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RESEARCH PAPER

# Radiotherapy in palliation of thoracic tumors: a phase I–II study (SHARON project)

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## Abstract

The main clinical goal for patients with advanced or metastatic thoracic cancer is palliation of tumor-related symptoms and improvement of quality of life. The aim of this phase I–II trial was to define the maximum tolerated dose (MTD) of a short-course of palliative radiotherapy (RT) and to evaluate its efficacy in terms of palliative response. A phase I trial was planned with escalating dose increments. Total doses ranged from 16 to 20 Gy delivered (BID) in two consecutive days. Dose limiting toxicity was defined as any acute grade $\geq 3$ toxicity based on the RTOG scale. MTD was used in the phase II trial to evaluate the efficacy of this regimen using a two stage Simon's design. Fifty-four patients were enrolled. The upper dose level of 20 Gy was defined as the MTD. In patients treated with this dose, the overall palliative response rate was 96.5% (CI 0.95: 81.3–99.9%). Complete pain relief rate was 50.0%. Median survival without symptomatic progression was 3 months. The tested short course accelerated regimen was well tolerated and effective in the palliative setting of metastatic or locally advanced chest cancer. A phase III trial is ongoing to validate this RT schedule.
Trial registration: NCT03465553.

**Keywords** Lung cancer · Radiotherapy · Palliative care · Pain · Quality of life · Phase I–II

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### Abbreviations

| | |
|---|---|
| CTV | Clinical target volume |
| CT | Computed tomography |
| DLT | Dose limiting toxicity |
| DVH | Dose-volume histograms |
| GTV | Gross tumor volume |
| MTD | Maximum tolerated dose |
| NSCLC | Non-small cell lung cancer |
| OaR | Organs at risk |
| PTV | Planning target volume |
| QoL | Quality of life |
| RT | Radiotherapy |
| SHARON | SHort course Accelerated RadiatiON therapy |
| VAS | Visual Analogue self-assessment Scale |

## Introduction

Lung cancer is the leading cause of cancer-related death globally, accounting for about 19.4% of all malignancies [1]. Moreover, the lung is a frequent site of hematogenous metastases. Palliative chest radiotherapy (RT) plays a significant

role in patients with advanced or metastatic lung cancers. In fact, in patients not amenable to curative treatments, the main clinical goal is to relieve tumor-related symptoms such as cough, hemoptysis, chest pain, dyspnea, and mediastinal syndrome [2, 3]. In this setting, the optimal RT fractionation regimen has not yet been established [4].

In palliative RT, the use of regimens lasting a few days is considered very useful. The reasons for preferring short treatments are several: (1) the short life expectancy, (2) the need for systemic treatments which could be delayed or interrupted in case of prolonged RT, (3) the need for hospitalization to undergo RT for patients with worse physical conditions, and therefore the usefulness of minimizing the duration of stay outside their home, (4) the frequent need for admission to Hospice which would be delayed in case of prolonged treatments.

Furthermore, a short palliative treatment is particularly useful for patients who live far from RT centers. These patients have to face uncomfortable daily shifts or must temporarily relocate to stay nearer to the RT center. These problems produce obvious physical, psychological, and economic discomfort.

For these reasons, in our center we tested a regimen of accelerated RT (BID, in two consecutive days of treatment) in different settings [5–9]. All these trials are part of a project aimed at the optimization of palliative RT (SHARON: SHort course Accelerated RadiatiON therapy). In the design of these studies, we considered that the reduction in treatment duration is potentially related to a higher incidence of acute toxicity. Therefore, in the different clinical situations, the experimentation began with phase I trials aimed at maximum tolerated dose (MTD) definition [6, 7, 9]. Once MTD was established, phase II studies were performed to evaluate the symptomatic response [5, 6, 8, 9].

Therefore, the aim of this analysis is to present the results of the phase I and the phase II trials performed in the setting of advanced chest neoplasms.

## Materials and methods

### Eligibility

Patients with histologically proven advanced lung cancer (non-small cell lung cancer—NSCLC and small cell lung cancer) not amenable for curative treatments, or with radiologically proven metastases in the chest from any primary site were enrolled in the study. Inclusion criteria were the following: age $\geq 18$ years, performance status $\leq 3$ (ECOG scale), no prior RT to the same site, and exclusion from curative therapy due to disease stage and/or multiple comorbidities and/or poor performance status. Systemic therapies were allowed only with $\geq 10$ days interval from RT.

### Patients evaluation

Clinical history, physical examination, complete blood test, chest computed tomography (CT) scan, data about symptoms, performance status, and quality of life (QoL) were recorded at baseline and at each follow-up visit. A Visual Analogue self-assessment Scale (VAS) was used to score pain [10]. Pain intensity and the use of analgesics were also scored according to the International Atomic Energy Agency scale (pain and drug scores) [11]. QoL was evaluated with the CLAS visual analogue scales [12].

### Study design

#### Phase I trial

A dose-escalation study was performed to establish the MTD. Once reached, the MTD was subsequently used in the phase II trial to evaluate the symptomatic response. The MTD was defined as the dose level below the highest delivered dose associated with dose limiting toxicity (DLT) in at least one-third of patients. A DLT was considered as any grade $\geq 3$ acute toxicity based on the RTOG scale [13]. A minimum of six patients, observed almost 3 months after RT to allow a complete evaluation of acute toxicity, were enrolled at each dose level. If DLT was observed in $< 2/6$ patients at a given dose level (provided that at least 3 months of follow-up had passed since the sixth patient enrolled at the last dose level completed the RT), the trial proceeded to the next dose level. If DLT occurred in 2/6 patients at a given dose level, treatment of six additional patients was required at the same dose level. If DLT occurred in $> 2/6$ patients, dose escalation was stopped and the dose level below that was considered as the recommended phase II dose. If DLT occurred in $\geq 4$ patients of an expanded 12-patient cohort, dose escalation was stopped and the next lower dose level below that was considered the recommended phase II dose. If DLT occurred in $< 4$ patients of an expanded 12-patient cohort the trial proceeded to the next level.

#### Phase II trial

Data on treatment efficacy were analyzed in phase II of the trial with the sample size calculated based on the Optimal Simon's two-stage design [14]. This statistic design verified the null hypothesis that the symptomatic response rate would improve from 10.0 to 30.0% without and with RT, respectively, with an $\alpha$ and $\beta$ error of 0.05 and 0.2, respectively. Based on this design, the enrolment of ten patients was planned in the first stage of the trial. In case of $\leq 1$ symptomatic response recorded in the first ten patients, the closure

of the study was planned, and the treatment evaluated in the trial would have been considered ineffective. In case of at least two symptomatic responses were recorded in the first 10 patients, the continuation of the study was planned with the inclusion of an additional 19 patients. In this second scenario the treatment would have been considered ineffective in case of ≤ 5/29 symptomatic responses. Based on this study design, in the case of a true response probability of 10%, the expected sample size and the probability of early termination of the trial were 15.0 and 0.74, respectively.

### End-points

The primary end-point was to establish the MTD in the phase I trial, while in the phase II trial the primary end-point was the symptomatic response. Secondary end-points were the evaluation of treatment impact on QoL and duration of symptomatic relief.

### Planning

All patients underwent a pre-treatment CT-scan simulation and treatment in supine position with their arms over the head. Planning CT slices for each patient were obtained at 5-mm intervals. The gross tumor volume (GTV) was defined as the primary tumor or as the metastatic site visible on the CT scans. The clinical target volume (CTV) was defined as the GTV with an expansion of 1 cm in all directions. The planning target volume (PTV) included the CTV plus 1-cm expansion in radial direction and 1.5 cm in cranial-caudal direction. The following organs at risk (OaRs) were also delineated: spinal cord, heart, and oesophagus. RT was planned and delivered with three-dimensional conformal technique. Dose prescription and specification were done according to the ICRU Report 62 [15]. The dose distribution was analyzed with the dose-volume histograms (DVH) to ensure maximum target coverage and optimal OaRs sparing.

### Treatment

RT was delivered using an Elekta Precise Linac (Elekta, Crawley, UK) equipped with standard multi leaf collimators (MLC). Three total dose levels were planned in the phase I trial: 16 Gy, 18 Gy, and 20 Gy in 4 Gy, 4.5 Gy, and 5 Gy per fraction (BID for two consecutive days), respectively. According to the linear-quadratic model and using an $\alpha/\beta$ ratio = 3 for late toxicity, the equivalent dose in 2 Gy fractions corresponded to 24.1 Gy, 27.8 Gy, and 32.0 Gy, respectively [16]. The two daily fractions were separated by an 8 h interval to allow normal tissue repair. Treatment planning was verified through a quality assurance procedure based on several independent checks and before each fraction a set-up verification was performed using an electronic portal imaging device as previously described [17, 18].

### Follow-up

Follow-up assessment included an update on the patients' anamnesis, physical examination, and full blood panel at 2 weeks and then every 2 months after RT. Data about RT-induced toxicities, symptomatic response, performance status, and QoL were recorded and scored. RTOG and EORTC–RTOG scales were used to evaluate acute and late toxicities, respectively [16]. A VAS score of 0 was considered as complete pain resolution while a reduction of pain severity or drug score were considered as partial response. In addition, the reduction of other symptoms and/or of the related medications was considered as partial response, while the disappearance of the symptom and the interruption of the related medications was considered as a complete response.

### Statistical analysis

The IBM SPSS Statistic version 20 software package was used for statistical analysis. Categorical variables were evaluated using absolute and relative frequencies while continuous variables were reported as median and range. Symptomatic response was calculated from the date of RT completion until the date of symptoms recurrence or progression using the Kaplan–Meier method [19].

### Ethical issues

All patients signed an informed written consent before enrolment in the trial. The study was approved by the institutional review board and was performed according to the International Conference on Harmonization—Good Clinical Practice (ICH-GCP). The trial was registered in an international public registry (ClinicalTrials.gov: NCT03465553).

## Results

### Patient characteristics

A total of 54 patients were enrolled in this trial (phase I: 25 patients; phase II: 29 patients). Figures 1 and 2 illustrate the Consolidated Standards of Reporting Trials diagrams of phase I and phase II trials, respectively. Patients characteristics are shown in Table 1. 34 (63.0%) and 20 (37.0%) patients had locally advanced lung cancer and metastases in the lungs, respectively. The overall primary sites were: lung (63.0%), uterus (9.3%), colon (7.4%), rectum (5.5%),

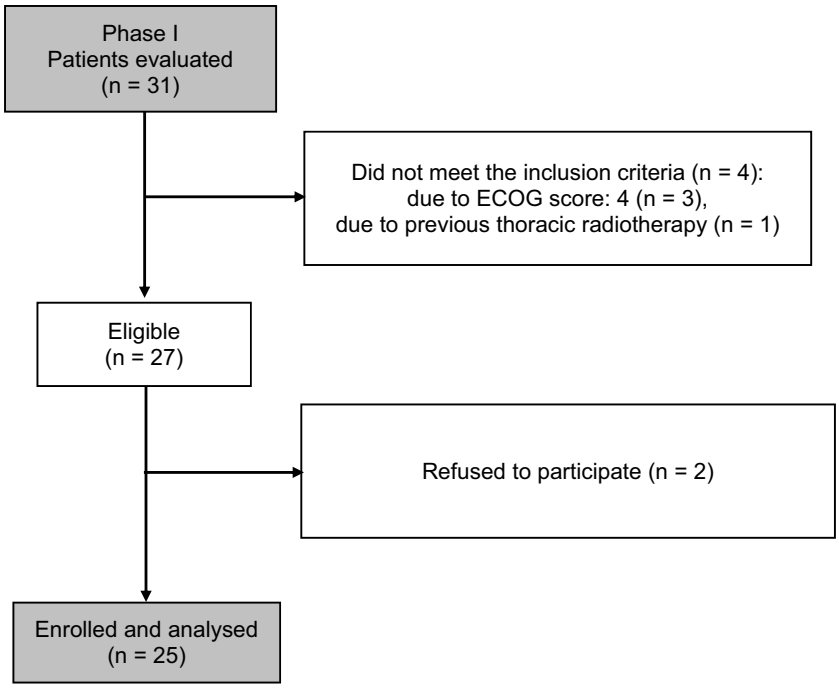


**Fig. 1** Consolidated Standards of Reporting Trials diagram of the phase I trial

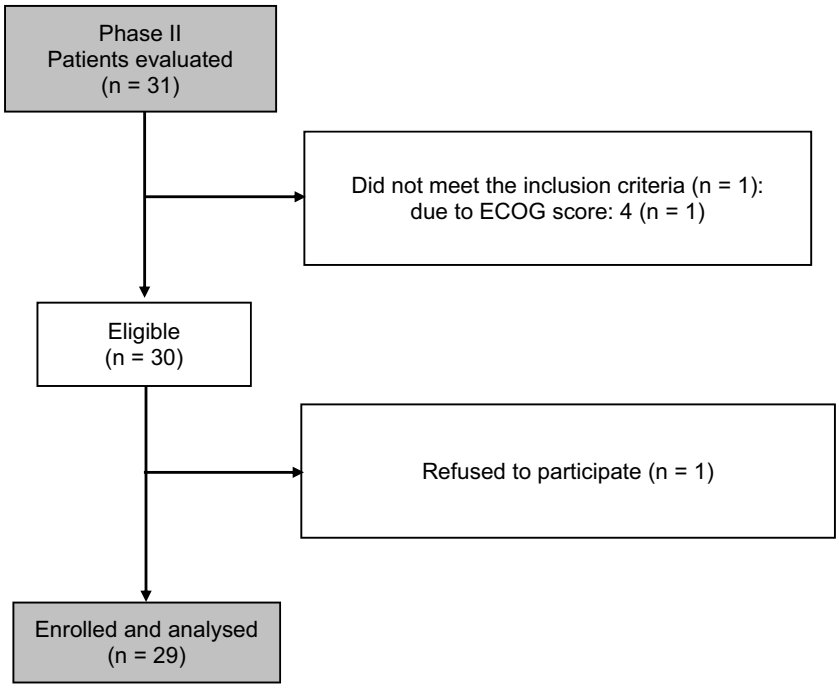


**Fig. 2** Consolidated Standards of Reporting Trials diagram of the phase II trial

breast (5.5%), esophagus (1.9%), thyroid (1.9%), larynx (1.9%), skin (1.9%), and unknown primary (1.9%). Histopathology of the primary tumors is detailed in Table 2. The index symptoms (i.e., the symptom considered the main indication for palliative RT) were dyspnea (40.7%), chest pain (33.3%), hemoptysis (7.4%), mediastinal syndrome (5.6%), dysphagia (11.1%), and cough (1.9%).

## Phase I: definition of the MTD

At each dose level were enrolled at least six patients with 3 months of follow-up after RT to completely assess acute toxicity. Table 3 shows the acute toxicities recorded at each dose level. One patient with severe dyspnea and poor general clinical conditions experienced acute grade 5 lung toxicity at 1st dose level (16 Gy) and died 3 weeks after

**Table 1** Phase I–II study: patients characteristics

| | Number of patients | % |
|---|---|---|
| Patients | 54 | 100 |
| Age (years) | | |
| Median | 69.5 | |
| Range | 44–93 | |
| Gender | | |
| Male | 41 | 75.9 |
| Female | 13 | 24.1 |
| ECOG | | |
| 0 | 2 | 3.7 |
| 1 | 17 | 31.5 |
| 2 | 30 | 55.5 |
| 3 | 5 | 9.3 |

**Table 2** Phase I–II study: site of primary tumor and histopathology

| | Number of patients | % |
|---|---|---|
| Patients | 54 | 100 |
| Lung | 34 | 63.0 |
| Squamous cell carcinoma | 23 | 42.6 |
| Adenocarcinoma | 11 | 20.4 |
| Uterus | 5 | 9.3 |
| Adenocarcinoma | 4 | 7.4 |
| Squamous cell carcinoma | 1 | 1.9 |
| Colon | 4 | 7.4 |
| Adenocarcinoma | 4 | 7.4 |
| Rectum | 3 | 5.5 |
| Adenocarcinoma | 3 | 5.5 |
| Breast | 3 | 5.5 |
| Invasive ductal carcinoma | 3 | 5.5 |
| Esophagus | 1 | 1.9 |
| Squamous cell carcinoma | 1 | 1.9 |
| Larynx | 1 | 1.9 |
| Squamous cell carcinoma | 1 | 1.9 |
| Skin | 1 | 1.9 |
| Squamous cell carcinoma | 1 | 1.9 |
| Thyroid | 1 | 1.9 |
| Papillary carcinoma | 1 | 1.9 |
| Adenocarcinoma of unknown primary | 1 | 1.9 |

RT. Given the severity of this event, it was decided to double the cohort at the first dose level up to a total of 12 patients although the study design required an expansion of the cohorts only in the case of 2/6 DLT. No other patient showed DLT (grade $\geq 3$ acute toxicity) and the 20 Gy dose level was established as the MTD. Treatment was also well tolerated by 17 patients (68.0%) undergoing systemic therapies.

### Phase II: symptomatic response

Based on the Simon design, ten patients were initially enrolled and treated with a total RT dose of 20 Gy. A symptomatic partial response was recorded in nine patients (90.0%) and no symptomatic change in one patient (10.0%).

In the 2nd stage, 19 patients were enrolled to achieve a total number of 29 patients treated at 20 Gy dose level. Overall symptomatic response rate in the two stages was 96.5% (CI 0.95: 81.3–99.9%) with a median duration of 3 months (range 1–10 months) (Table 4). 12 out of 29 patients (41.4%) presented chest pain before RT. The overall pain response rate (complete plus partial) was 100% (CI 0.95: 78.4–100%). These patients showed a mean VAS value before and after RT of 5.9 and 2.0 ($p < 0.001$), respectively. More specifically, six patients (50.0%) had complete pain resolution (VAS = 0), and 6 (50.0%) a partial pain relief with a median $\Delta$ VAS of 3.7 (range 2.5–6.0). Moreover, 20% of patients with dyspnea reported complete symptom resolution, 70.0% partial response, and 10.0% experienced no change. All patients with dysphagia and hemoptysis showed partial and complete symptomatic resolution, respectively. One patient with cough experienced symptom reduction.

### Phase II: performance status and QoL assessment

At the first follow-up visit, 48.3%, 41.4%, and 10.3% of patients showed improved, stable, or worse ECOG performance status, respectively. Considering the QoL evaluation, improvement in overall wellbeing, fatigue, and ability to perform daily activities were reported by 62.0%, 48.3%, and 55.2% of patients, respectively.

### Follow-up

Considering all the 54 patients (phase I–II), with a median follow-up of 5 months (range 1–36 months), 35 patients (64.8%) died due to disease progression. No case of late toxicity was observed due to short follow-up and poor life expectancy. Moreover, 12 patients out of 54 (22.2%) who experienced persistent or recurrent symptoms (pain in 58.3% of cases) underwent a second RT cycle with the same regimen (16–20 Gy, BID, in two consecutive days). Median retreatment interval was 4 months (range 1–4 months) from the end of the 1st cycle. Symptomatic response rate was 83.3% without patients experiencing grade $\geq 3$ acute toxicity.

## Discussion

To the best of our knowledge, this is the only trial prospectively evaluating MTD and symptomatic response in the palliative RT of advanced or metastatic cancer to the chest.

**Table 3** Phase I study, acute toxicity

| Dose level | Grade | 1st (16 Gy) | | 2nd (18 Gy) | | 3rd (20 Gy) | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| Enrolled patients | | 12 | 100 | 7 | 100 | 6 | 100 |
| Acute toxicity | | | | | | | |
| Lung | 1 | 1 | 8.3 | 0 | 0.0 | 0 | 0.0 |
| | 2 | 1 | 8.3 | 0 | 0.0 | 0 | 0.0 |
| | 3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | 4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | 5 | 1 | 8.3 | 0 | 0.0 | 0 | 0.0 |
| Upper gastrointestinal | 1 | 1 | 8.3 | 0 | 0.0 | 0 | 0.0 |
| Esophagus | 1 | 0 | 0.0 | 0 | 0.0 | 3 | 50.0 |
| Skin | 1 | 2 | 16.6 | 0 | 0.0 | 0 | 0.0 |
| Patients experiencing DLT | | 1 | 8.3 | 0 | 0.0 | 0 | 0.0 |

*DLT* dose limiting toxicity

**Table 4** Phase II study: symptomatic response

| Response | Dyspnea No. (%) | Chest pain No. (%) | Dysphagia No. (%) | Haemoptysis No. (%) | Cough No. (%) |
|---|---|---|---|---|---|
| Complete symptoms remission | 2 (20.0) | 6 (50.0) | 0 (0.0) | 2 (100.0) | 0 (0.0) |
| Partial symptoms remission | 7 (70.0) | 6 (50.0) | 4 (100.0) | 0 (0.0) | 1 (100.0) |
| No changes | 1 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Progression of symptoms | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

In this phase I–II study, an accelerated hypo-fractionated regimen of 20 Gy in four fractions in two consecutive days, twice a day, was tested. The MTD was defined as 20 Gy and the overall symptomatic response rate was 96.5% hence supporting the use of short RT courses in this setting.

Only one case of severe toxicity was recorded. The patient was treated at the 1st dose-level (16 Gy), experienced acute grade 5 lung toxicity and died 3 weeks after RT. This patient had poor performance status (ECOG: 3) and worsening dyspnea before RT. He was treated on a peripheral and small lung lesion due to severe pain produced by ribs involvement. The irradiated lung volume was minimal based on DVH ($V_{20Gy}$: 6%, $V_{5Gy}$: 17%). Based on the short interval from RT to death, we prudentially considered it as an adverse event and consequently we enrolled six extra patients in the 1st patients' cohort. However, considering the small lung volume that was irradiated and the excellent tolerance recorded with higher doses (18 and 20 Gy), we can reasonably hypothesize that this event was not correlated with the RT schedule.

We initially highlighted some advantages of this regimen for the patients and particularly less discomfort due to the short treatment duration. Among the other advantages of this treatment, we can underline the lower costs due to lower number of delivered RT fractions and the positive impact on RT waiting lists. These issues could be particularly useful in low resourced settings.

Nowadays, in the palliation of chest cancer and particularly of advanced lung tumor, there is no clear consensus about standard RT dose and fractionation. In fact, several fractionation schedules have been investigated and compared but without a clear advantage of a specific treatment protocol. In the ASTRO guidelines published in 2011, after an extensive literature review, the authors stated that higher dose/fractionation schedules (e.g. 30 Gy in ten fractions) are associated with a modest (5%) improvement of 1-year survival but also with higher rates of toxicity [20]. They concluded that the ideal fractionation schedule to optimize the therapeutic ratio is still unclear.

In this scenario, our regimen may represent a compromise among standard or high dose schemes (30 Gy in 10 fractions, 39–45 Gy in 12–15 fractions) and shorter schemes (10 Gy in 1 fraction, 16–17 Gy in 2 weekly fractions, 20 Gy in 5 fraction). The use of a very accelerated treatment is theoretically associated with an improved RT efficacy due to the inverse correlation between treatment time and tumor control probability.

This hypothesis seems to be confirmed while comparing our results with the ones of the randomized study published by Senkus-Konefka et al. [21]. The authors compared two treatment arms, in one of which the same total dose of our study was prescribed (20 Gy) but in five daily fractions. They reported the response rates for dyspnea (54%), dysphagia (67%), hemoptysis (80%), and chest pain (83%). Our

rates were constantly higher being 90% for dyspnea, and 100% for dysphagia, hemoptysis, and chest pain. However, it should be noted that all patients enrolled in that study had NSCLC while in our trial also other primary neoplasms were included.

Main limitations of our study are lack of QoL evaluation with specific scales for chest/lung tumors, and lack of Patients Reported Outcome measures reporting. We also need to admit that this type of treatment may not be suitable for all settings and in all departments. For example, for a frail patient, waiting for 8 h in the RT center can be tiring unless the treatment is carried out on an inpatient basis. Moreover, for centers where the activity takes place in a single shift of 6–8 h, this type of therapy is obviously not feasible.

The results of this phase I–II trial show that the SHARON regimen is effective in achieving high symptomatic control rates with acceptable incidence of toxicity in patients with locally advanced primary neoplasm or metastases in the chest. In our opinion, it can be used in daily clinical practice especially in patients for whom a more prolonged treatment is problematic. From the scientific point of view, the results of this trial justify a direct comparison of our regimen with a "traditional" palliative treatment. Therefore, a multicenter randomized trial is ongoing to compare the SHARON schedule with the traditional 30 Gy delivered in ten fractions (NCT03465553).

## Compliance with ethical standards

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

**Ethical approval** The study was approved by our institutional Ethics Committee in accordance with the Helsinki Declaration. All patients provided written informed consent before study entry.

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