



## Phase III randomised trial

## Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: A prospective multi-centre randomized trial of the International Atomic Energy Agency

Eduardo Rosenblatt<sup>a,\*</sup>, Glenn Jones<sup>b</sup>, Ranjan K. Sur<sup>c,d</sup>, Bernard Donde<sup>e</sup>, Joao V. Salvajoli<sup>f</sup>, Sarbani Ghosh-Laskar<sup>g</sup>, Ana Frobe<sup>h</sup>, Ahmed Suleiman<sup>i</sup>, Zefen Xiao<sup>j</sup>, Subir Nag<sup>k</sup>

<sup>a</sup>International Atomic Energy Agency, Vienna, Austria; <sup>b</sup>Peel Regional Oncology Program, Credit Valley Hospital, Mississauga ON, Canada; <sup>c</sup>McMaster University, Hamilton, ON, Canada; <sup>d</sup>Juravinski Cancer Centre, Hamilton, ON, Canada; <sup>e</sup>University of Witwatersrand, Parktown, South Africa; <sup>f</sup>Hospital do Cancer A.C. Camargo, Sao Paulo, Brazil; <sup>g</sup>Tata Memorial Hospital, Mumbai, India; <sup>h</sup>University of Zagreb Faculty of Medicine, Croatia; <sup>i</sup>Radiation and Isotopes Centre, Khartoum, Sudan; <sup>j</sup>Chinese Academy of Medical Sciences, Beijing, China; <sup>k</sup>Kaiser Permanente Radiation Oncology, Santa Clara, CA, USA

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## ABSTRACT

**Background:** Whether the combination of high dose-rate brachytherapy (HDRBT) and External Beam Radiation Therapy (EBRT) is superior to HDRBT alone for the palliation of oesophageal cancer has only been explored in a previous IAEA pilot randomized trial.

**Methods:** Two hundred and nineteen patients were randomized to adding EBRT or not, after receiving two fractions of HDRBT within 1 week. Each HDRBT consisted of 8 Gy prescribed at 1 cm from source centre. Patients randomized to EBRT received 30 Gy in 10 fractions. The primary outcome was dysphagia-relief experience (DRE). Additional outcomes included various scores, performance status, weight and adverse events. A majority of charts, imaging and radiotherapy plans were externally audited.

**Results:** Median follow-up was 197 days, with a median OS of 188 days and an 18% survival rate at 1 year. DRE was significantly improved with combined therapy, for an absolute benefit of +18% at 200 days from randomization ( $p = 0.019$ ). In longitudinal regression analyses, scores for dysphagia ( $p = 0.00005$ ), odynophagia ( $p = 0.006$ ), regurgitation ( $p = 0.00005$ ), chest pain ( $p = 0.0038$ ) and performance status ( $p = 0.0015$ ) were all significantly improved. In contrast, weight, toxicities and overall survival were not different between study arms.

**Conclusion:** Symptom improvement occurs with the addition of EBRT to standard HDRBT. The combination is well tolerated and relatively safe.

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Oesophageal cancer is the sixth most common cancer worldwide in males, and ninth in females [1]. Greater incidence is observed in some developing countries, particularly in Asia and Africa, and the incidence in developed Western countries is increased [2]. Median survival is typically less than 6 months, with 80% of deaths related to progressive local disease [2]. This starkly contrasts with the outlook for the minority of patients who have limited disease who may be treated for a survival advantage with a protracted chemo-radiotherapy regimen [3] or tri-modality therapy [4].

Where palliation is the primary concern, prior studies have identified high dose-rate intra-luminal brachytherapy (HDRBT) as an efficient and safe mono-therapy [2,5–13]. An established regimen is two fractions of 8 Gy, each prescribed at 1.0 cm, which

has been tested in a previous IAEA-randomized trial [7]. It resulted in a median survival of 237 days and the incidences of strictures (11%) and fistulae (10%) were considered acceptable. Building on the success of an HDRBT-based approach can be problematic. First, adding concurrent chemotherapy to HDRBT increased toxicity and reduced dysphagia-free experience, in a non-curative regimen [14]. Second, the combination of HDRBT plus EBRT was shown to be superior to EBRT alone [15], but the converse, of adding EBRT to HDRBT, has not been studied.

The IAEA completed a prospective pilot-randomized trial [16] with 60 patients randomized to HDRBT vs. HDRBT plus EBRT, to determine the relative safety of combined therapy and to estimate any possible benefit in dysphagia-relief. Median survival was similar in both study arms (220 days) while dysphagia-relief was increased by an absolute +18% at 200 days, though without statistical significance ( $p = 0.4$ ).

Based on these pilot study findings, it was decided to conduct a prospective multi-centre randomized trial, as a replication with sufficient power to answer the question of whether the combination

\* Corresponding author. Address: Applied Radiation Biology and Radiotherapy Section, Division of Human Health, IAEA Wagramer Strasse 5, Vienna A-1400, Austria.

E-mail address: e.rosenblatt@iaea.org (E. Rosenblatt).

of HDRBT plus EBRT is superior to HDRBT alone. The results of this new trial are reported herein [17,18].

## Methods

This was a prospective multi-centre randomized clinical trial. Six countries (Brazil, China, Croatia, India, South Africa and Sudan) participated in patient accrual, treatment and follow-up. All centres had local ethics review board approvals and all patients provided written informed consent. Treatment was assigned centrally by the Data Management Centre (DMC) stratified by centres with 1-to-1 allocation to either of the two therapeutic options. Therapies were administered in a non-blinded manner, without placebo. All statistical analyses were conducted in accordance with intention-to-treat principles.

Baseline assessment included demographics, height and weight (body-mass index), and either chest X-ray or thorax CT, as well as abdominal ultrasound, blood work, endoscopy or barium swallow, and biopsy. Endoscopic ultra-sonography of the oesophagus was not required. Patients were staged using the TNM system, but with T assigned solely using the biopsy findings (i.e. pathology); i.e. tumour classification (T) was determined exclusively by biopsy. Nodal disease was noted based on chest X-ray or CT of the thorax. Screening for distant disease was not required, but suggestive symptoms were investigated to rule out metastases.

Study-eligible patients were those with: dysphagia prior to treatment; performance status Eastern Cooperative Oncology Group (ECOG) 1 to 2 (19); squamous cell carcinoma of the oesophagus; successful completion of one HDRBT insertion; and signed informed consent. Exclusion criteria included: fistulae at baseline; perforation during the first HDRBT; prior therapy (e.g. chemotherapy, laser, surgery, stent) except one prior dilatation; disease beyond the mediastinum, or being eligible and agreeing to potentially curative therapies. After completing the first HDRBT session, plus baseline symptom questionnaires, patients were randomized to HDRBT alone or to HDRBT plus EBRT. In patients with advanced local-regional disease, curative treatment was not indicated. In patients with earlier tumours, age, co-morbidities or patient's preference precluded the use of definitive therapy.

It was intended that all patients would receive their second HDRBT session between 2 and 7 days after the first session. Each session consisted of placing a standard 1.7 mm diameter catheter into applicators of 6–8 mm diameter in the lumen across the lesion under fluoroscopic or endoscopic guidance, and using X-ray imaging to confirm catheter position and determine dummy source positions. To facilitate HDRBT, dilatation was used where required prior to applicator insertion. The prescribed dose was 8 Gy at 1-cm from the active dwell positions, using equal dwell times, with the treatment length including the tumour plus a 2 cm margin at each end. The prescription was at 1-cm as is common practice for most oesophageal brachytherapy protocols [5–16]. It is to be noted that prescribing at 1 cm gives a dose of 16–27 Gy on the surface of an oesophageal

applicator of 1–0.6 cm diameter, respectively. Equal dwell times were used to reduce dosimetric “hot-spots” at each end of oesophageal mucosal surface. The prescribed dose was 8 Gy at 1-cm from the active dwell positions, using equal dwell times, with the treatment length including the tumour plus a 2 cm margin at both ends.

EBRT was planned to commence within 7 days of the second HDRBT session, and within 14 days of the first HDRBT session. Anterior and posterior fields were used to administer 30 Gy in 10 fractions over 2 weeks to the midline, with a minimum width of 7 cm to cover the mediastinum, and with both upper and lower field edges to be 3 cm distal from tumour limits. The energies used were from 1.25 MV up to 15 MV photons.

During the first 6 weeks, allowed co-interventions included dilatation if required. Medications for acute symptoms, nutrition supplements and a feeding gastrostomy were allowed as required. Other interventions were proscribed (e.g. oesophageal surgery, stent, non-study-assigned EBRT). However, where metastases developed within 6 weeks, external beam radiation was allowed for these, recording whether such radiation overlapped into the mediastinum.

Patients were followed identically regardless of initial treatment assignment, except for the 2 weeks during which EBRT was administered. After completing all therapies, patients were assessed for 6 weeks after randomization, and then on every month. Assessments included symptom scoring, weight and performance status, plus a general clinical review. Scores and performance status were determined by physicians interviewing patients. Patients were not routinely screened for loco-regional recurrence, progression or distant metastases, but arising symptoms were used to direct further clinical and imaging investigations. Table 1 presents the definition of scores used to measure dysphagia, odynophagia, regurgitation, chest-back pain, and ECOG performance status [19,22].

### Definition of dysphagia-relief experience (DRE)

Dysphagia-relief experience (DRE) was determined in the same manner as in the preceding pilot study [20] and a previous IAEA-randomized trial comparing two brachytherapy methods [21].

To constitute a significant event during follow-up: (a) patients must have experienced an increase in dysphagia score over baseline to an absolute 3 (dysphagia to liquids) or 4 (total obstruction); or (b) the score deteriorated to a 2 (dysphagia to semi-solids) which was sustained for 1 month, scored at the time of the first occurrence of a “2”; or (c) a diagnosis of a trachea-oesophageal fistula (TEF) was made; or (d) additional treatment intended to relieve dysphagia (e.g. placing a stent, dilatation, EBRT to the oesophagus) was given. Censoring occurred if the patient was: (a) still well at last follow-up; (b) chemotherapy was initiated within 6 weeks from first HDRBT session (one patient); or (c) radiation to a metastasis exposed the mediastinum to radiation (one patient). This approach to determine a dysphagia event combines data from serially measured

**Table 1**  
Definition of scores for symptoms, performance status and quality of life (QOL).

	0	1	2	3	4
Dysphagia	Able to eat normal diet	Able to swallow some solids	Able to swallow only semi-solid foods	Able to swallow liquids only	Unable to swallow anything/complete obstruction
Odynophagia	No pain on swallowing	Mild pain	Moderate pain	Severe pain	–
Regurgitation	None	Infrequent	Frequent	Constant	–
Chest-back pain	None	Relieved by non-narcotics	Relieved by narcotics	Not relieved by narcotics	–
ECOG performance status scale	Asymptomatic, normal activity	Symptomatic but fully ambulatory	Symptomatic, in bed less than 50% of the time	Symptomatic, in bed more than 50% of the time	Bedridden
QOL score	“A lot better”	“A little better”	“The same”	“A little worse”	“A lot worse”

dysphagia scores using the Mellow–Pinkas categorization [22] with clinical events, such as TEF or stent placement.

Toxicities were assigned when diagnosed subsequently to the first HDRBT treatment. A serious adverse event (SAE) meant a procedure-related death, perforation, massive bleeding, fistulae, strictures or ulcers. Overall survival (OS) was determined in days from the date of the first HDRBT session until last follow-up or death. During follow-up, local and distant failures were recorded with their dates of occurrence.

Data quality was assessed by auditing the patient's charts, radiotherapy plans and related imaging. Sudan and South Africa contributed a majority of patients. Overall, 80% of cases were centrally reviewed.

Statistical aspects of this study were conducted at the DMC using Stata (versions 8, 10 and 11; College Station TX). Initial sample size was calculated assuming an alpha of 0.05, a 2-sided log-rank test, an expected difference of +18%, and a control group benefit of 45% for the primary outcome of dysphagia-relief; 220 patients were needed (power = 77%). The Kaplan–Meier method was used to generate time-dependent, right-censored plots referenced to the date of first HDRBT for each patient, with tests for significance by log-rank. Hierarchical Cox regression analyses for overall survival were conducted to determine significance. Data for ordinal scales were panel-longitudinal, and so were first explored by Response Feature Analyses plus Area Under the Curve (AUC) as recommended by Fayers and Machin [23]. Regression models were developed for each scale: dysphagia, odynophagia, regurgitation, chest pain, and ECOG. Panel data for weight were explored using General Linear and Mixed Modeling [24].

## Results

The primary study question was whether “dysphagia-relief experience” (DRE) is improved by adding EBRT to HDRBT. That finding is presented later in this section, as DRE is comprised of a combination of several events that are presented first individually.

### Patient and disease characteristics

From March 2003 to June 2006, 219 patients entered the study: 73 from Sudan, 66 from South Africa, 29 from India, 20 from Croatia, 16 from China, and 15 from Brazil. Median delay from diagnostic biopsy to first HDRBT was under 2 weeks. Randomization was to HDRBT alone ( $n = 109$ ) or to combined therapy ( $n = 110$ ). No patients were excluded from the study after the first HDRBT, as randomization occurred rapidly. Baseline patients' characteristics for the whole trial

( $n = 219$ ) and according to study arm are shown (Table 2), and there were no statistical differences. By Analysis of Variance, body-mass index was associated with both sex ( $p = 0.021$ ) and ECOG ( $p < 0.0001$ ), and weight was associated with T stage ( $p = 0.046$ ; 51.6 kg for T1, 49.4 kg for T2, and 44.0 kg for T3), but not with N ( $p = 0.8$ ). ECOG was not significantly associated with T or N. Stages according to the TNM-UICC system are also presented (Table 2).

### Protocol therapies

All 219 patients completed the first HDRBT session successfully prior to randomization. Only 212 were able to receive a second HDRBT session as 3 expired early, 2 HDRBT were attempted but failed, and 2 patients refused a second application. The average days to second HDRBT ( $n = 212$ ) was 4.9 (median 5 days, range 1–19, with only five (2%) of patients exceeding 7 days due to patient preference or scheduling difficulties. Randomization to EBRT was revealed prior to the second HDRBT, but there were no statistical differences between the study arms in days-to-second-HDRBT, type of guidance for HDRBT, use of NG tube, and length of the second HDRBT (each  $p > 0.2$ ). The average treated length was 10.6 cm (range 6–19) for both the first and second HDRBT's.

For those patients randomized to EBRT ( $n = 110$ ), 102 received at least one fraction of EBRT because 4 patients expired early, and 4 further patients refused EBRT. In all, 98/110 (89%) patients received exactly 30 Gy in 10 fractions over 2 weeks. Average field width was 7.4 cm (range 7–10, median 7), and average length was 12.7 cm (range 9–18, median 13). Machine energy was Cobalt-60 in 85% of patients; 3–5 MV in 6%; and 6–15 MV in 9%. Overall, 98% of plans were 2-dimensional, based on a single horizontal contour at the isocenter.

Patients were eligible for co-interventions based on acute symptoms, and were eligible for eventual EBRT if there was a locally progressive disease later. Only two patients received ‘inappropriate’ co-interventions during the first 6 weeks. The first received systemic chemotherapy 33 days after the first HDRBT session, and the other received a stent 10 days after the first HDRBT session. These were not statistically significant across study arms. Of the 109 control patients who were not assigned to EBRT by random allocation, 21 received delayed EBRT. The average field size was 7.4 cm by 12.1 cm, and the most typical schedule was 30 Gy in 10 fractions as per protocol.

### Follow-up and overall survival (OS)

By Kaplan–Meier plot, median follow-up for all 219 patients was 197 days (range 0–774 d; median 161, 95% CI: 151–188 d)

**Table 2**  
Patient initial characteristics.

Variable	Whole group $N = 219$ (range)	HDBT group $N = 109$	HDBT + EBRT group $N = 110$	2-Tailed $p$ -value for difference
Age, yr	61.3 (15–102)	61.9	60.7	0.45
Male:Female	130:89 (59%:40.6%)	60:49 (27%:22%)	70:40 (32%:18%)	0.22
Height, cm	159 (123–190)	159	160	0.66
Weight, kg	49.1 (21–131)	49.7	48.5	0.51
Body-mass-Index	19.4 (10.7–40.2)	19.8	19.0	0.24
ECOG (1:2)	169:50 (77%:23%)	85:24 (38.8%:11%)	84:26 (38%:12%)	0.67
T (1:2:3)	49:139:31 (22.3%:63%:14%)	24:68:17 (11%:31%:7.7%)	25:71:14 (11%:32%:6.4%)	0.85
N (0:1)	189:30 (86%:14%)	95:14 (43.3%:6.4%)	94:16 (43%:7%)	0.85
TNM (UICC) stage	Stage I – 43 (19%) Stage IIA – 143 (65%) Stage IIB – 13 (6%) Stage III – 17 (8%)	Stage I – 24 (22%) Stage IIA – 71 (65%) Stage IIB – 5 (5%) Stage III – 9 (8%)	Stage I – 22 (21%) Stage IIA – 72 (65%) Stage IIB – 8 (7%) Stage III – 8 (7%)	0.85
Tumour length	6.7 cm (2–15)	6.7	6.6	0.97
Grade (1:2:3:n/a)	30:108:36:45 (13.6%:49%:16%:20.5%)	22:12:56:19 (10%:5.4%:25.5%:8.6%)	23:18:52:17 (10.5%:8%:23.7%: 7.7%)	0.66
Location (proximal:distal)	46:173 (21%:79%)	24:85 (11%:39%)	22:88 (10%:40%)	0.55

HDBT: High dose-rate brachytherapy.  
EBRT: External Beam Radiation Therapy.

**Table 3**

Occurrence of significant events. The numbers in the table represent events. Some patients had more than one type of event.

Event	Whole group N = 219	HDBT group N = 109	HDBT + EBRT group N = 110	2-Tailed p-value for difference
Perforation	4	1	3	0.62
Stricture	6	1	5	0.21
Stent	11	3	8	0.22
Dilatation	28	13	15	0.84
Fistulae	19	7	12	0.34
Second-line EBRT	21	21	0	n/a
Chemotherapy	2	1	1	1.00

HDBT: High dose-rate brachytherapy.  
EBRT: External Beam Radiation Therapy.

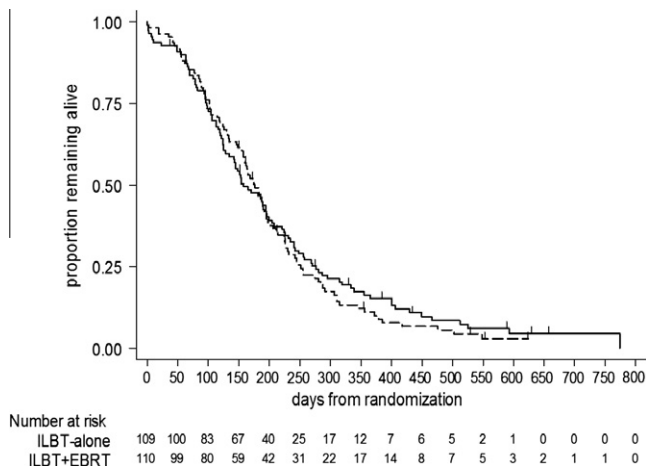
with a one-year OS of 18%. The Kaplan–Meier plots for OS by study arm are shown (Fig. 1). At the last follow-up, 46 patients were alive (i.e. censored at last follow-up) and there were 173 deaths (a 79% crude mortality). Of 128 patients identified with progressive disease in the oesophagus during follow-up, 110 had expired. Of 26 patients identified with distant failure during follow-up, 19 were deceased (11 of these 19 also had local failure). Attributed causes of death for the 173 patients deceased were: 69% due to oesophageal cancer (over 90% of these were from local failure); 3% from adverse events, 23% from infections and from cardiovascular events, and 5% from an uncertain cause but were not treatment-related.

The log-rank, 2-tailed *p*-value, with stratification by country, was 0.35 comparing both study arms. Overall survival was significantly influenced by both age and ECOG on a univariate log-rank analysis. Step-wise regression led to a model with only older age ( $p = 0.002$ ) and lower ECOG ( $p = 0.038$ ) as significant predictors of better survival. Thus, randomization to EBRT was clearly not associated with improved overall survival.

#### Important clinical events

##### Toxicities

There were four perforations. Three were related to HDRBT, but one was related to dilatation. Their impact is captured in the overall survival analyses, since all four patients died from these events. One additional patient died from dehydration following the first HDRBT session, failing to return to hospital.



**Fig. 1.** Overall survival by study arm. There is no difference between study arms in overall survival. X axis: days from randomization in intervals of 50 days. Y axis: proportion without event. Solid line: HDR + EBRT. Dashed line: HDR alone. The following patients were at risk in each arm of the study (HDR/HDR + EBRT) at the following time points: at 0 days 109 and 110 patients, respectively: at 100 days, 83 and 80 patients: at 200 days, 40 and 42 patients and at 300 days, 17 and 22, at 400 days, 7 and 14 patients. HDR: intra-luminal brachytherapy. EBRT: External Beam Radiation Therapy.

##### Dilatation and fistulae (Table 3)

The log-rank, 2-tailed *p*-values, for the ordering of these events stratified by country are 0.97 and 0.36, respectively. The chance of receiving a dilatation was about 20% at 400 days of follow-up, and the chance of a fistula was about 25%.

##### Strictures and stents (Table 3)

Strictures were not scored as a dysphagia-event unless they were associated with dysphagia for which dilatation may have been administered. Otherwise, discovery of a stricture ( $n = 6$ ), mucositis ( $n = 1$ ) and necrosis ( $n = 1$ ) were incidental, found on a follow-up endoscopy. By Kaplan–Meier method, the chance of developing a stricture was about 10% at 400 days of follow-up. Placing a stent was an “event” for dysphagia analysis, but in all 11 cases where a stent was used it was directly associated with another reason for a dysphagia-event (i.e. second-line EBRT, trachea-oesophageal fistula, and dilatation, or an increase in dysphagia score). By Kaplan–Meier method, the chance of requiring a stent was about 15% at 400 days of follow-up.

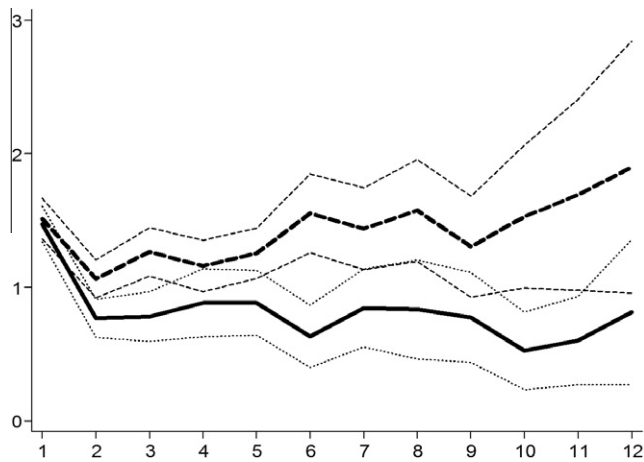
Metastases: Overall, 26 patients (12%, 13 patients on each arm) developed distant metastases during follow-up. The estimated risk was similar in both arms of the study, 25% at a follow-up of 400 days. Nine of the 47 locations of distant metastases were irradiated. Two of the HDRBT-alone patients received radiation overlying the mediastinum for metastases, and one patient required this subsequent to combined therapy. Protocol EBRT to the oesophagus had no influence on occurrence, time-to metastases, and patterns of distant metastases. There were two events that required statistical censoring of subsequent follow-up for the DRE analyses. These were administration of chemotherapy in one patient, and radiation for metastases overlying the mediastinum in another. The remaining two patients who received chemotherapy, and the two patients who received radiation overlying the mediastinum for metastases, did not contribute as censored events, as these occurred subsequently to a previous study-relevant event.

At the median 188 days of OS we observed: perforations 2%, strictures 2%, dilatations 16%, TEF 7%, stent placement 4%, metastasis 10%, 2nd EBRT course 11% and any event 13% at 188 days and 39% at 400 days.

##### Symptoms

At baseline, the scores for all four initial symptoms (dysphagia, regurgitation, odynophagia and chest/back pain scores) were not statistically different. Baseline scores are included in all analyses that compare findings across study arms.

After treatment, the global mean dysphagia scores were 1.23 for HDRBT alone, and 0.79 for HDRBT + EBRT, which is a difference of  $-0.44$  (i.e. dysphagia was improved) (Fig. 2). Similarly, mean odynophagia scores were 0.81 and 0.58 for a difference of  $-0.23$  (improved). The global mean regurgitation scores were 0.72 and 0.36 for a difference of  $-0.36$  (improved). The mean ECOG score for



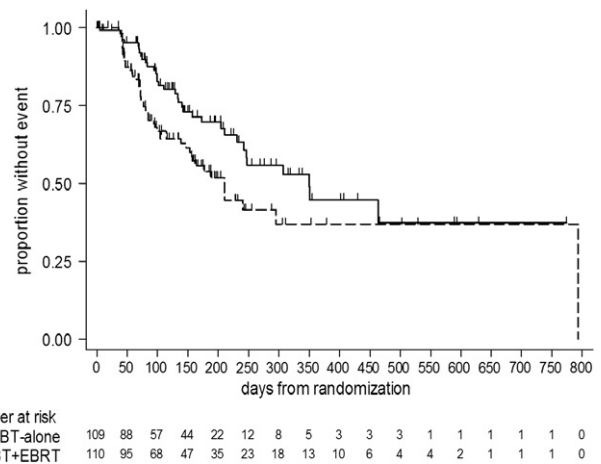
**Fig. 2.** Dysphagia scores during follow-up. Dysphagia score is lowered in the group receiving combined modality therapy. X axis: time in weeks from randomization. Y axis: dysphagia score. Solid line: HDR + EBRT. Dashed line: HDR alone. HDR: intra-luminal brachytherapy. EBRT: External Beam Radiation Therapy. The following table details the number of patients at risk at various time intervals.

Month	HDR arm	HDR + EBRT arm
1	109	110
2	96	90
3	83	82
4	69	68
5	63	60
6	56	49
7	41	45
8	33	36
9	23	31
10	17	21
11	13	20
12	10	16

the HDRBT group was 1.29, and it was 0.89 with combined therapy, so ECOG was lower by an average of  $-0.40$  points for the HDRBT + EBRT study arm (improved).

#### Dysphagia-relief experience (DRE)

Reasons for assigning a dysphagia-event by study arm are presented (Table 4), and the resultant DRE plot is shown (Fig. 3). The log-rank, 2-tailed  $p$ -value, stratified by country, for a statistically significant difference between arms was 0.019, less than the alpha cut-off value of 0.04. Therefore, this randomized trial is a 'positive study' regarding the primary end-point, showing benefit of EBRT added to HDRBT in the palliation of oesophageal cancer. At 100 days, the DRE was 66.7% with HDRBT alone, but it was 82.7%



**Fig. 3.** Dysphagia-relief experience by study arm. The difference in absolute, estimated per cent chance of not having experienced a dysphagia-event, and in favor of the addition of EBRT to HDRBT, was of +18% at 200 days. X axis: days from randomization in intervals of 50 days. Y axis: proportion without event. Solid line: HDR + EBRT. Dashed line: HDR alone. HDR: intra-luminal brachytherapy. EBRT: External Beam Radiation Therapy. Numbers of patients at risk for the study arms HDR and HDR + EBRT are, respectively, 22 and 35 at 200 days, and 3 and 10 at 400 days.

with combined therapy. At 200 days, the respective values were 51.8 and 69.6%; at 300 days these were 36.9 and 55.9%, indicating a continued benefit. Therefore the estimated differences in absolute percent chance of not having experienced a dysphagia-event, and in favor of the addition of EBRT to HDRBT were +16.0%, +17.8% and +19.0%, respectively. These findings confirm the estimated benefit in the pilot-randomized study of +18% at 200 days. Cox regression analyses were conducted hierarchically. For the addition of EBRT the  $p$ -value was 0.022, ignoring other variables. Then, during stepwise addition of covariates,  $p$ -values were always  $<0.02$ , and the final  $p$ -value was 0.014 in favor of a combined therapy, stratified by country. No other variable was significantly associated with DRE once the addition of EBRT was taken into account.

Stratified analyses by country were conducted for the main outcomes, and  $p$ -values for the corresponding non-stratified analyses were similar,

#### Quality assurance

In total, over 80% of cases in the trial were audited. In addition, at the time of analysis 97% of all expected forms had been submitted for this study to the DMC. With no differences across study arms, 81% of patients had complete records and 19% had an interruption in follow-up of 6 weeks or more, but typically only one or 2 months of follow-up were missed due to patient non-compliance with scheduled visits.

**Table 4**

Co-interventions during the first 6 weeks. The numbers in the table represent events. Some patients had more than one type of event.

Action	Whole group N = 219	HDBT group N = 109	HDBT + EBRT group N = 110	2-Tailed $p$ -value for difference
Feeding bypass	9	7	2	0.091
Nutritional supplements	21	8	13	0.24
I.v. nutrition	10	5	5	0.99
Prescriptions for pain medications	63	30	33	0.62
Systemic steroids	23	11	12	0.81
Anti-nauseants	5	1	4	0.17
Radiation to distant metastases	1	1	0	0.32

HDBT: High dose-rate brachytherapy.  
EBRT: External Beam Radiation Therapy.

## Discussion

Patients with loco-regionally advanced non-resectable cancer of the oesophagus are frequently treated with combined chemo-radiotherapy with a median overall survival of approximately 11–15 months [3,25–27]. Chemo-radiotherapy with definitive intent may be difficult to implement in countries with limited resources, cure is very rare and in practical terms the main clinical problem faced is the palliation of severe dysphagia.

Patient populations in the mentioned trials were specifically selected following eligibility criteria which included a Karnofsky performance status of 60 or greater, an adequate nutritional intake, absence of medical co-morbidities and signing informed consent for definitive therapy. These selection criteria were not used in the present population of patients.

In the present trial, patients with extra-mediastinal disease were excluded in order not to have two populations of patient with different survival rates; those with and those without metastatic disease. Squamous carcinoma histology was selected since it is the prevalent histology in developing countries.

In the curative setting, using brachytherapy after EBRT appears more appropriate to be able to fully dose the entire tumour diameter therefore delivering not much lower doses to the peripheral tumour parts. In the series reported by Sur et al. [15] EBRT was given first in order to facilitate HDRBT applicators insertion. In the present study, dilatations have been used for this purpose when indicated.

The main conclusion from this trial is that the addition of EBRT to HDRBT improved dysphagia-relief experience (DRE). The average benefit was an absolute +18% improvement in DRE which was sustained between 50 to 350 days of follow-up. The overall improvement in mean dysphagia score was  $-0.44$ . While HDRBT alone produced, on average, a relatively stable dysphagia score, the addition of EBRT led to a further reduction in the score compared with that from HDRBT alone. Analyses using longitudinal ordinal regression as appropriate for categorical data and using all available data in the trial demonstrated clear statistical differences in dysphagia scores over study arms through follow-up. Despite clearly improved function and symptoms, local failure remained the dominant cause of death. Overall survival was not statistically different between the two study arms. It is to be noted that prescribing the brachytherapy dose at 1 cm gives a dose of 16–27 Gy on the surface of an oesophageal applicator of 1–0.6 cm diameter, respectively. This high dose can be expected to produce oesophageal fibrosis and strictures in the long term.

Strengths of this trial include: design (prospective, random allocation); inclusion of patients from six countries (generalizability); confirmation of an hypothesis developed in a smaller pilot study (replication); inclusion of associated measures such as weight and performance status (convergence); mature follow-up, with little loss to follow-up; audits of 80% of radiation prescriptions, physics plans and imaging; therapies proficiently given as per protocol; fewer than 20% cross-over to second-line EBRT; and data regarding second HDRBT and co-interventions confirmed as not different between study arms. A limitation in the reporting of this study is that the determination of initial stage of disease, as in classifying tumour (T) only by biopsy, and nodes (N) only by chest X-ray or, in a minority of cases, by CT scan, may under-stage disease. However, field sizes and audits of simulator, X-ray and CT images confirmed that most patients had disease that was locally extensive, likely to be a T3 or T4 and possibly with positive nodes. Some patients certainly had more limited local disease, but these were included in this trial because they also had substantive co-morbidities, or a patient preference not to experience chemo-radiation or radical radiotherapy. Noteworthy is that the benefit of adding EBRT to

HDRBT was seen uniformly across T and N status in this trial, so including some patients with limited disease but with co-morbidities or other preferences is not a limitation of the study, but a factor that may increase generalizability of the findings. Fewer patients with T3–4 disease entered the trial because dilatation to facilitate the first HDRBT was not always undertaken and furthermore, only patients with a successful first HDRBT session were eligible to be randomized. Another limitation in an international clinical trial is that socio-cultural factors may influence patient experience of symptoms, or interpretations of symptom questions. However, stratified analyses by country were conducted for the main outcomes, and *p*-values for the corresponding non-stratified analyses were similar, so stratification did not actually affect the main conclusion. In summary, potential limitations draw attention to the need for further research, but these do not detract appreciably from the main finding of this trial.

There was no evidence in this trial that toxicities and adverse events differed significantly between the study arms. Crude rates and time-to-development of important clinical events such as fistulae and strictures were comparable, with non-significant 2-tailed *p*-values. Although the estimated chance of developing one or more of these events by Kaplan–Meier method approached 25% during follow-up out to 400 days, fewer than 18% of patients are exposed to such risks due to a low one-year overall survival. Within a context of relatively short survival, mostly due to local failure, present levels of toxicity appear clinically acceptable and should not limit the use of combined therapy if given as described in this study.

Other methods of palliation for oesophageal cancer are optional. One randomized trial compared placing a stent to a single HDRBT session of 10 Gy [28]. That study demonstrated in the short term that a stent was superior to HDRBT, but in the longer term the HDRBT was superior to the stent. In our trial, HDRBT consisted of 8 Gy  $\times$  2 fractions, and EBRT provided additional benefit to HDRBT. This suggests that HDRBT plus EBRT should be superior to placing a stent, but a randomized trial of these two options may be required to definitively answer the question.

In conclusion, a brief course of ten fractions of EBRT may be safely added to HDRBT. It improves positive outcomes for patients with squamous cell carcinoma of the oesophagus for palliation of dysphagia. Whether the course of EBRT can be further shortened in the palliative setting is currently under investigation [29].

## Conflict of interest statement

The authors hereby declare that they have no personal or financial interests with people or organizations that could inappropriately influence their work. The sole source of sponsorship of this trial has been the International Atomic Energy Agency (IAEA) under Coordinated Research Project E3.30.21. The IAEA has had an active role in the planning, study design, analysis and interpretation of the data.

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