Stereotactic Body Radiation Therapy (SBRT): An optimal approach in the treatment of lung cancer and pulmonary metastases – a Portuguese center experience

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RESUMO

A radioterapia estereotáxica corporal (SBRT) é um método não-invasivo, seguro e eficaz no tratamento do cancro do pulmão de estadio inicial e em lesões pulmonares secundárias, em doentes selecionados. Embora não exista consenso na dose ideal e esquema de fracionamento, uma dose biológica efetiva (BED) ≥100 Gy está associada a um aumento significativo do controlo local e sobrevivência. O objetivo deste estudo é analisar os esquemas de fracionamento, toxicidade e sobrevivência de doentes com doença pulmonar primária e secundária, tratados com SBRT de Janeiro/2016 a Dezembro/2021 no nosso centro. Toxicidade avaliada segundo escala CTCAE 5.0 e a análise de sobrevivência com método Kaplan–Meier. Incluídos 90 doentes (110 tumores) com idade mediana 71 anos e Karnofsky ≥90% em 74,4%. 42 doentes (43 tumores) tinham cancro do pulmão, a maioria adenocarcinoma (76,2%), cT1b-cN0 (66,7%) e com tumores periféricos (83,7%) de tamanho mediano 20,5mm (8-50). 48 doentes (67 tumores) tinham lesões pulmonares secundárias, maioritariamente de cancro colorretal (66,7%), 70,1% tumores periféricos de tamanho mediano 11,5 mm (4-43 mm). Quanto a toxicidade, registou-se: 8,9% com pneumonite (grau 1/2), 11,1% com dor torácica e 5,6% com fratura de costela (grau 1). Tempo de follow-up mediano de 22 meses. Na doença pulmonar primária, a taxa de controlo tumoral (TC), sobrevivência global (OS) e sobrevivência livre de doença (DFS) aos 2 anos foi de 84,6%, 71,6% e 51,4%. Na doença pulmonar secundária, registou-se TC de 86,8%%, OS de 74% e DFS de 34,4% aos 2 anos. SBRT é um tratamento bem tolerado e com resultados favoráveis.

Palavras-chave: Radioterapia, SBRT, Cancro do pulmão, Metástases pulmonares

ABSTRACT

Stereotactic Body Radiation Therapy (SBRT) is a noninvasive, safe, and effective treatment for early-stage lung cancer and metastatic lung disease in selected patients. Although there is no current consensus on the ideal dose

and fractionation schedule for pulmonary SBRT, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival.The purpose of this study was to analyze fractionation schedules, toxicity and survival outcomes in patients with early-stage lung cancer and lung metastases treated with SBRT between January 2016 – December 2021 in our center. Toxicity was evaluated using CTCAE v5.0 and survival outcomes by the Kaplan–Meier method. We included 90 patients (110 tumors total) with a median age of 71 years and Karnofsky Performance Status≥90% in 74,4%. 42 patients (43 tumors) had early-stage primary lung cancer, mostly adenocarcinoma (76,2%), stage cT1b-cN0 (66,7%) and peripheral tumors (83,7%) with a median size of 20,5mm (8-50). 48 patients (67 tumors) had secondary lung disease mostly from colorectal cancer (66,7%), 70,1% were peripheral tumors with a median size of 11,5 mm (4-43 mm). Regarding toxicity, 8,9% of patients had pneumonitis (grade 1 and 2), 11,1% reported chest pain and 5,6% had rib fracture (grade 1). Median follow up was 22 months. In primary lung cancer, the 2-year tumor control (TC), overall survival (OS) and disease free survival (DFS) was 84,6%, 71,6% and 51,4%, respectively. Patients with lung metastases had a 2-year TC of 86,8%%, OS of 74% and DFS of 34,4%. SBRT is a well tolerated treatment option with favorable outcomes.

Keywords: Radiotherapy; SBRT; Lung cancer; Lung metastases.

INTRODUCTION

Lung cancer is the second most common cancer in both men and women and the leading cause of cancer related death[1]. The lung is also one of the most frequent sites of metastization - around 20–54% of cancer patients have lung metastases at some point during the course of their disease[2].

According to the most recent international guidelines, stereotactic body radiation therapy (SBRT) is recommended for patients with non-small cell lung cancer (NSCLC) stage I and II (cT1–3N0M0) who are medically inoperable[3]. SBRT can also be considered in lung metastases, on an oligometastatic setting, with improvement in OS as shown in recent studies. The maximum number of lesions for ablative therapy has yet to be determined[4,5].

Over the past 2 decades, technological developments in target delineation, motion management, conformal treatment planning, and daily image guidance have allowed development and implementation of this technique, which uses ablative and highly conformal radiation doses delivered to limited size targets, while minimizing toxicity to surrounding tissues[6,7].

There is no current consensus on the ideal dose and fractionation for SBRT in lung lesions. However, one aspect that is uncontested is the need to achieve a high biologically effective dose (BED) of ≥100 Gy[6].

Central vs peripheral tumors

It is known that the location of the tumor can influence toxicity rates when specific SBRT dose-fractionation schedules are used. The widely accepted ASTRO definition, describes a central tumor as a tumor located within 2 cm of the proximal tracheobronchial tree, otherwise it is considered a peripheral tumor[7]. Other definitions, such as the one in the RTOG 0813 protocol, includes on the central tumor definition any tumor with location within 2 cm of the mediastinal structures such as heart, major vessels and esophagus[8].

Primary lung cancer

For patients with operable early-stage NSCLC, SBRT is not proven equivalent to lobectomy. The only two randomized phase 3 trials (STARS and ROSEL) that compared SBRT to lobectomy did not complete accrual. A pooled analysis of these two trials showed higher 3-year OS after SBRT compared to surgery (95% vs 79%, p=0·037) and similar 3-year recurrence-free survival (86% vs 80%, p=0.54)[9]. Later, a report of the long-term results of the revised STARS trial showed no significant difference in OS[10]. Other smaller studies have shown similar overall survival and cancer-specific survival[11,12]. This does not provide sufficient data to change the standard of care, but it is promising and confirms that SBRT is an alternative to surgery for patients with potentially operable disease who are high risk surgical patients or who refuse surgery.

Also, compared to conventionally fractionated radiation therapy (RT), SBRT has achieved higher local control rates and OS[7]. The phase III multicentric Australian TROG/ALTG randomized trial (CHISEL) compared SBRT (54Gy/3Fr or 48Gy/4Fr) with conventional RT (66Gy/33Fr or 50Gy/20Fr) and showed improved local control and OS with SBRT, with low toxicity[13]. The Scandinavian randomized trial (SPACE) also compared SBRT (66Gy/3Fr) with conventional RT (70Gy/35Fr) and showed similar local control and OS, but lower incidence of pneumonitis and oesophagitis with SBRT[14].

Regarding treatment of lung lesion with SBRT, most studies included mainly peripheral tumors, where common fractionation schedules are 48Gy/4fr, 54Gy/3fr or single fractions (30-34Gy).

The RTOG 0236 was the first North American multicenter phase II trial to test SBRT in medically inoperable patients with peripheral early-stage NSCLC. The prescription dose was 54 Gy/3Fr and showed high local control rates, with 5-year primary failure of 7% and moderate treatment related morbidity (toxicity grade 3 in 27% and grade 4 in 3%)[15]. This fractionation schedule was also evaluated in patients with operable NSCLC with similarly high rate of primary tumor control and infrequent need for surgical salvage[16].

Singh et al., assessed 30 Gy/1 fr vs. 60 Gy/3 fr and showed no significant difference in local control, progression free survival (PFS) or OS, but better social functioning and less dyspnea with the single fraction treatment[17].

Another important study, the RTOG 0915 phase II trial, evaluated two schedules (34 Gy /1Fr vs 48 Gy/4 Fr) with primary tumor failure at 5 years of 10.6% vs 6.8%, and acute effects in 10.3% vs 13.3%, respectively[18].

For central tumors there is limited prospective evidence. RTOG 08-13 was a multicentre phase II study that assessed the safety and efficacy of a five fraction schedule (dose range of 50Gy--60Gy) for central NSCL tumors. The 3-year local control and OS was 75%, with no grade 3 toxicity. Higher doses per fraction were associated with improved efficacy but also increased risk of severe toxicities[8].

The 8-fraction schedule (such as 60Gy/8Fr) is commonly used particularly in Europe and Canada. Kimura et al. (phase I trial) evaluated 5 dose levels (52Gy to 60Gy) in 8 fractions and determined the recommended dose of 60Gy with acceptable efficacy and toxicity rates[19]. Also, a systematic review suggests that treatments with BED 10Gy ≥100 Gy and BED 3Gy ≤210 Gy, such as 60 Gy in 8 fractions, result in acceptable efficacy and toxicity rates[20]. The ongoing SUNSET trial evaluates the 60Gy/8fr in central and ultra-central tumors[21].

Secondary lung lesions

In secondary lung lesions, metastasectomy is the historical treatment, but it requires medically

fit patients with adequate general conditions as well as cardiovascular and respiratory functions. Therefore, SBRT started to be used as a curative option in patients unsuitable for surgery based on the favorable results in NSCLC[22]. on the metastatic setting it has also demonstrated excellent local control rates, with 2-year local control 91-96%, depending on histologic subtype. The first randomized trial for treatment of pulmonary oligometastases was SAFRON II, where patients with 1-3 pulmonary peripheral metastases received either single a 28 Gy fraction or 48 Gy in 12 Gy fractions (on non-consecutive days over 2 weeks). There was no significant difference for local control or treatment related grade ≥3 adverse effects[23].

There is limited information regarding efficacy and safety of central lesions in the context of oligometastatic disease. Patients with central disease were excluded of SAFRON II.

MATERIALS AND METHODS

We retrospectively reviewed patients treated with SBRT in our center between January 2016 and December 2021.

We included patients with NSCLC stage I - II (cT1–3N0M0) histology proven who were medically inoperable or refused surgery, and patients with lung metastases documented on PET-CT or CT scan, maximum tumor size of 5 cm and a minimum follow-up of 1 year.

Four dimensional computed tomography (4DCT) with abdominal compression was acquired in most patients for treatment planning and cone beam computer tomography (CBCT) was acquired before and after each treatment.

With regards to volume delineation, gross tumor volume (GTV) was contoured on CT images (1 mm thickness); clinical target volume (CTV) was considered to be the same as GTV; internal target volume (ITV) was contoured according to the respiratory motion of the tumor; planning target volume (PTV) was defined as a 5 mm isotropic margin from the ITV.

Dose was prescribed according to location, size, performance status and OARs dose constraints. For central lesions prescription dose was 60Gy/8fr (7,5Gy/fr) and for peripheral lesions doses ranged between single fraction (25-34Gy), 40Gy/3Fr, 45Gy/3fr (15Gy/fr), 48Gy/4fr (12Gy/fr), 50Gy/5fr (10Gy/fr) 60Gy/8fr (7,5Gy/fr) and 70Gy/10fr (7Gy/fr).

All treatments were planned for a TrueBeam linear accelerator equipped with a Millennium MLC and calculated with 6MV FFF photon beams with a 1.0 mm dose grid size, and AAA eclipse algorithm. Volumetric Arc Therapy (VMAT) was used on all treatment plans using a PTV coverage primary goal of V100% > 95%. Organs at risk (OAR) dose constraints were mostly based on the RTOG 0813 and 0915 protocols and AAPM Report 101 (American Association of Physicists in Medicine).

After treatment, patients were followed every 3 months the first 2 years and every 6 months thereafter. Imaging with CT scan or 18F-FDG PET/CT was used to assess treatment response.

Tumor control (TC) was defined as the absence of increased tumor dimension or SUV max in imaging assessment response (CT scan or 18F-FDG PET/CT), disease free survival (DFS) was the time from beginning of treatment to lack of tumor control, regional failure, distant metastasis or disease related death, and overall survival (OS) was defined as the time from beginning of treatment to date of death from any cause. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Survival rates and curves were calculated by the Kaplan–Meier method.

This study was approved by the ethical committee responsible.

RESULTS

We analyzed 90 patients with a total of 110 tumors/lesions: 42 patients with early stage lung cancer and 48 with lung metastasis. The baseline characteristics of the patients are shown in Table 1 and 2.

Regarding primary lung cancer, mostly were staged IA2 (31%) and IA3 (35,7%) who were considered high risk for or refused surgery. Biopsy was performed in all of them, with adenocarcinoma being the most common histology (76,2%). We treated a total of 43 tumors (1 patient had two tumors), with a median size of 21 mm (8-50). All central tumors were prescribed 60Gy/8Fr (BED10Gy = 105Gy). Peripheral tumors were given 48Gy/4Fr (BED10Gy = 105,6Gy) in 75% and 50Gy/5Fr (BED10Gy =100 Gy) in 19,4%. Characteristics are summarized in Table 3.

Concerning the forty eight patients with secondary lung disease, nineteen had two or more metastases that were treated separately with different PTVs, giving a total of sixty seven lesions, with a median size of 12 mm (4-43). The most frequent site of primary tumor was colorectal (66,7%) followed by lung disease(12,5%). Concerning fractionation schedules, all central lesions (n=20) were prescribed 60Gy/8Fr ((BED10Gy = 105Gy). Forty-

Table 1. General primary lung cancer patients characteristics (n=42)

Age (Years)		77 (53-90)
Gender	Masculine	59,5%
	Feminine	40,5%
KPS	90-100%	58,6%
	≤ 80%	41,4%
Smoker	Yes	52,9%
	No	47,1%
Staging AJCC 8th edition	cT1aN0M0	4,8% (n=2)
	cT1bN0M0	31% (n=13)
	cT1cN0M0	35,7% (n=15)
	cT2aN0M0	14,3% (n=6)
	cT2bN0M0	7,1% (n=3)
	cT3N0M0	7,1% (n=3)
Histology	Adenocarcinoma	76,2% (n=32)
	SCC	11,9% (n=5)
	Other[1]	11,9% (n=5)
Number of lesions treated per patient	1	97,6% (n=41)
	2	2,3% (n=1)
	3	–
	4	–

[1] Include: adenosquamous carcinoma, large cell neuroendocrine carcinoma.

Table 2. General lung metastases patients characteristics (n= 48)

Age (Years)		67 (16-90)
Gender	Masculine	64,6%
	Feminine	35,4%
Karnofsky	90-100%	88,9%
	≤ 80%	11,1%
Smoker	Yes	29%
	No	71%
Primary Tumor	CCR	66,7% (n=32)
	Lung	12,5% (n=6)
	Esophageal	4,2% (n=2)
	Ovarian	4,2% (n=2)
	Other[1]	12,5% (n=6)
Number of lesions treated per patient	1	62,5% (n=30)
	2	25% (n=12)
	3	10,4% (n=5)
	4	2,1% (n=1)

[1] Include: Prostate cancer, endometrial cancer, renal cell cancer, Ewing sarcoma, oral cavity cancer, laryngeal cancer.

Table 3. Primary lung cancer

		Central tumors (n=7)	Peripheral tumors (n=36)
Lung	Right	42,9% (n=3)	52,8% (n=19)
	Left	57,1% (n=4)	47,2% (n=17)
Lobe	Superior	57,1% (n=4)	66,7% (n=24)
	Medial	14,3% (n=1)	5,6% (n=2)
	Inferior	28,6% (n=2)	27,8% (n=10)
Size (mm)	Median	25	20,5
	Min.-Max.	15-46	8-50
Fractionation schedules	**70Gy/10Fr** BED_{10Gy} = 119 Gy	–	2,8% (n=1)
	60Gy/8Fr BED_{10Gy} = 105 Gy	100% (n=7)	–
	50Gy/5Fr BED_{10Gy} = 100 Gy	–	19,4% (n=7)
	48Gy/4Fr BED_{10Gy} = 105.6 Gy	–	75% (n=27)
	40Gy/3Fr BED_{10Gy} = 93.2 Gy	–	2,8% (n=1)
PTV (cc)	Median	45,9	29,4
	Min.-Máx.	11,6-78	4,7-115

Table 4. Lung metastases (n=67 lesions)

		Central lesions (n=20)	Peripheral lesions (n=47)
Lung	Right	60% (n=12)	66% (n=31)
	Left	40% (n=8)	34% (n=16)
Lobe	Superior	40% (n=8)	31,9% (n=15)
	Medial	15% (n=3)	8,5% (n=4)
	Inferior	45% (n=9)	59,6% (n=28)
Size (mm)	Median	17	11,5
	Min.-Max.	9-33	4-43
Fractionation schedules	**25Gy/1Fr** BED_{10Gy} = 87.5 Gy	–	2,1% (n=1)
	30Gy/1Fr BED_{10Gy} = 120 Gy	–	10,6% (n=5)
	34Gy/1Fr BED_{10Gy} = 149.6 Gy	–	8,5% (n=4)
	45Gy/3Fr BED_{10Gy} = 117 Gy	–	2,1% (n=1)
	48Gy/4Fr BED_{10Gy} = 105.6 Gy	–	48,9% (n=23)
	50Gy/5Fr BED_{10Gy} = 100 Gy	–	21,3% (n=10)
	60Gy/8Fr BED_{10Gy} = 105 Gy	100% (n=20)	6,4% (n=3)
PTV (cc)	Median	13,9	11,8
	Min.-Máx.	4,8-97,8	4,3-105

seven were peripheral lesions that were given mostly 48Gy/4Fr (BED10Gy = 105,6Gy) in 48,9% and 50Gy/5Fr (BED10Gy =100 Gy) in 21,3%. Other fractionation schedules, such as single fraction, were given according to metastases location and size and OARS dose constraints. Secondary lung lesions characteristics of are summarized in table 4.

In most cases all the OARs dose constraints were met. In peripheral tumors, the PTVs often overlap the ribs and therefore the rib optimal constraints were not considered.

All patients underwent their treatment as planned. Two patients presented acute adverse events (acute dermatitis and esophagitis, both grade 1). Regarding late adverse events, 9,2% of patients had pneumonitis (grade 1 and 2), 11,5% reported chest pain and 5,7% had rib fracture (grade 1). No grade ≥ 3 adverse events were observed.

The median follow up time was 22 months. In primary lung cancer, the 2-year tumor control (TC), disease free survival (DFS) and overall survival (OS) were 84,6%, 51,4% and 71,6% respectively (Figure 1). We obtained 46,5% complete clinical responses, 27,9% partial clinical responses (decreased tumor size and/or SUVmax) and 14% stabilized (maintained same tumor size and/or SUVmax). Two patients (4,8%) had local failure

Figure 1. Survival curves – primary lung cancer.

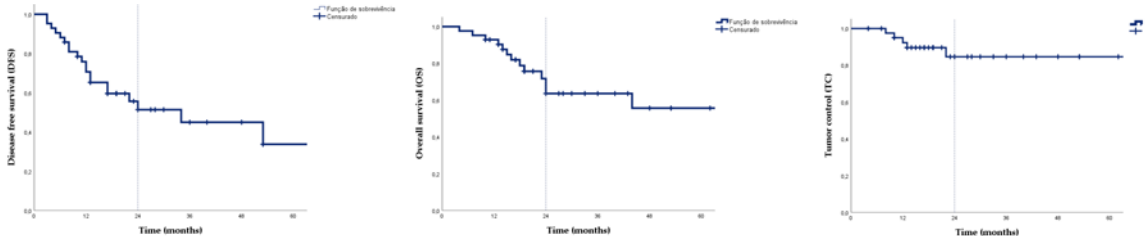
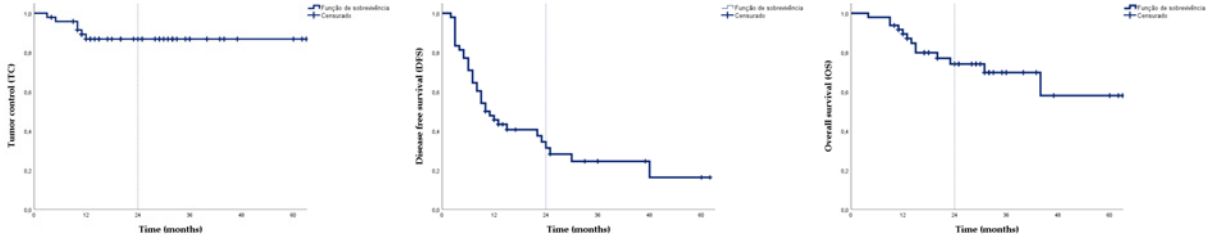


Figure 2. Survival curves – Secondary lung disease.



and fifteen (35,7%) had systemic pro-gression, mostly within the lung, the liver and the adrenal gland.

Patients with lung metastases had a 2-year TC of 86,8%, DFS of 34,4% and OS of 74% (Figure 2). In 53,7% of lesions we observed a complete clinical response, 16,4% a partial clinical response and 17,9% stabilized. Six patients (12,5%) experienced local failure and 27 patients (56,3%) systemic progression, with the most frequent site being lung and liver.

DISCUSSION

This study demonstrated that SBRT is a safe and an effective treatment option.

The optimal dose of SBRT has not yet been determined. Even though multiple fractionation schedules were used in previous studies, the results have been consistently favorable, with high local control and survival rates, while maintaining low toxicity.

In peripheral tumors we used mostly the 48Gy/4Fr and 50Gy/5Fr fractionation schedule. When we compare our results with the classic RTOG trials (0236, 0915, 0618) that report 3-year tumor control rates around 92-97% in primary lung cancer lesions, we have a slightly lower tumor control rate[15,16,18]. This can be due to the fact that these trials include a bigger proportion of cT1 tumors, whereas in our sample 28,5% of patients are cT2-3. Also, they only include peripheral tumors, while 16,3% of our sample of patients with primary lung cancer has central tumors, that were treated with a schedule with increased number of fractions (60Gy/8Fr) and hence a lower achievable BED. In fact, when we look at the RTOG 0813 results (for central tumors) the 2-year local control rate of 89,4% is closer[8].

In some cases, we were able to use single fractionation treatment schedules (25-34Gy). The-

re are 3 completed randomized phase 2 trials comparing single to mul-ti-fraction treatment schedules. Two (RTOG 0915, RPCI-124407) were conducted in medically inoperable early-stage lung cancer patients and have been fully published[18,24]. The third (SAFRON II) involves treatment of oligometastatic disease to the lungs[23]. They all used different single fraction schedules, with total dose ranging from 28Gy to 34Gy.

More evidence is emerging supporting single fraction when choosing SBRT schedules in peripheral tumors, since it shows similar outcomes but smaller overall treatment time, even in the absence of a phase 3 trial. In fact, it was the preferred option for treating peripheral early-stage NSCLC during the COVID-19 pandemic in a European Society for Radiotherapy and Oncology–American Society for Radiation Oncology consensus statement[25].

Regarding the group of patients with lung metastases, our study has comparable results with the SAFRON II trial. This trial reported results at 3-years with tumor control rates of 64% in the single fraction arm and 80% in the multi-fraction arm[23].

As described in literature, the predominant pattern of failure after treatment with SBRT is the development of distant metastases. Despite the high rates of local control in patients receiving commonly employed regimens of BED of 100 Gy or greater, local recurrence after SBRT can be seen in up to 20% in large series with long-term follow-up[26]. This is also compatible with our results, where in patients with primary lung cancer, 35,7% had systemic progression versus 4,8% who had local failure. Same in patients with secondary lung lesions where 56,3% developed other metastasis and 12,5% had local failure.

Regarding the size of the treated lesions, we established the consensual limit of a maximum 5 cm size[27]. For tumors above 5 cm SBRT can also be considered an appropriate option if acceptable dosimetric constraints are achievable. However, this applies to primary lung tumors, with conditional strength of recommendation and a low quality of evidence, so those were not included in this sample[7].

Regarding toxicity, we reported a low toxicity rate with pneumonitis (grade 1 and 2) in 9,2%, chest pain in 11,5% and rib fracture (grade 1) in 5,7%. These numbers are lower than in other studies since we didn't observe any grade 3 events. However, these results must be interpreted with caution because the retrospective nature of this data can lead to bias or underestimation.

Early studies demonstrated higher risk of severe toxicity (~50%) in the treatment of central tumors[28]. The often-quoted study by Timmerman et al. from Indiana University reported increased toxicities in patients with centrally located tumors treated with 60–66 Gy in 3 fractions; on multivariate analysis, tumor location was the strongest predictor for toxicity[29]. However, later studies have shown improved tolerability with the use of more protracted (e.g., 4 or more fractions) or lower BED schedules. Even though central tumors represent 24,5% of our entire sample, we didn't detect a statistically significant toxicity difference in patients with central tumors versus peripheral tumors. This can be due to a reduced number of events.

The main limitations of this study are related to its retrospective design, the variation in dose-fractionation schedules and the sample heterogeneity, as patients in the metastatic setting had tumors with different histologic subtypes, multiple primary tumor locations and the administered systemic therapy was made at the discretion of the assistant medical oncologist.

CONCLUSIONS

Outcomes from this study in regards to local control, survival rates and toxicity, are comparable to the ones from randomized trials. SBRT is achievable in routine practice and has been sustained over time. These data support the continued use of this technique in daily clinical practice.

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