Outcomes of definitive or preoperative IMRT chemoradiation for esophageal cancer

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Abstract

Objectives Intensity-modulated radiation therapy (IMRT) is evolving for the treatment of gastrointestinal cancers. The purpose of this study is to analyze our outcomes utilizing IMRT chemoradiation for esophageal cancer.

Methods IMRT was incorporated into esophageal cancer treatment at our center in 2006. Patients treated between 2006 and 2011 with either preoperative or definitive IMRT chemoradiation to 50–60 Gy prescribed to the gross tumor volume and 45–50.4 Gy to the clinical target volume concurrently with chemotherapy were evaluated. IMRT techniques included multifield segmented step and shoot, compensator-based, and volumetric arc therapy. Overall survival (OS) and disease-free survival (DFS) were analyzed by Kaplan–Meier and log-rank analysis. Multivariate analysis (MVA) for OS and DFS were performed with a Cox proportional hazard ratio model.

Results We identified 108 patients with a median follow-up of 19 months. Median OS and DFS were 32 and 21.6 months, respectively. Fifty-eight (53.7 %) patients underwent surgical

resection. There was no difference in OS or DFS in patients who underwent surgery compared to patients treated definitively without surgery. Median weight loss was 5.5 %. Rates of hospital admissions, feeding tube placement, stent placement, dilation, and radiation pneumonitis were 15.7, 7.4, 4.6, 12, and 1.9 %, respectively. Long-term radiation pneumonitis was observed in six (5.6 %) patients. MVA revealed that age, stage, and surgery were prognostic for DFS, while gender and histology were not. Gender, histology, and stage were prognostic of OS on MVA, while surgery and age were not.

Conclusions IMRT chemoradiation for esophageal cancer is safe and effective when compared to published series of 2D or 3D conformal radiation therapy. This is the largest single institutional series with long-term follow-up, confirming that IMRT is a viable treatment option for the curative treatment of esophageal cancer.

Keywords Intensity-modulated radiation therapy · Chemoradiation · Esophageal cancer · Survival · Toxicity · Surgery

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Introduction

In 2011, an estimated 17,000 cases of esophageal cancer will be diagnosed in the USA, with approximately 15,000 people dying from the disease [1]. Worldwide, an estimated 482,000 new esophageal cancer cases were diagnosed with approximately 407,000 deaths in 2008 [2]. Squamous cell carcinoma and adenocarcinoma account for >90 % of all esophageal cancer cases. While the incidence of squamous cell carcinoma has declined due to long-term reductions in smoking and alcohol consumption, the incidence of AC has

been rising due to increases in obesity and gastroesophageal reflux disease [2].

The management of esophageal or gastroesophageal junction (GEJ) cancers has shifted from surgery or radiation single modality approaches to trimodality with the addition of chemotherapy. RTOG 85-01 demonstrated a survival benefit with the addition of platinum-based chemotherapy to radiation over radiation alone for non-surgical esophageal cancer patients [3]. Several meta-analyses have also confirmed the survival benefit of trimodality therapy over surgery alone [4].

Intensity-modulated radiation therapy (IMRT) delivers highly conformal radiation therapy to tumor targets while sparing surrounding normal tissues from excessive doses of radiation. For the treatment of gastrointestinal malignancies, IMRT has been shown to reduce toxicity in anal [5], gastric [6], and pancreatic [7] cancers. There have been few reports on IMRT in esophageal cancer with small numbers of patients [8–11]. We present the largest series of esophageal cancer patients treated with IMRT with long-term follow-up.

Methods

Patients

An IRB-approved radiation oncology database was queried for patients treated preoperatively or definitively with IMRT chemoradiation for esophageal cancer (squamous cell carcinoma or adenocarcinoma). Staging included a computed tomography (CT) scan of the chest and abdomen, 18-fluorodeoxyglucose positron emission tomography, and endoscopic ultrasound (EUS) of the esophagus. Most patients had fiducials endoscopically placed at the time of EUS (Fernandez et al. [12]). Staging was performed according to the American Joint Committee on Cancer (AJCC) 7th edition staging guidelines.

Radiation treatment planning

CT-based planning was performed with the patients lying supine with arms up on a Vac-Lok immobilization device (Civco Medical Solutions). 4D CT simulation scans were obtained to assess tumor motion by respiration. IMRT motion management strategies included an MLC-based approach using abdominal compression or a solid compensator-based (Dot Decimal, Orlando, FL, USA) approach. Internal target volumes of gross disease were generated (internal gross tumor volume (GTV), IGTV). A clinical target volume (CTV) encompassing a 3–4-cm superior margin, 3–4-cm distal margin, and 3–5-mm radial margin was contoured. For upper thoracic tumors, bilateral supraclavicular lymphatics were included in the CTV. For distal esophageal and gastroesophageal cancers, celiac, para-aortic, gastrohepatic, splenic hilar, and portal lymphatics were included in the CTV. For patients with suspicious lymph nodes

identified in the gastrohepatic ligament, the field was extended to include superior mesenteric artery and vein as well as the portal confluence (portal vein, superior mesenteric vein, and splenic vein). Planning target volumes (PTVs) were created with margins individualized based on whether daily image guidance was used. Most patients were treated to a dose of 50.4 Gy in 1.8 Gy fractions; three patients underwent a sequential boost to the GTV to a total dose of 59.4 Gy. Thirty-seven patients underwent a simultaneous integrated IMRT boost, where a 3–5-mm margin around the GITV was treated to a dose of 50–60 Gy in 2 Gy fractions while the CTV was simultaneously treated with 1.7–1.8 Gy fractions to 45–54 Gy. IMRT techniques included volumetric arc therapy, solid state compensators, or a segmented multileaf collimator step and shoot technique delivered in five to nine fields. IMRT normal tissue constraints consisted of: lung (mean < 16 Gy, V20 < 30 %, V5 < 60 %), heart (mean < 30 Gy), spinal cord (max < 50 Gy), kidneys (mean < 12 Gy), and liver (V30 < 30 %). Patients were simulated with empty stomachs and after drinking 8 oz of water to account for changes in daily gastric distention. Radiation treatment planning was carried out on a non-contrast CT scan. Figure 1 displays the isodose lines for a 3D conformal plan for comparison with an IMRT plan at 1.8 Gy per fraction and a simultaneous integrated boost plan at 1.8/2.0 Gy per fraction.

Chemotherapy and surgery

Concurrent chemotherapy was delivered in all patients with the regimen chosen at the discretion of the medical oncologist. The majority of patients received cisplatin and continuous infusion 5-fluorouracil (5FU). Other regimens included cisplatin and bolus 5FU, weekly carboplatin and taxol, and oxaliplatin and infusional 5FU. All patients underwent restaging with PET-CT scans at 6 weeks after completion of chemoradiotherapy. Nonmetastatic patients who underwent cardiac and pulmonary clearance and were determined low to moderate risk underwent open, laparoscopic, or robotic transhiatal or transthoracic esophagectomy at the discretion of the surgeon.

Response

Pathologic response was determined by comparing clinical tumor and nodal staging to pathologic tumor and nodal staging. Tumor regression grading (TRG) scores were used to determine the pathologic response after neoadjuvant chemoradiotherapy. Tumor regression was determined based on the amount of residual disease and fibrosis. Tumor regression was classified into four grades: TRG0—no residual carcinoma (complete response), TRG1—1–10 % residual carcinoma, TRG2—11–50 % residual carcinoma, and TRG3—>50 % residual carcinoma (no response) [13].

Fig. 1 Axial, sagittal, and coronal displays of 3D conformal, IMRT, and simultaneous integrated boost IMRT plans. All plans have ≥ 95 % coverage of PTV. **a** 3DCRT plan for distal esophageal cancer delivering a dose of 50.4 Gy in 1.8 Gy fractions. Initially treated with AP-PA to 36 Gy followed by 14.4 Gy with a 3F off-cord technique (AP, RPO,

LPO); **b** IMRT plan for distal esophageal cancer delivering a dose of 50.4 Gy in 1.8 Gy fractions with VMAT; **c** simultaneous integrated boost plan for distal esophageal cancer delivering a dose to 50.4 Gy in 1.8 Gy fractions to CTV and 56 Gy in 2 Gy fractions to GTV using VMAT

Toxicity

All patients were seen at least weekly for evaluation and management of treatment-related toxicities. Follow-up after treatment completion was performed according to the National Comprehensive Cancer Network guidelines. Acute toxicities were considered to have occurred ≤ 3 months after chemoradiation completion, and late toxicities occurred > 3 months later. Acute and late toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events, version 4.0.

Statistics

Kaplan–Meier and log-rank analysis was performed to evaluate the end points of overall survival (OS) and disease-free survival (DFS). Each endpoint was calculated from the date of initial biopsy to date of recurrence or death. Multivariate analysis was calculated by the Cox proportional hazard ratio model for age, stage, surgery, gender, and histology. All analysis was performed with STATA IC (Stata Statistical Software, Release 10.0; Strata Corp., College Station, TX, USA).

Results

We identified 108 patients treated with T1–4N0–3M0 squamous cell carcinoma or adenocarcinoma of the esophagus treated with either definitive or preoperative IMRT chemoradiation therapy between 2006 and 2011. Patient characteristics are presented in Table 1. The median follow-up was 19 months. Fifty-eight (53.7 %) patients underwent surgical resection. The majority of patients were treated to 50.4 Gy in 1.8 Gy fractions. The median GTV dose was 50.4 Gy (range 45–60 Gy). The median CTV dose was 50.4 Gy (range 45–54 Gy). Thirty-seven patients were treated with a simultaneous integrated boost technique, and three patients underwent a sequential boost to the GTV to a total dose of 59.4 Gy. The median age was 65 years. Most of the patients in the analysis were male, had stage III adenocarcinoma located in the distal esophagus or gastroesophageal junction, and underwent surgical resection.

Figure 2 displays OS and DFS. Median and 2-year OS and DFS for the whole group were 32 months and 57.3 % and 21.6 months and 47.1 %, respectively (Fig. 2a, b). There was a significant difference in survival stratified by stage (Fig. 2c, d). Median and 2-year OS for stage I–II patients versus stage III patients were 42 months and 82.7 % versus

Table 1 Patient characteristics

Variable	Number (percent)
Median age (years) (range)	64.9 (32–93)
Gender	
Male	90 (83.3)
Female	18 (16.7)
AJCC T-stage (7th edition)	
T1	14 (13)
T2	11 (10.2)
T3	61 (56.5)
T4	19 (17.6)
Tx	3 (2.7)
AJCC N-stage (7th edition)	
N0	14 (13)
N1	64 (59.3)
N2	25 (23.1)
N3	3 (2.8)
Nx	2 (1.9)
AJCC stage (7th edition)	
IA	3 (2.7)
IB	4 (3.7)
IIB	24 (22.2)
IIIA	36 (33.3)
IIIB	19 (17.6)
IIIC	19 (17.6)
X	2 (1.9)
Location	
Upper	5 (4.6)
Middle	7 (6.5)
Distal	46 (42.6)
GEJ	50 (46.3)
Histology	
Adenocarcinoma	90 (83.3)
Squamous cell carcinoma	18 (16.7)
IMRT technique	
Segmented MLC	45 (41.7)
Compensator	22 (20.4)
VMAT	41 (37.9)
Median # of fields (range)	6 (5–9)
Median radiation dose (Gy)	
GTV	50.4 (45–60)
CTV	50.4 (45–54)
Surgery	
Yes	58 (53.7)
No	50 (46.3)

GEJ gastroesophageal junction, MLC multileaf collimator, VMAT volumetric arc therapy, GTV gross tumor volume, CTV clinical tumor volume

22.8 months and 48.5 % ($p=0.0055$), respectively (Fig. 2c). Median and 2-year DFS for stage I–II patients versus stage

III patients were 42 months and 64.7 % versus 16.5 months and 40.3 % ($p=0.0076$), respectively (Fig. 2d). There was no difference in survival for patient undergoing surgical resection (Fig. 2e, f). Median and 2-year OS for surgical patients versus nonsurgical patients were 32.9 months and 63.7 % versus 25.2 months and 52.3 % ($p=0.2059$), respectively (Fig. 2e). Median and 2-year DFS for surgical patients versus nonsurgical patients were 23.8 months and 48.8 % versus 17.9 months and 45 % ($p=0.2457$), respectively (Fig. 2f).

Fifty-eight patients underwent surgical resection. Three patients died within 30 days of surgery. Causes of death were sepsis, anastomotic breakdown, and respiratory failure. One patient died 34 days after surgery of pneumonia. Table 2 displays the pathological and tumor regression grading (TRG) scores for the 58 patients. Pathologic complete, partial, and no responses were observed in 39.7, 48.3, and 12 %, respectively. TRG scores of 0, 1, 2, and 3 were observed in 39.7, 32.8, 10.3, and 17.2 %, respectively.

Multivariate analysis for OS and DFS are presented in Table 3. For OS, female gender and stage III disease were prognostic for higher mortality, while squamous cell carcinoma was prognostic for lower mortality. Age, surgery, and radiation dose were not prognostic for survival. For DFS, age and surgery were associated with decreased mortality, while stage III disease was associated with increased mortality. Gender, histology, and radiation dose were not prognostic.

Table 4 shows acute and long-term toxicity of IMRT patients. In terms of acute toxicity, the median weight loss was 5.5 % (range −1.5–16.7 %), 15.7 % of patients required hospitalization or rehabilitation, 7.4 % required a feeding tube, 12 % required esophageal dilation, 4.6 % of patients required stent placement, and 1.9 % had radiation pneumonitis requiring steroids and oxygen. There were very few long-term complications. Two patients (1.9 %) had persistent pericardial and pleural effusions requiring aspiration, six patients with radiation pneumonitis requiring steroids and oxygen, two patients with esophageal stenosis requiring multiple dilations, three patients with esophageal ulcer requiring narcotics, and two patients who developed a tracheoesophageal fistula. Of the two patients with acute radiation pneumonitis, one had a history of Crohn's disease and active sarcoidosis while the other patient had previous chest radiation. Of the six patients with chronic radiation pneumonitis, two had previous chest radiation. Of the two patients with tracheoesophageal fistula, one had previous chest radiation.

Discussion

Chemoradiation for esophageal cancers has resulted in increased survival over radiation or surgery alone; however, it is fraught with high rates of acute toxicity and long-term

Fig. 2 Kaplan–Meier survival curves for OS and DFS: **a** OS for whole group; **b** DFS for whole group; **c** OS for stage I–II versus stage III patients; **d** DFS for stage I–II versus stage III; **e** OS for surgical versus

non-surgical patients; **f** DFS for surgical versus nonsurgical patients. Statistical analysis was performed with the log-rank test

esophagitis. We present the largest series of esophageal cancer patients treated with preoperative or definitive IMRT chemoradiation. With a median follow-up of 19 months, we report a median survival of 32 months. Survival was affected by stage but not by surgical resection on univariate

analysis. Multivariate analysis showed that stage, gender, and histology were prognostic for OS and that age, stage, and surgery were prognostic for DFS. There were low rates of hospital admission, feeding tube requirements, stent placement, and radiation pneumonitis.

Table 2 Pathologic response to neoadjuvant chemoradiotherapy

Pathologic response	Number (percent)	TRG response	Number (percent)
Complete	23 (39.7)	0	23 (39.7)
Partial	28 (48.3)	1	19 (32.8)
None	7 (12)	2	6 (10.3)
		3	10 (17.2)

TRG tumor regression grade

The benefit of IMRT over 3D radiation planning is better target conformality and sparing of the surrounding normal tissues. Kole et al. showed that IMRT significantly reduced the dose to the heart compared to 3D conformal radiotherapy (3DCRT) [14]. They analyzed 19 patients treated with IMRT and compared three-field and four-field 3DCRT plans on those same patients. They showed a significant reduction in mean dose (22.9 versus 28.2 Gy) and V30 (24.8 versus 61.0 %) ($p<0.05$). They also showed a significant improvement in the target conformity with IMRT as measured by the conformality index (ratio of total volume receiving 95 % of prescription dose to the planning target volume receiving 95 % of prescription dose), with the mean conformality index reduced from 1.56 to 1.30 using IMRT. Nguyen et al. analyzed nine patients in a feasibility study to compare lung and heart doses between 3DCRT and tomotherapy [15]. Mean lung (7.4 versus 11.8 Gy; $p=0.004$) and heart ventricle (12.4 versus 18.3 Gy; $p=0.006$) doses were significantly reduced with tomotherapy. Nicolini et al. compared volumetric arc therapy (VMAT) to multifield IMRT and 3DCRT plans in esophageal

cancer patients [16]. They showed that VMAT and IMRT provided similar target coverage better than 3DCRT. The conformity index was 1.2 for VMAT and IMRT and 1.5 for 3DCRT. The mean lung dose was 12.2 for IMRT, 11.3 for VMAT, and 18.2 for 3DCRT. The V20 was 23.6 % for IMRT, 21.1 % for VMAT, and 39.2 % for 3DCRT. However, an analysis from India on 45 esophageal cancer patients treated with either 3DCRT or IMRT resulted in higher rates of radiation pneumonitis in IMRT patients correlating with higher V20 and V30 values [17].

An additional concern in the chest is that there is respiratory associated esophageal tumor motion that can now be quantified with a 4D CT scan used routinely at many centers for treatment planning [18]. Concerns about respiratory associated tumor motion are particularly important in the setting of gastroesophageal junction tumors. At our institution, fiducials are endoscopically placed into the submucosa to delineate the superior and inferior extent of endoscopic tumor that we can then image on our 4D treatment planning scans. Investigators have demonstrated increasing radial esophageal motion the more distal the tumor location [18]. With advanced technology such as IMRT, there is concern that motion could affect the dose distribution. In fact, Kim et al. have reported that respiratory motion can reduce the delivered dose to lung tumors that move in the range of 1 cm up to 30 % [19]. Motion management strategies should be considered if using IMRT to prevent potential tumor underdosage. Abdominal compression with a device placed to decrease diaphragmatic excursion used daily has been shown to decrease the superior to inferior motion by approximately half [20]. Another strategy would be to consider a solid IMRT approach whereby brass compensators are placed into the pathway of each treatment field to prevent the potential tumor motion mismatch with a static beamlet [21]. Finally, there is also the possibility of incorporating respiratory gating techniques such that the treatment machine only beams “on” during a specified phase of the breathing cycle. This is something we are beginning to employ at our institution as this can now accommodate volumetric arc therapy.

In addition to concerns about breathing motion, there is also variability in the day-to-day stomach motion due to differences in gastric filling with tumors at the GEJ. Bouchard et al. reported an MD Anderson analysis of eight patients who were instructed to fast for 3 h before daily treatment [22]. The treatment was planned on both a full stomach initial CT scan and an empty stomach initial scan and re-measured with repeat CT scans weekly during treatment. The results showed that the full stomach volumes were a mean of 3.3 (range 1.7 to 7.5) times greater than empty stomach volumes. When analyzed for target coverage to the prescribed standard dose of 50.4 Gy, stomach filling was found to have a negligible impact on prescribed dose.

Table 3 Multivariate analysis

	HR	95 % CI	<i>p</i> value
Overall survival			
Age ^a	0.989	0.953–1.025	0.556
Gender (versus male)	4.034	1.344–12.110	0.013
Histology (versus AC)	0.120	0.026–0.555	0.007
Stage (versus stages I–II)	3.320	1.386–7.955	0.007
Surgery (versus none)	0.499	0.235–1.061	0.071
Radiation dose (versus ≤ 50.4 Gy)	1.260	0.546–2.904	0.588
Disease-free survival			
Age ^a	0.966	0.934–0.998	0.036
Gender (versus male)	1.300	0.480–3.428	0.605
Histology (versus AC)	0.480	0.159–1.465	0.197
Stage (versus stages I–II)	2.771	1.302–5.900	0.008
Surgery (versus none)	0.429	0.214–0.862	0.017
Radiation dose (versus ≤ 50.4 Gy)	1.019	0.493–2.104	0.959

AC adenocarcinoma, HR hazard ratio, CI confidence interval

^a Continuous variable

Table 4 Toxicities

Complications	Number (percent)
Acute	
Median weight loss (%)	5.5 (−1.5 to 16.7)
Hospital admission/rehab	17 (15.7)
Requiring feeding tube	8 (7.4)
Requiring dilation	13 (12.0)
Requiring stent	5 (4.6)
Radiation pneumonitis	2 (1.9) ^a
Long term grade 3 or greater	
Pleural effusions	2 (1.9)
Pericardial effusions	2 (1.9)
Radiation pneumonitis	6 (5.5) ^a
Esophageal stenosis	2 (1.9)
Esophageal ulcer	3 (2.8)
Tracheoesophageal fistula	2 (1.9) ^b

^a One patient with history of sarcoidosis and Crohn's; two patients with previous history of chest radiation

^b One patient with previous history of chest radiation

However, the investigators also analyzed plans with the patient receiving a simultaneous boost to the tumor each day and found that in this situation, the coverage to the primary tumor was compromised. These data emphasize the importance of daily treatment verification when utilizing advanced technologies, a technique termed image-guided radiation therapy (IGRT). IGRT can be incorporated with a daily CT scan on the treatment machine itself (termed a cone beam CT or CBCT) that can be fused with the planning CT to ensure the reproducibility of the setup. With fiducials, CBCT can be used to verify the position of the intended target. Fluoroscopy is available on treatment units and can be used to quantify the amount of motion if fiducials have been implanted into the esophagus. Finally, daily kilovoltage images can also be viewed of the spine and matched to the initial scan. All of these techniques improve the setup accuracy and allow smaller treatment margins to protect more normal tissue.

Clinical data are now emerging to support the role of intensity-modulated radiation therapy for esophageal cancer, with studies showing acceptable toleration and outcomes. Wang et al. analyzed seven patients treated with five- to nine-field IMRT chemoradiation to deliver a total dose of 59.4–66 Gy to the primary tumor [10]. With a median follow-up of 15 months, all patients achieved a complete response with three of the seven patients having no further evidence of disease. However, two developed local recurrences and two had distant metastases. Long-term effects included two patients requiring frequent dilation for

esophageal stricture and one patient developing a tracheal–esophageal fistula. A Chinese study reported the outcomes of 37 patients with cervical and thoracic esophageal cancer treated with IMRT chemoradiation between 2006 and 2008 [9]. Dose to the GTV was 64.56 ± 1.72 Gy with the CTV receiving 62.93 ± 1.45 Gy. The V5, V10, V20, and V30 of the lungs were 59.6 ± 12.8 , 39.5 ± 8.7 , 22 ± 5.4 , and 12.0 ± 4.3 %, respectively. The mean lung dose was 11.8 ± 2.5 Gy. The overall response rate was 97.3 % with a median follow-up of 13 months. Grades 3–4 acute and late esophagitis and grades 2–4 acute and late pneumonitis were 16.2 and 7.2, 10.8, and 8.1 %, respectively. The 1- and 2-year local control rates were 72.9 and 72.9 %, respectively. The 1- and 2-year overall survival rates were 80.9 and 67.4 %, respectively. Local recurrence (69.2 %) was the main reason of treatment failure. A Stanford series reported on 30 esophageal cancer (18 definitive; 12 preoperative) patients treated with IMRT chemoradiation between 2003 and 2007 [8]. The median dose delivered was 50.4 Gy. Median follow-up of surviving patients from the start of RT was 24.2 months. The 2-year LRC was 83 versus 51 % for patients treated preoperatively versus definitively ($p=0.32$). The 2-year DFS and OS were 38 and 56 %, respectively. Twelve patients (40 %) required feeding tube placement, and the average weight loss was 4.8 %. Twelve (40 %) patients experienced grade 3+ acute complications, and one patient died of complications following feeding tube placement. Three patients (10 %) required a treatment break. Eight patients (27 %) experienced grade 3 late complications. No grade 4 complications were seen. IMRT was effective and well tolerated. Finally, a Chinese study compared the outcomes of 60 esophageal cancer patients treated with either IMRT or 3DCRT concurrent with cisplatin and docetaxel. A total dose of 64 Gy was delivered in 30 fractions [11]. Response rates (complete and partial remissions) were higher in the IMRT group (90 versus 80 %; $p<0.05$). There was no difference in survival between IMRT and 3DCRT (3-year OS IMRT 66.7 % versus 3DCRT 63.3 %; $p>0.05$). Radiation-induced esophagitis was similar between IMRT and 3DCRT.

Conclusions

IMRT chemoradiation therapy for esophageal cancer with motion management is safe and effective with minimal toxicity. We report on the largest series of esophageal cancer patients with long-term follow-up showing low rates of radiation esophagitis and radiation pneumonitis. Prospective trials are needed to evaluate the role of IMRT in the management of esophageal cancer with potential promise in the exploration of simultaneous integrated boost strategies.

Conflict of interest The authors declare that they have no conflict of interest.

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