value
Early Toxicities (any grade)				
Esophagitis	57 (74.0)	10 (77.0)	73 (83.0)	0.363
Pericardial effusion	10 (13.0)	1 (7.7)	15 (17.0)	0.674
Early Toxicities (grade ≥ 3)				
Esophagitis	8 (10.4)	6 (46.2)	18 (20.5)	0.008
Pericardial effusion	0 (0)	0 (0)	1 (1.1)	1.000
TE-fistula	0 (0)	1 (7.7)	8 (9.1)	0.010
Late Toxicities (any grade)				
Pneumonitis	54 (70.1)	10 (77.0)	67 (76.1)	0.675
Esophageal Stricture/Stenosis	29 (37.7)	5 (38.5)	26 (29.5)	0.484
Late Toxicities (grade ≥ 3)				
Pneumonitis	8 (10.4)	0 (0)	14 (15.9)	0.247
Esophageal Stricture/Stenosis	24 (31.2)	3 (23.1)	11 (12.5)	0.010
TE-fistula	1 (1.3)	2 (15.4)	2 (2.3)	0.070
Intervention Requirement for Esophageal stenosis/stricture-no. (%)				
Balloon/Endoscopic Dilation	24 (31.2)	3 (23.1)	4 (4.5)	< 0.001
Esophageal Stent	0 (0)	0 (0)	7 (8.0)	0.026

Data are presented as counts and percentages. Adverse events were graded according to CTCAE version 5.0. Acute toxicities were defined as events occurring within 6 months after completion of radiotherapy. Late toxicities were defined as events occurring beyond 6 months after completion of radiotherapy. *P* values were calculated using the Fisher-Freeman-Halton exact test and a two-sided *p* value < 0.05 was considered statistically significant. Abbreviations: ILBT, intraluminal brachytherapy; CCRT, concurrent chemoradiation; dCCRT, definitive concurrent chemoradiation; nCCRT, neoadjuvant concurrent chemoradiation; TE-fistula, tracheoesophageal fistula.

manageable. Furthermore, early grade ≥ 3 toxicities of tracheoesophageal (TE) fistula formation (9.1%, $P = 0.010$) and the need for esophageal stent placement (8.0%, $P = 0.026$) were significantly higher in the dCCRT alone cohort. In contrast, in the CCRT + ILBT cohort, only one patient (7.7%) developed an early treatment-related TE fistula. This patient subsequently underwent salvage esophagectomy and the final pathology confirmed a pathological complete response (pCR), demonstrating that the fistula was caused by tumor regression unmasking a structural defect rather than tumor progression. Additionally, beyond 6 months after the completion of ILBT, two patients (15.4%) developed TE fistulas. Both of these events were primarily attributed to disease progression, and no significant difference was observed across the three groups ($P = 0.070$). Regarding late grade ≥ 3 esophageal stricture or stenosis, the incidence was highest in the nCCRT + surgery cohort (31.2%), followed by the CCRT + ILBT (23.1%) and dCCRT alone (12.5%) cohorts ($P = 0.010$). Consequently, the need for endoscopic or balloon dilation was significantly higher in the nCCRT + surgery cohort (31.2%, $P < 0.001$). Specifically, in the CCRT + ILBT cohort, five patients (38.5%) developed

late strictures and three patients (23.1%) required dilation intervention. Importantly, only one case (7.7%) was treatment-related toxicity, whereas four cases (30.8%) resulted from tumor progression. Remarkably, while the ILBT boost initially predisposes patients to a higher rate of transient severe acute esophagitis, this early toxicity is medically manageable and confers an advantage by preventing severe toxicities.

Treatment response dynamics of primary tumor

The Sankey diagrams dynamically mapped the longitudinal evolution of primary tumor responses among the three cohorts (**Figure 4A-C**) and described in **Table 3**. Distinct response conversion was noticed across different treatment strategies. Notably, the CCRT + ILBT cohort demonstrated a marked dynamic shift toward cCR status, with half of patients (5 of 10) with cPR after initial CCRT were successfully converted to cCR status after the ILBT. The total cCR rate was escalated from 23.1% to 61.5% at 1 year follow-up after the ILBT. The overall response rate (ORR), including cCR and cPR, was 69.2% in the CCRT + ILBT cohort, indi-

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Figure 4. A-C. Sankey Diagrams of primary tumor responses among (A) CCRT + ILBT, (B) nCCRT + surgery, and (C) dCCRT alone cohorts. The Sankey Diagrams dynamically map the longitudinal evolution of primary tumor responses during treatment and 1 year follow-up. The leftmost blue bar represents the initial status of the entire treatment-naïve cohort. The middle bars reflect the clinical response evaluated by MTB after the completion of initial CCRT. The rightmost bars demonstrate the final primary tumor response status following their subsequent interventions respectively at the timepoint of 1-year follow-up (clinically for CCRT + ILBT and dCCRT alone cohorts; pathologically for the nCCRT + surgery cohort). The gray connecting bands illustrate the patient trajectories and transitioning individually between response states. Colors of bars denote specific response categories: dark green for complete response (CR), light green for partial response (PR), yellow for stable disease (SD), and red for progressive disease (PD).

Table 3. Dynamic evolution of primary tumor treatment response between three cohorts

cohorts	After initial CCRT				After surgery or ILBT or observation			
	CR	PR	SD	PD	CR	PR	SD	PD
nCCRT + Surgery	21	52	4	0	38 [†]	11 [†]	25 [†]	3 [†]
CCRT + ILBT	3	10	0	0	8	1	0	4
dCCRT alone	13	57	14	4	30	20	3	35

Treatment responses following surgery in the nCCRT + surgery cohort represent pathological responses based on the resected specimens, whereas responses in the other cohorts reflect clinical evaluations. [†]Pathological responses. Abbreviations: ILBT, intraluminal brachytherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; dCCRT, definitive concurrent chemoradiation; nCCRT, neoadjuvant concurrent chemoradiation.

cating the dual role of the brachytherapy in consolidating the initial treatment response and the eradivative potential against residual disease (**Figure 4A**). In the nCCRT + surgery cohort, the pCR rate of primary tumor was 49.4% and the ORR was 63.7% following radical resection (**Figure 4B**). In contrast, the conversion ability was limited in the dCCRT alone cohort. Although the cCR rate increased from 14.8% to 34.1% and the ORR was 56.8%, a substantial proportion of patients (39.8%) eventually developed to cPD status (**Figure 4C**).

Swimmer plot of survival trajectories in the CCRT + ILBT cohort

The longitudinal monitoring of the 13 patients (A001-A013) with their primary tumor response in the CCRT + ILBT cohort is visualized in the swimmer plot (**Figure 5**). Following the initial CCRT and prior to the ILBT boost (marked by ★), the cohort consisted of three patients who achieved cCR status (marked by green bars) and ten patients with cPR status (marked by blue bars). Following the ILBT and 1-year evaluation period (marked by hatched gray bars), the therapeutic conversion and consolidative effect became clinically evident. Remarkably, eight patients (A002-A004, A006-A010) who achieved a final cCR status demonstrated long-term disease control and survival. Moreover, patient A002 received two brachytherapy sessions and underwent salvage surgery (marked by gray square) due to TE fistula formation and clinically suspected local recurrence during follow-up. However, the final pathological examination confirmed a true pCR status without viable tumor. Conversely, the plot elucidates specific failure patterns and their detrimental impact on survival. Among four patients devel-

oping cPD (marked by red bars) and one patient remaining in cPR (marked by blue bars), local recurrences (marked by ✕) were noted in four patients (A005, A011, A012, and A013) and distant metastases (marked by ▲) were noted in three patients (A001, A005, and A013). Moreover, two patients (A011 and A013) developed TE fistula due to tumor progression. These failure events correlated with inferior survival duration, as four of

the five patients ultimately succumbed to the disease progression (marked by ●) within 25 months. In summary, these individual clinical trajectories further confirm that successful tumor response conversion and consolidative capacity via the ILBT directly translates into durable organ preservation and long-term survival.

Discussion

In this study, we prospectively enrolled 13 non-surgical patients who received the ILBT after CCRT. To reflect the real-world clinical landscape, we simultaneously evaluated the other two comparative cohorts treated during the same study period, thereby providing a more authentic comparison to observe the therapeutic and safety outcomes among the different cohorts. Our findings demonstrate that the addition of ILBT using the novel BRAXX balloon applicator following CCRT is a feasible and highly promising approach for consolidative dose-escalation. Notably, we observed a consistent trend toward improved FFLTR, OS, and DPFS in the ILBT cohort when compared to the dCCRT alone cohort, effectively bridging the survival gap between dCCRT alone and nCCRT followed by radical surgery. This efficacy was evidenced by the dual capacity of the brachytherapy to maintain the initial cCR status and further eradicate residual disease in patients with cPR, achieving an ORR of 69.2% and ensuring long-term survival with organ integrity in the ILBT cohort. Furthermore, the addition of ILBT did not disproportionately increase the risk of complications. If externally validated in large-scale trials to confirm its clinical benefit and long-term safety, ILBT after CCRT could serve as a safe and effective consolidative dose-escalation strategy for non-surgical patients with esophageal cancer.

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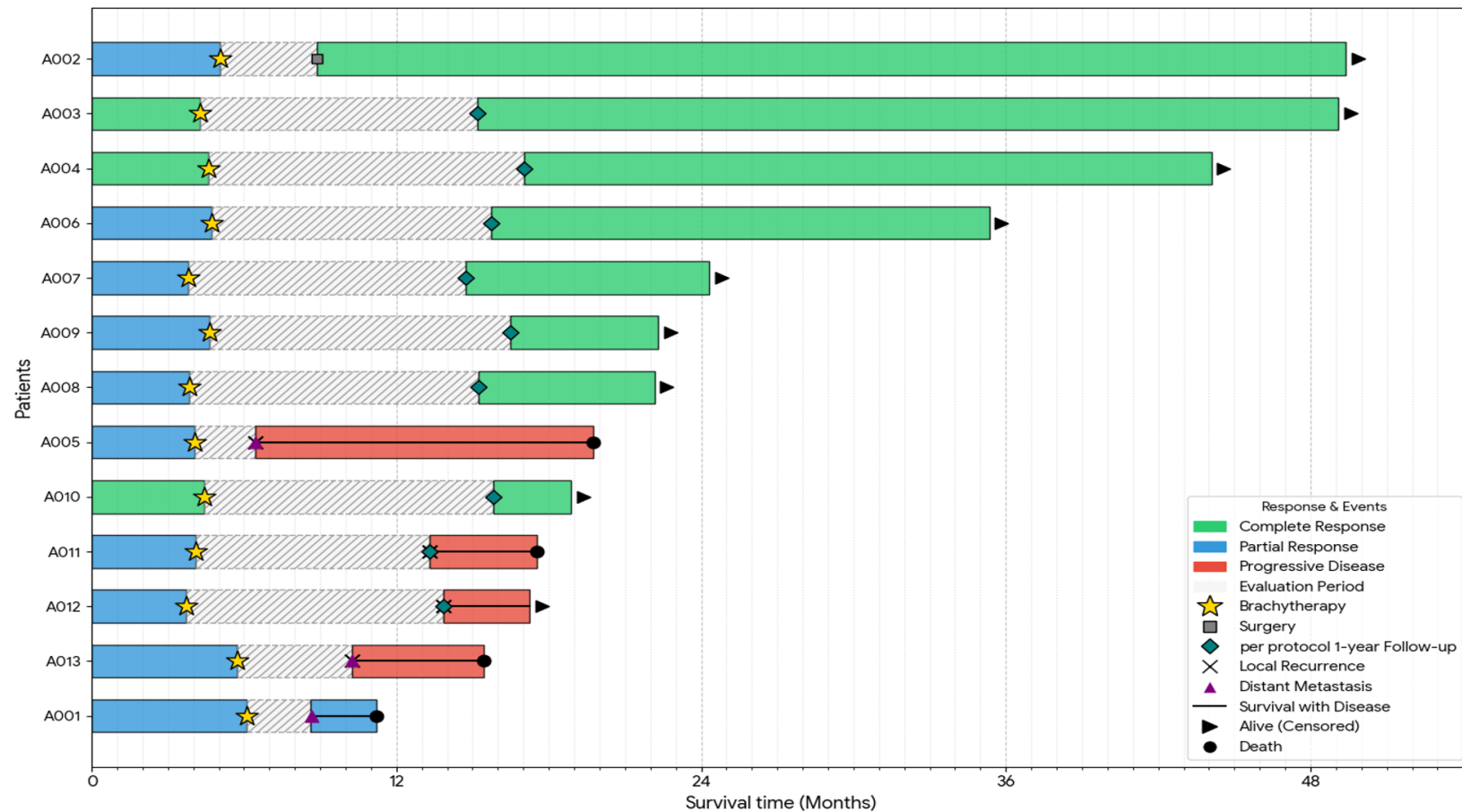


Figure 5. Swimmer plot of the CCRT + ILBT cohort. Each bar represents an individual patient and documents their events, treatment response, the duration of survival (calculated from the first day of CCRT). The solid-colored bars indicate the clinical response (Green: cCR; Blue: cPR; Red: cPD). The gold star (★) marks the timing of the brachytherapy (Case A002 underwent two brachytherapy sessions, with the star demonstrating the final session, whereas all other patients received a single session). The hatched gray segment indicates the follow-up period, ending upon the completion of the 1-year follow-up (green diamond, ◆) or salvage surgery (gray square, ■). Disease progression events are denoted by crosses (X) for local recurrence and purple triangles (▲) for distant metastasis. Solid black lines extending from these event markers indicate the duration of survival with disease progression. Black right-pointing triangles (►) denote patients who are alive (censored) at the last follow-up, while black circles (●) indicate death.

Prior research regarding esophageal brachytherapy is highly heterogeneous, characterized by wide variations in treatment intent (curative or palliative), procedural protocols, applicator designs, and prescribed dose-fractionation regimens [25-32]. The first landmark trial proposed by Okawa et al. in the 1990s demonstrated that the addition of HDR or LDR-ILBT (delivering 10 Gy in 2 fractions via a 1 cm diameter balloon-based applicator) to 60 Gy EBRT significantly improved cause-specific survival in patients with tumors ≤ 5 cm in length (64.0% vs. 31.5% at 5 years; $P = 0.025$) [29]. Transitioning to the modern era, the establishment of standard management for esophageal cancer redefined the new therapeutic paradigm for brachytherapy. A retrospective study performed by Mangesius et al. across two centers reported an Ir-192 HDR-ILBT (delivering 10 Gy in 2 fractions via median 1 cm diameter Bonvoisin-Gérard applicator with 2D planning) with or without chemotherapy following dCCRT (50.4 Gy in 28 fractions with a 9 Gy sequential boost if indicated) significantly improved median local progression-free survival (18.7 vs. 6.0 months; $P < 0.0001$), local control (30.5 vs. 11.3 months; $P = 0.008$), and overall survival (22.7 vs. 9.1 months; $P < 0.0001$) but esophageal stenosis was higher in the ILBT group (22.5%) [30]. Similarly, another prospective observational study conducted by Nag et al. investigated an HDR-ILBT boost (delivering 10 Gy in 2 fractions via a ^{60}Co source using 6-mm diameter applicator with CT-based planning) following CCRT (50 Gy in 25 fractions). Echoing our findings, 65% of patients maintained a CR status at 1-year post-treatment. However, this protocol was burdened by a high rate of severe late toxicities, including strictures (40%) and fistulas formation (10%) [28]. In alignment with our multimodal approach that simultaneously compared with surgery, a multi-institutional study carried out by Tessa et al. utilized 60 Gy of dCCRT followed by HDR-ILBT using Ir-192 sources (delivering 5-7 Gy in 1-2 fractions with a 12-mm diameter Savary-like applicator) for clinical responder and reserved esophagectomy for selected candidates. Most notably, a subgroup of non-surgical patients who achieved a cCR demonstrated long-term outcomes, with 5-year overall survival and local control rates reaching 65% and 75%, respectively [33]. Collectively, our results resonate with these investigations, reaffirming that adding ILBT to standard CCRT is a highly prognostic manage-

ment, with the most pronounced impacts on survival and local control.

Nevertheless, previous literatures were differed from ours in both study design and clinical scope, and our study extends these findings in several important ways. First, while prior efforts mandated ILBT as a component of the initial treatment plan, our study prospectively enrolled non-surgical candidates to receive ILBT only after institutional MTB evaluation [28-30]. We aimed to retain a surgical arm within our multimodal framework to ensure that operable patients could secure the optimal survival advantage through radical resection [34, 35]. Second, our study exclusively enrolled a well-defined curative intent population of non-T4 or M1 (non-nodal organ-involvement) disease, while previous investigations included a subset of patients with stage IV disease [30, 33]. Including these patients within a single analysis may introduce clinical heterogeneity and confound survival outcomes or dilute treatment effects. Third, the external beam radiotherapy utilized in earlier studies were largely restricted to 3D-CRT [29, 30]. Since the proven benefits of IMRT over 3D-CRT in minimizing toxicities and improving survival outcomes, our study employed highly conformal VMAT and IMPT for the external beam radiotherapy phase [36-38]. This modernized radiotherapeutic techniques significantly improves the therapeutic ratio, offering a safer and more consistent treatment in our study. Fourth, there is no consensus regarding the target delineation of the treatment length of ILBT, and most studies applied pre-EBRT GTV with 1-5 cm margin or marked by radio-opaque surgical clips [30, 33, 39]. To address this uncertainty, we dynamically tailored the target volume with re-contouring for every patient based on an on-site planning CT simulation acquired immediately prior to the procedure. Moreover, we also integrated staging 18-FDG PET-CT prior to initial CCRT to delineate the tumor extent by combining metabolic activity and anatomical changes prior to brachytherapy. This highly sensitive examination enabled the detection of subtle metabolic alterations and ensured that the treatment volume was precisely localized to tumor, thereby minimizing the risk of out-field treatment delivering. Finally, the implementation of the novel BRAXX applicator confers critical advantages from both dosimetric and procedural workflow. In the aspect of radiation dose distribution, the inflat-

able balloons consistently center the radiation source within the esophageal lumen. This design effectively mitigates mucosal hot spots, successfully overcoming the severe dose heterogeneity and source eccentricity typically associated with conventional single-channel or NG-based applicators. Furthermore, applicator placement in prior efforts necessitate the assistance of a gastroenterologist for transoral intubation under endoscopy before the brachytherapy [28, 30]. To streamline the workflow, the BRAXX applicator is specifically designed for transnasal deployment to mimic the routine insertion of a nasogastric tube. This innovative design successfully overcomes the logistical hurdles of previous devices, increases the patient tolerance and comfort, and allows radiation oncologists to independently manage the insertion process.

Regarding the toxicities, the RTOG92-07 trial reported an alarming 12% incidence of treatment-related esophageal fistulas developing within 7 months among patients who received an HDR brachytherapy boost (initially 15 Gy in 3 fractions, later reduced to 10 Gy in 2 fractions) following standard CCRT. This life-threatening side effect is a stark warning that prompted investigators to caution against the integration of brachytherapy concurrently with chemotherapy [39]. In contrast, only 1 patient (7.7%) in our cohort developed a treatment-related fistula within 6 months, while the other 2 cases (15.4%) were secondary to tumor progression beyond 6 months. Several factors may account for the favorable safety profile in our study. First, our brachytherapy dose (10 Gy in 2 fractions in 1 patient; 5 Gy in 1 fraction in 12 patients) was lower than the doses employed in RTOG 92-07. Surprisingly, 5 of the 6 patients who developed fistulas in the RTOG 92-07 had received a high dose of 15 Gy, aligning with a dose-dependent toxicity relationship. Second, instead of single-channel applicator, our research utilized the novel BRAXX balloon applicator to ensure source centralization and dose homogeneity to avoid mucosal hot spots. Third, to prevent the synergistic chemoradiation toxicity reported in RTOG 92-07, we avoided the concurrent administration of chemotherapy with brachytherapy in the same week. In summary, our findings suggest that the profound toxicity concerns raised by RTOG 92-07 can be effectively mitigated through dose selection, re-contoured for every

patient based on an on-site planning CT simulation prior to the procedure before brachytherapy, modern applicator technology, and the avoidance of concurrent chemotherapy.

Limitation

Several limitations of this study must be acknowledged. First, as a single-center, non-randomized pilot study, the sample size of the ILBT cohort is relatively small ($n = 13$). This limited cohort size restricts the generalizability of the findings to a broader population and limits our statistical options, such as propensity score matching or multivariable regression, which would otherwise be employed to enhance statistical robustness. Thus, we did not perform the aforementioned analyses between cohorts to adjust confounders and minimize selection bias. However, from a clinical perspective, our institution is the largest tertiary referral medical center in northern Taiwan and serves a highly diverse and voluminous patient population, thereby may partially mitigate this concern. Second, although multidisciplinary tumor board (MTB) evaluations prioritized radical surgery to maximize survival outcomes for eligible candidates, final treatment allocations were ultimately influenced by patient preference. This inevitably introduces inherent selection bias. Nevertheless, this compromise reflects the realities of real-world clinical practice and should be carefully considered when interpreting our findings. Third, although the median follow-up of 25.2 months is adequate to capture primary tumor treatment response and late toxicities, an extended longitudinal follow-up is warranted to definitively confirm the long-term survival benefits and safety. Fourth, our analysis did not collect and assess the concurrent or sequential use of immunotherapy. Considering the proven survival benefits of ICIs in esophageal cancer, their potential to confound both efficacy and toxicity outcomes cannot be entirely ruled out. Future studies should evaluate the clinical synergy of combining modern ILBT with systemic immunotherapy. Fifth, distinguishing treatment-related toxicity from disease progression remains a limitation, especially in our retrospective cohorts (dCCRT alone and nCCRT + surgery). Since adverse events were diagnosed solely via imaging and clinical presentation without routine pathological confirmation, the exact underlying etiologies (e.g., attribution to the radiation-induced

inflammation or fibrosis, rapid tumor regression induce structural defect, or tumor progression) could not be definitively confirmed. Thus, we could only report the absolute incidence of these complications in the two standard-of-care cohorts. Resolving this diagnostic challenge will require future rigorous prospective studies incorporating strict and standardized pathological verification. Finally, the lack of a universal consensus regarding the optimal dose-fractionation regimens, applicator selection, and target delineation remains a broader challenge in esophageal brachytherapy.

Conclusions

Our study highlights the therapeutic improvement of incorporating HDR-ILBT utilizing the novel BRAXX balloon applicator following CCRT for non-surgical esophageal cancer. By leveraging its distinct dosimetric advantages and streamlined workflow, this targeted consolidative approach effectively bridges the survival gap between surgery and non-surgery cohorts without disproportionately increasing the incidence of toxicities. The efficacy is evidenced by its dual capacity to consolidate disease-free status and eradicate residual disease, thereby ensuring durable survival while preserving esophageal integrity. Moreover, for initially inoperable patients, integrating HDR-ILBT could prolong survival, providing a therapeutic window for systemic therapies and potentially acting as a “bridge to surgery” to optimize long-term outcomes. While our preliminary results are encouraging, further validation through large-scale, prospective clinical trials is warranted to confirm the clinical benefit and long-term safety of this approach. If further validated, this strategy could offer a meaningful addition to the current treatment paradigm.

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For patients prospectively enrolled in the investigational brachytherapy arm (CCRT + ILBT cohort), written informed consent was obtained from all participants.

Disclosure of conflict of interest

None.

Abbreviations

18-FDG PET, F-18-fluorodeoxyglucose positron emission tomography; 3D-CRT, Three-dimensional conformal radiation therapy; 5-FU, 5-fluorouracil; AJCC, American Joint Committee on Cancer; CCRT, Concurrent chemoradiotherapy; CR, Complete response; CT, Computed tomography; dCCRT, Definitive concurrent chemoradiotherapy; DPFS, Disease progression-free survival; EGD, Esophagogastroduodenoscopy; ESD, Endoscopic submucosal dissection; ESR, Endoscopic submucosal resection; EUS, Endoscopic ultrasound; GTV, Gross tumor volume; HDR, High-dose-rate; HRs, Hazard ratios; ILBT, Intraluminal brachytherapy; IMPT, Intensity modulated proton therapy; IQR, Interquartile ranges; Ir-192, Iridium-192; MTB, Multidisciplinary tumor board; nCCRT, Neoadjuvant concurrent chemoradiotherapy; OS, Overall survival; PD, Progressive disease; PR, Partial response; RT, Radiotherapy; SD, Stable disease; TE-fistula, Tracheoesophageal fistula; VMAT, Volumetric modulated arc therapy.

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Supplementary Table 1A. Post-hoc analysis of FFLTR between three cohorts[†]

	P Value
CCRT + ILBT vs. Definitive CCRT Alone	0.200
CCRT + ILBT vs. Neoadjuvant CCRT + Surgery	0.220
Neoadjuvant CCRT + Surgery vs. Definitive CCRT Alone	< 0.001*

Abbreviations: ILBT, intraluminal brachytherapy; CCRT, concurrent chemoradiation. [†]FFLTR between two groups were assessed using Pairwise Log-Rank Test with a Bonferroni correction. *P-values were calculated using the Log-Rank test. And significance threshold was adjusted using the Bonferroni correction for 3 comparisons (0.0167).

Supplementary Table 1B. Post-hoc analysis of OS between three cohorts[†]

	P Value
CCRT + ILBT vs. Definitive CCRT Alone	0.209
CCRT + ILBT vs. Neoadjuvant CCRT + Surgery	0.418
Neoadjuvant CCRT + Surgery vs. Definitive CCRT Alone	< 0.001*

Abbreviations: ILBT, intraluminal brachytherapy; CCRT, concurrent chemoradiation. [†]OS between two groups were assessed using Pairwise Log-Rank Test with a Bonferroni correction. *P-values were calculated using the Log-Rank test. And significance threshold was adjusted using the Bonferroni correction for 3 comparisons (0.0167).

Supplementary Table 1C. Post-hoc analysis of DPFS between three cohorts[†]

	P Value
CCRT + ILBT vs. Definitive CCRT Alone	0.092
CCRT + ILBT vs. Neoadjuvant CCRT + Surgery	0.456
Neoadjuvant CCRT + Surgery vs. Definitive CCRT Alone	< 0.001*

Abbreviations: ILBT, intraluminal brachytherapy; CCRT, concurrent chemoradiation. [†]DPFS between two groups were assessed using Pairwise Log-Rank Test with a Bonferroni correction. *P-values were calculated using the Log-Rank test. And significance threshold was adjusted using the Bonferroni correction for 3 comparisons (0.0167).

Supplementary Table 2. Dose-volume histogram (DVH) parameters of the GTV for the 13 patients in the HDR-ILBT cohort

Case	Volume (%) of					Dose (%) of				
	100% Dose	95% Dose	90% Dose	50% Dose	30% Dose	100% Volume	95% Volume	90% Volume	50% Volume	30% Volume
A001	89.97	92.30	94.27	100.70	100.70	58.80	87.58	99.61	160.70	216.18
A002	89.20	91.66	93.97	100.03	100.03	64.37	87.60	98.37	174.48	237.32
A003	97.42	98.85	99.54	100.04	100.04	76.82	106.33	116.53	189.66	257.24
A004	55.84	59.56	63.63	98.75	100.03	44.10	56.25	62.06	108.75	153.55
A005	64.45	68.33	72.44	97.30	100.04	30.87	56.90	66.54	122.10	171.44
A006	86.07	90.05	93.49	100.03	100.03	68.81	87.38	95.07	145.48	197.57
A007	93.87	96.50	98.44	100.03	100.03	77.18	98.03	106.34	162.53	218.10
A008	69.77	74.59	79.30	99.98	100.03	48.58	68.90	77.05	123.69	166.00
A009	87.15	91.09	94.36	99.98	100.04	47.88	88.83	96.48	146.24	195.76
A010	96.36	98.14	99.20	100.03	100.03	70.86	102.76	110.44	162.67	217.84
A011	86.72	89.19	91.32	100.06	100.07	53.22	78.80	93.16	159.36	216.46
A012	93.37	95.58	97.45	100.08	100.08	72.47	96.39	106.45	169.73	229.10
A013	90.92	93.68	95.86	100.04	100.04	61.13	92.04	101.33	161.34	221.28