Tumoral reduction in patients with intra-abdominal tumors treated with CyberKnife: A single-center experience

Reducción tumoral en pacientes con tumores intraabdominales tratados con CyberKnife: experiencia de un solo centro

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Suggested citation: Mora Tous L, Rodríguez Márquez I, Massaro Ceballos M, Giraldo J, Jaramillo Jiménez E, Gómez Duque D. Tumoral reduction in patients with intra-abdominal tumors treated with CyberKnife: a single-center experience. Salud UIS. 2022; 54: e22067. doi: https://doi.org/10.18273/saluduis.54.e:22067

Abstract

Introduction: To estimate tumoral reduction and overall survival in patients with abdominal tumors treated with body fractionated stereotactic radiotherapy (SBRT) after one year. **Methods:** A case series with an analytical approach of patients with abdominal tumors, that were treated with image guided SBRT using a CyberKnife system and who had post-treatment follow-up and control images. The study was completed at the Neurological Institute of Colombia in a five-year period from January 2013 to January 2018, in Medellín, Colombia. **Results:** A total of 16 patients were included, and 75% of the cases involved patients under 65 years of age. The treated lesions were in the pancreas (37.5%), abdominopelvic lymph nodes (25%), liver (25%), and retroperitoneum (12.5%). Most of the treated patients required up to two fiduciary markers (93.7%). The SBRT dose administered ranged from 24 to 60 Gy, mostly in 3 fractions (81.3%). Mean tumoral reduction after treatment was 15.6 mm (SD ±13.5), being statistically significant ($p < 0.0003$). According to RECIST 1.1 criteria, a complete response was achieved in 6.2% (n = 1) of the cases, a partial response in 56.3% (n = 9), and stable disease in 37.5% (n = 6). No disease progression was documented in any patient during the follow-up period. The one-year overall survival rate was 93.7%. **Conclusion:** Experience at this center shows that CyberKnife radiosurgery in both primary and metastatic abdominal tumors provides, in the short term, an adequate local control rate and improved one-year overall survival.

Keywords: Abdominal neoplasms; Radiosurgery; Radiation oncology; Radiotherapy; Neoplasm recurrence local; Radiotherapy; Image-Guided; Neoplasm metastasis.

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Recibido: 28/07/2021 **Aprobado:** 02/08/2022

Resumen

Introducción: estimar la reducción tumoral y la supervivencia global al año en una serie de pacientes con tumores abdominales tratados con radioterapia estereotáctica fraccionada corporal (SBRT). **Métodos:** un estudio de serie de casos de un alcance analítico de pacientes con tumores abdominales, tratados con SBRT guiada por imagen mediante el sistema CyberKnife y que tenían imágenes de seguimiento y control postratamiento. El estudio se completó en el Instituto Neurológico de Colombia en un período de cinco años, desde enero de 2013 hasta enero de 2018, en Medellín-Colombia. **Resultados:** se incluyeron 16 pacientes. El 75 % de los casos eran menores de 65 años. Las lesiones tratadas se localizaron en páncreas (37,5 %), ganglios linfáticos abdominopélvicos (25 %), hígado (25 %) y retroperitoneo (12,5 %). La mayoría de los pacientes tratados requirieron hasta dos marcadores fiduciarios (93,7 %). La dosis de SBRT administrada osciló entre 24 y 60 Gy, principalmente en 3 fracciones (81,3 %). La reducción tumoral media tras el tratamiento fue de 15,6 mm (DE ± 13,5), estadísticamente significativa ($p < 0{,}0003$). Según los criterios RECIST 1.1, se logró una respuesta completa en el 6,2 % (n = 1) de los casos, una respuesta parcial en el 56,3 % (n = 9) y enfermedad estable en el 37,5 % (n = 6). No se documentó progresión de la enfermedad en ningún paciente durante el período de seguimiento. La tasa de supervivencia global a un año fue del 93,7 %. **Conclusión:** la experiencia en este centro muestra que la radiocirugía CyberKnife en tumores abdominales primarios y metastásicos proporciona, a corto plazo, una tasa de control local adecuada y una mejora de la supervivencia global a un año.

Palabras clave: Neoplasias abdominales; Radiocirugía; Oncología por radiación; Radioterapia; Recurrencia local de neoplasia; Radioterapia guiada por imagen; Metástasis de la neoplasia.

Introduction

Radiation therapy has been used as a regional treatment for certain types of cancers. Among the most advanced techniques is image-guided radiotherapy using fiduciary markers. This technique allows a better dose delivery, by being able to locate, through images, the target to be treated, increasing target dose accuracy with a better tolerance of healthy tissue, favoring the reduction of tumor size while preserving the surrounding healthy tissue[1,2].

Radiosurgery, a technique developed by Lars Leksell in 1950, allows treatment of brain lesions, with local control rates ranging from 80-90%[3,4]. For the treatment of lesions that move with respiration, it required a technique that conforms to target movements. The CyberKnife system synchronizes external movement with the internal position of the target through a system of optical markers based on the position of the implanted fiduciary markers[5–7].

In patients with hepatocellular carcinoma, surgical resection allows a cumulative 5-year survival of 23%[8]. Conversely, Schoenberg M. et al. reported a tumor-free survival rate of 79.4% at one year and 29.8% at three years in patients with unresectable tumors treated with radiosurgery using the CyberKnife system[9,10]. In most patients with liver metastases treated with Stereotactic Body Radiotherapy (SBRT), local control rates ranging from 60% to 94% at two years have been reported[11].

In patients with locally advanced pancreatic tumors, radiosurgery improves local control of the disease, which could lead to a better quality of life[12]. Three-year local control rates of 64% have been reported in patients with colorectal cancer and abdominal lymph node metastases treated with CyberKnife radiosurgery[13]. Despite favorable results reported in radiation therapy centers in the United States, Canada, and Europe, we did not find any published literature in Latin America evaluating tumoral size behavior in patients with intra-abdominal tumors treated with SBRT. This study aimed to estimate tumoral reduction and overall survival at one year in a series of patients with intra-abdominal tumors treated with fiduciary marker-guided radiation therapy using a CyberKnife system in a specialized center.

Material and methods

Methodology

This study used a case series with an analytical approach. We analyzed patients with solid or hollow viscus intra-abdominal tumors, who were treated with guided radiotherapy using a CyberKnife system at the Neurological Institute of Colombia, between January 2013 and January 2018, in Medellín, Colombia. Approval of the study was obtained from the institution's ethics committee.

Participants

Adult patients with intra-abdominal tumors from solid or hollow viscera (primary or metastatic), treated with SBRT using the CyberKnife system who completed post-treatment follow-ups with diagnostic images (computed tomography or magnetic resonance imaging) in a period of up to 24 months were included. Patients with prostate tumors, patients without follow-up images after radiosurgery, and those previously irradiated were excluded.

Variables and data sources

The following variables were included: age, sex, location of the treated lesion (affected organ), lesion type (primary or metastatic), previous treatments to CyberKnife, number of implanted fiduciary markers, radiation dose (Gy), and number of fractions. Additionally, the planning image and radiosurgery dates were identified including the follow-up image dates. Also, the vital status was identified by contacting the patient or family member, or the date of death, depending on the case. The rest of the variables were obtained from clinical records. Age, SBRT dose, and the number of fractions were categorized.

SBRT using the CyberKnife System

All patients were discussed at the institution's tumor board to corroborate the indication and relevance of radiosurgery. The medical board was made up of a radiotherapist, a medical physicist, and a radiologist who specialized in body image, in communication with the treating oncologist. Patients were simulated in the supine position without immobilization. The treatment images were acquired 8 days after the insertion of fiducial marks. The tomography images were acquired using a Siemens Somatom Definition Flash equipment, with the following specifications: 1 mm thickness, 120 kVp, 300 mAs, and the anatomical region included the whole abdomen, with a minimum of 15 cm cranially and caudally to the region to be treated. Simple series were acquired for the calculation of the dose and the generation of digitally reconstructed radiographs to monitor the lesion, and contrasted series were used to facilitate organ delimitation. Contrasted magnetic resonance images were also used, and in some cases, positron emission tomography images merged with computed tomography planning images.

Treatment planning was done using the Multiplan 4.6 system, including sequential inverse optimization. Patients were treated with the CyberKnife system, using the IRIS collimator, the Xsight Synchrony method, and fiducial tracking; allowing them to follow the internal movements of the target due to the patient's breathing.

Response evaluation

Simulation and post-treatment follow-up images were analyzed. Measurement of all lesions before and after treatment was completed by the principal investigator. Post-treatment follow-up images were taken between 2 and 24 months after radiosurgery. For the evaluation of local treatment response, the RECIST 1.1 criteria (Response evaluation criteria in solid tumors) were applied[14]. These criteria define that the evaluation of lesions should be done using tomography or magnetic resonance imaging, on the axial plane. Imaging acquisition techniques used to evaluate the lesions were always the same. When the evaluation was done using tomography, intravenous contrast was used and analyzed in the same vascular phase and when it was done using magnetic resonance, images were evaluated always using the same sequence (T1 with gadolinium). The RECIST 1.1 classification system has four grades of tumor response: disease progression (increase of at least 20% of the lesion), partial response (decrease of at least 30% of the lesion), complete response (disappearance of all lesions), and stable disease (does not meet any of the above criteria).

Data analysis

For the clinicopathological and treatment-related variables, frequencies and proportions were calculated. For the quantitative variables, means or medians were presented with their respective measure of dispersion depending on their distribution. Measures of central tendency and dispersion were presented according to the size distribution of the target lesion before and after SBRT using CyberKnife, as well as their difference.

An analysis was performed using target lesion sizes before and after SBRT treatment with the CyberKnife system. It was used an paired samples t-test, to determine if there was a significant reduction in the size of the tumoral lesion. To test normality, the Shapiro-Francia test was used. A p-values < 0.05 were considered statistically significant.

Overall survival was estimated with the Kaplan-Meier method, in subgroups of response to treatment according to RECIST 1.1 criteria. The Log-Rank test was used to compare the treatment response strata. A p-values<0.05 were considered statistically significant.

The statistical package STATA 14 (StataCorp, College Station, TX, USA) was used.

Results

Thirty-three patients with abdominal tumors were identified during the study period. However, 17 subjects were excluded, due to the lack of access to radiological images after radiosurgery, Supplementary File 1.

The study included 16 patients, 8 (50%) men and 8 (50%) women. In the sample studied, 12 patients (75%) were under 65 years of age. The mean age was 60 years (SD ±9.9). The treated lesions were in the pancreas (37.5%), liver (25%), abdominopelvic lymph nodes (25%), and retroperitoneum (12.5%). Half of the treated lesions were metastatic, and most of the treated patients had up to two fiduciary markers implanted (93.7%). The minimum dose of SBRT applied was 24 Gy, and the maximum was 60 Gy (IQR 24-35). In 81.3% of the patients three fractions were applied shown in **Table 1**.

Table 1. Clinicopathological and treatment-related characteristics of patients with abdominal tumors treated with radiosurgery (CyberKnife) at the Neurological Institute of Colombia.

Characteristics	n = 16 (100%)	
Sex		
Male	8	(50.0)
Female	8	(50.0)
Age (years)		
< 65	12	(75.0)
≥ 65	4	(25.0)
Location of the treated lesion		
Pancreas	6	(37.5)
Liver	4	(25.0)
Abdomino-pelvic lymph nodes	4	(25.0)
Retroperitoneum	2	(12.5)
Type of lesion		
Primary	8	(50.0)
Metastatic	8	(50.0)
Previous treatments		
Surgery + CT	5	(31.3)
CT	5	(31.3)
Surgery	2	(12.5)
Surgery + RT + CT	2	(12.5)
Surgery + RT	1	(6.2)
None	1	(6.2)
Fiduciary markers	0	(0.0)
1	5	(31.3)
2	10	(62.5)
6	1	(6.2)
SBRT dose		
24 Gy	9	(56.2)
>24 Gy	7	(43.8)
Number of fractions		
3	13	(81.3)
>3	3	(18.7)
Treatment response (RECIST 1.1)		
Complete	1	(6.2)
Partial	9	(56.3)
Stable	6	(37.5)

Abbreviations: CT: chemotherapy; RT: radiotherapy; SBRT: body fractionated stereotactic radiotherapy.

Local control

Lesions sizes before and after SBRT presented a normal distribution (Shapiro-Francia, $p = 0.572$, and $p = 0.250$, respectively). The imaging follow-up (months) presented a non-normal distribution (Shapiro-Francia $p = 0.000$). Table 2 shows local control data for the tumor lesions treated. The mean lesion size before the treatment with CyberKnife radiosurgery was 44.5 mm (SD ±20.5). The median imaging follow-up to assess the size of the treated lesions was 3 months (IQR 3-7). In the follow-up images after treatment with CyberKnife radiosurgery, the mean tumor lesion size measured on the axial axis was 28.9 mm (SD ±15.6). The reduction in tumor lesion size in the follow-up images was 15.6 mm (SD ±13.5), this reduction being statistically significant (paired samples t-test, $p < 0.0003$). Only in one treated lesion, there was a tumor size increase of 3 mm in follow-up images compared to the planning images.

When evaluating the local response to treatment in solid tumors, according to RECIST 1.1 criteria, 56.3% of the patients presented a partial response to treatment. A total of 37.5% showed local stability of the disease. No disease progression was documented in any patient according to Table 1.

Table 2. Local control in lesions treated with radiosurgery (CyberKnife) at the Neurological Institute of Colombia.

	Frequency	Mean (mm)	SD (±mm)	p value*
Pre-treatment injury	16	44.5	20.5	
Post-treatment injury	16	28.9	15.6	0.0003
Difference of injury before and after treatment		15.6	13.5	

Abbreviation: SD = standard deviation. *Paired samples t-test

In patients with locally advanced pancreatic cancer (n = 6), 50% showed stable disease, and the other half had a partial response. No patient during follow-up presented local progression after treatment; however, in one patient the lesion increased in size by 3 mm concerning the baseline measurements. The mean decrease in the size of the pancreatic lesions was 14 mm (SD ± 19 mm) as shown in Figure 1.

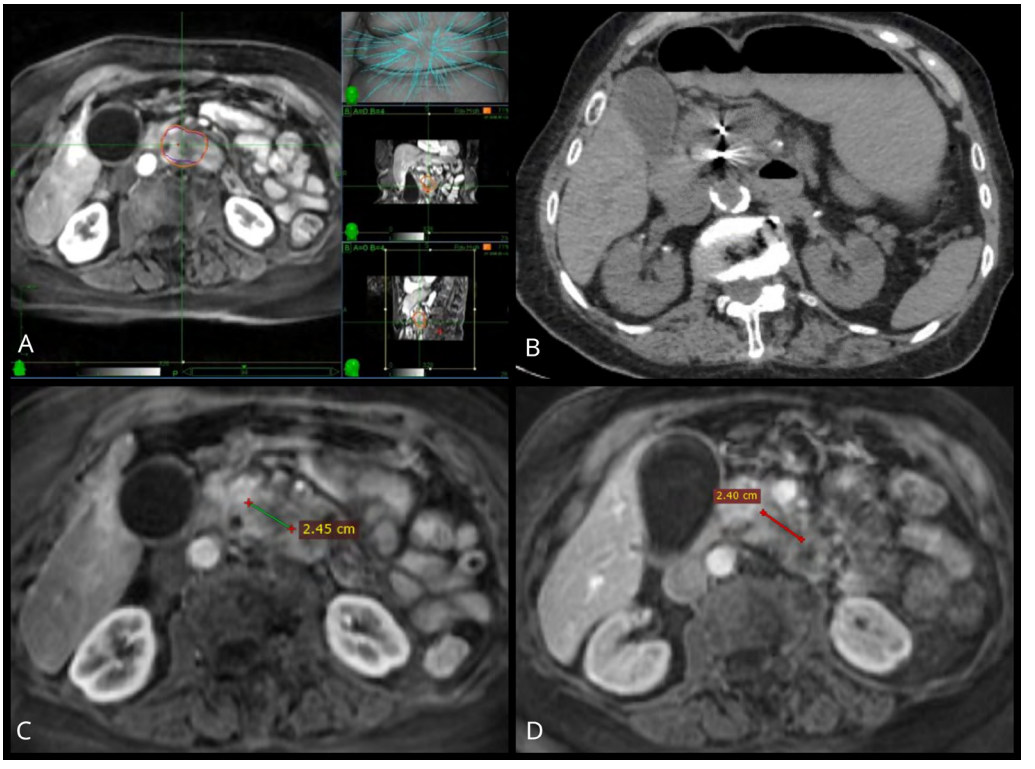

Figure 1. Tumor response in a patient with locally advanced pancreatic adenocarcinoma, treated with CyberKnife radiosurgery. (A) Treatment and dose distribution (24 Gy x 3 fractions). (B) Simple axial CT with fiduciary markers. (C) MRI T1 + C Fat Sat planning, with a 24-mm lesion in the uncinate process of the pancreas with vascular invasion. (D) MRI T1 Fat Sat control at 4 months, showing stable lesion.

Local control of the disease was obtained in the two patients with primary retroperitoneal sarcomas. One patient had a complete response, and the other had a stable disease. Pre-treatment lesions measured 10 and 63 mm and the mean reduction in tumor size was 12.5 mm (SD ± 3.5 mm).

In the metastases to the abdominal-pelvic lymph nodes, the primary tumors were in the rectum, duodenum, ovary, and gallbladder. In liver metastases, the most common primary tumor was gastrointestinal (colon, n = 1; gastrointestinal stromal tumors, n = 2). In post-treatment imaging controls, for lymph node metastases (n = 4), all patients had a partial response. For liver metastases (n = 4), 50% of the patients had a partial response and the other half had stable disease. The mean size decrease of the lymph node and liver lesions was 20.7 mm (SD ± 12.3 mm) and 14.5 mm (SD ± 10.1 mm), respectively according to **Figure 2** and **Figure 3**.

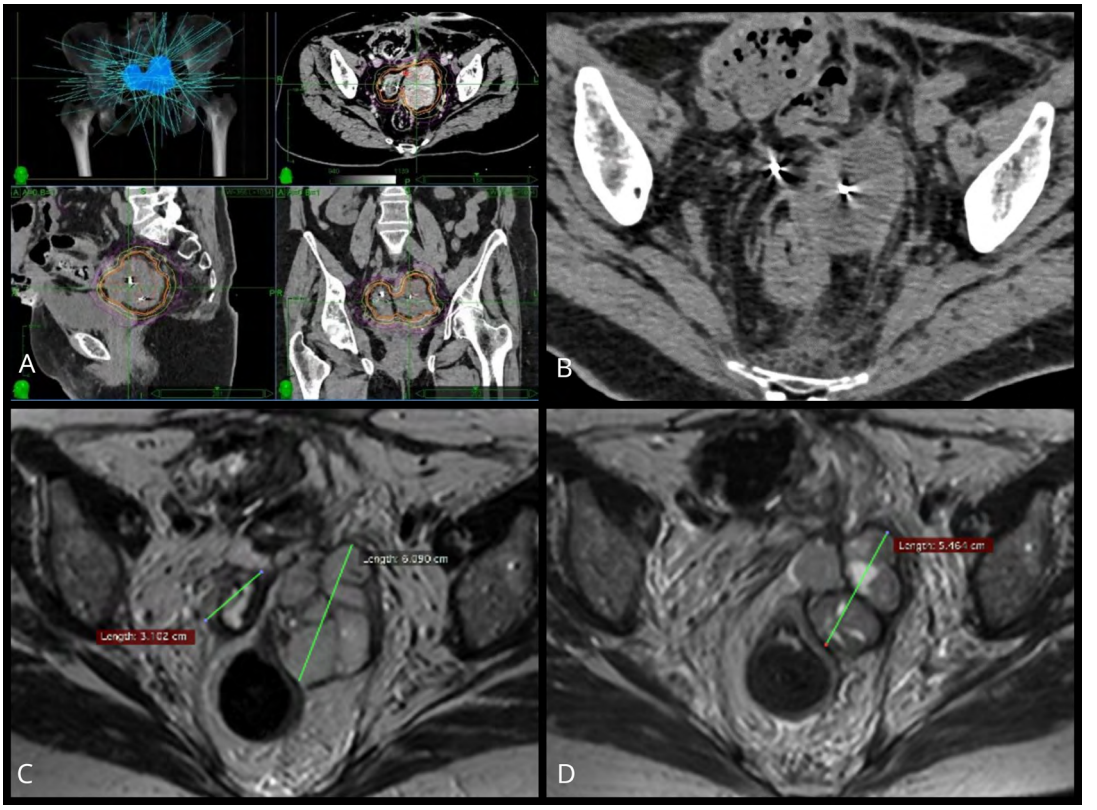

Figure 2. Tumor response in a patient with granulosa cell ovarian tumor and lymph node metastases (pararectal lymphadenopathy). (A) Treatment and dose distribution (30 Gy x 5 fractions). (B) Simple CT with fiduciary markers. (C) Planning T2 MRI: conglomerate of left pararectal adenopathy's of 60 mm and right of 31 mm. (D) Control T2 MRI at 18 months showing a 6mm decrease in the conglomerate of left pararectal lymphadenopathy and disappearance of the right pararectal adenopathy. RECIST 1.1: partial response.

Survival

One-year overall survival in patients with abdominal tumors, treated with radiotherapy using the CyberKnife was 93.7% (15/16). One patient with pancreatic cancer died four months after treatment. There were no significant differences in patient survival when comparing the response to treatment according to RECIST 1.1 criteria supported in Supplementary File 2.

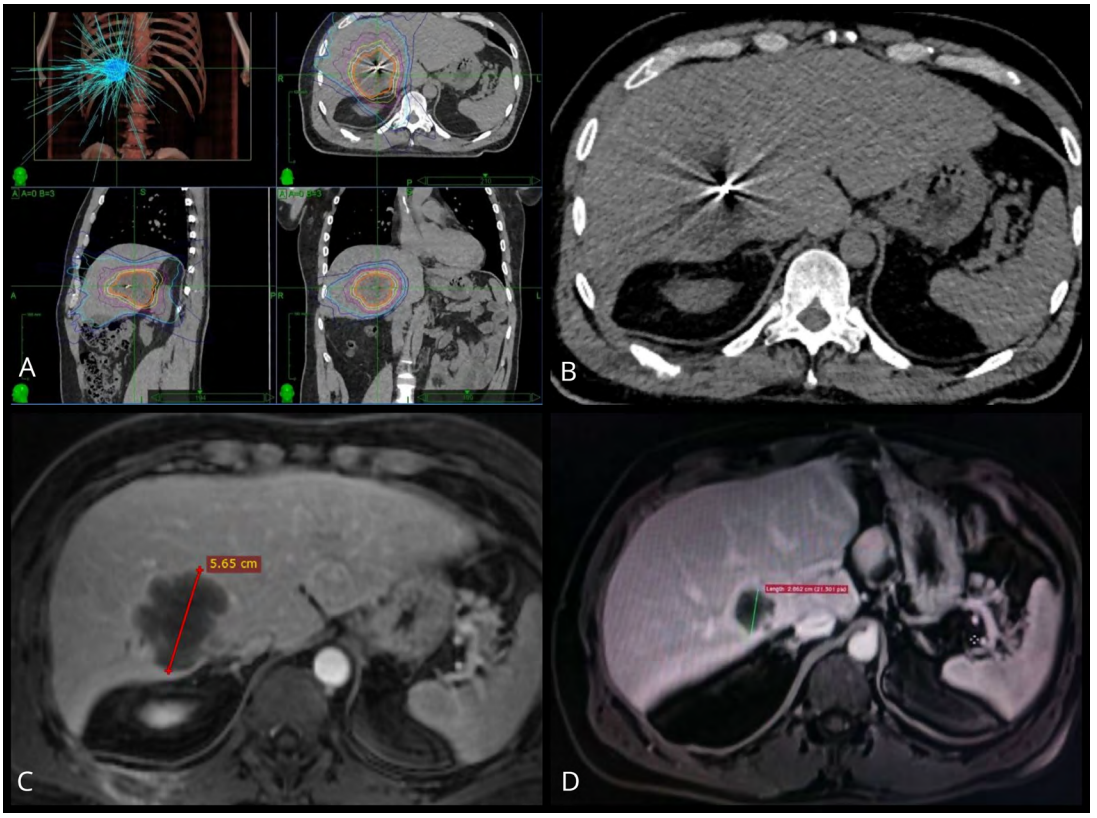

Figure 3. Tumor response in a patient with colon cancer and liver metastasis. (A) Treatment and dose distribution (45 Gy x 3 fractions). (B) Simple CT with fiduciary markers. (C) MRI T1 + C FatSat planning: liver metastasis involving segments VI and VII, measuring 56 mm. (D) MRI T1 + C FatSat control at 3 months showing a decrease of 28 mm of the lesion. RECIST 1.1: partial response.

Discussion

This study reports a single-center experience with short-term results on local control and overall survival in a series of patients with abdominal tumors treated with CyberKnife radiosurgery in Colombia. During the observation period, no progression of the disease was evidenced according to RECIST 1.1 criteria. The one-year overall survival after CyberKnife radiosurgery was greater than 90%.

Among the limitations of this study, 52% of the analyzed population was excluded due to the lack of diagnostic image availability, limiting sample size. This could generate a selection bias; however, similar proportions were observed in the excluded population with regard to age, sex, treated liver and pancreas tumors, and doses and fractions of radiosurgery. Tumor size measurements were done before and after radiosurgery without blinding, thus it may incur a measurement bias. To mitigate the latter, a standardized methodology widely used in clinical practice (RECIST 1.1) was used. We cannot assure that the reduction in tumor size was due solely and exclusively to radiosurgery with the CyberKnife system, influencing other therapeutic options such as chemotherapy.

In pancreatic cancer the probability of distant metastasis is high; however, local progression is also an important prognostic factor. Local control improves the quality of life by controlling pain and avoiding gastrointestinal obstruction[15,16]. Traditional conventional fractionated radiation therapy can only deliver a dose of approximately 50 Gy to these tumors and the local failure rate is very high (50-85%)[16]. Therefore, more powerful local treatment measures are needed to increase the local control rate of pancreatic cancer[15].

In a study by Lischalk et al., a 12-month local control rate of 78% was reported in a group of patients with metastatic pancreatic cancer treated with CyberKnife radiosurgery and a target planning volume of less than 147.3 cm^3 [17]. In our cohort, the patients who had locally advanced pancreatic cancer, the 1-year survival was greater (83%) than those reported in other studies (50%)[18,19]. Furthermore, the benefit of SBRT on the

survival of unresectable pancreatic cancer was analyzed in 14,331 patients registered in the United States National Cancer Database between 2004 and 2012[20]. This study reported a median survival of 13.4 months in the SBRT and chemotherapy group compared with 10.2 months in the chemotherapy-only group (log-rank test, $p<0.0001$). This suggests that patients with locally advanced pancreatic cancer may benefit from SBRT. Compared to traditional radiotherapy, the advantages of this technology are: (i) it increases the precision of the treatment, (ii) the incidence of toxicity associated with the treatment decreases, and (iii) the treatment time is shortened[21,22].

In patients with primary retroperitoneal sarcomas, the main therapeutic option is radiation therapy. However, the complex anatomy of the retroperitoneum and its proximity to vital organs make conventional radiotherapy a risk. Due to the above, the administration of high doses per fraction and the short courses of radiotherapy makes CyberKnife radiosurgery an adequate alternative[23]. There are few studies reported in the literature evaluating the response to guided radiotherapy with the CyberKnife system in patients with retroperitoneal tumors. A study by Zhuang H et al.,[23] reported a complete response and stability of the disease in 48% and 18% of the cases, respectively. Additionally, this study reported an overall response rate of 96% and an overall 1-year survival of 60%. In our study, two patients were treated for retroperitoneal sarcomas with adequate local control. This suggests that the response to CyberKnife radiosurgery treatment for retroperitoneal tumors achieves favorable local control results.

Talking about the oligometastatic disease, it occurred in the abdominopelvic lymph nodes and on the liver. In liver metastases, studies have shown local control rates between 71% to 100% at 1 year[24,25]. There are few published data on SBRT in abdominal lymph node metastases. Bignardi et al.[26] reported a freedom rate from local progression at one year of 77.8%. The above findings are consistent with our results and suggest that CyberKnife radiosurgery is feasible and safe.

The results of the present study demonstrate adequate local control of the disease in patients treated at our center. All treatments were completed in an outpatient setting of short duration (1 to 2 weeks). Each fraction, using high-intensity photon beams, was completed in a few minutes (less than 15 minutes). It should be considered that it was a descriptive study of a small series of patients, which covered several types of histologists, with few cases in each group. However, it represents the radiosurgery group experience in one institution and these results can only be interpreted at the local level. This study serves as the basis for considering prospective studies to confirm these findings.

In conclusion, this study shows an adequate response in local control in a series of patients with solid and hollow viscus abdominal tumors, whether primary or metastatic, treated with guided radiosurgery with the CyberKnife system in one center in Latin America. Additionally, the patients showed high survival rates at one year. These results are similar to those reported in studies conducted in the United States and Europe. These findings are the result of a potential synergistic effect between radiosurgery and other therapeutic options such as surgery and chemotherapy.

Ethical approval

Approval of the study was obtained from the institution's ethics committee.

Conflict of interest

The authors report no conflicts of interest.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supplementary File 1. Characteristics of excluded patients with abdominal tumors treated with radiosurgery (CyberKnife) at the Neurological Institute of Colombia.

Characteristics	**n = 17 (100%)**	
Sex		
Male	8	(47.1)
Female	9	(52.9)
Age (years)		
< 65	11	(64.7)
≥ 65	6	(35.3)
Location of the treated lesion		
Pancreas	7	(41.2)
Retroperitoneum	4	(23.5)
Liver	3	(17.7)
Bladder	2	(11.7)
Abdomino-pelvic lymph nodes	1	(5.9)
Type of lesion		
Primary	11	(64.7)
Metastatic	6	(35.3)
Previous treatments		
CT	6	(35.3)
Surgery + CT	5	(29.4)
Surgery + RT + CT	5	(29.4)
Surgery	1	(5.9)
SBRT dose		
24 Gy	10	(58.8)
>24 Gy	7	(41.2)
Number of fractions		
3	14	(82.4)
>3	3	(17.6)

Abbreviations: CT: chemotherapy; RT: radiotherapy; SBRT: body fractionated stereotactic radiotherapy.

Supplementary File 2. One-year overall survival curve of patients with abdominal tumors, treated with radiotherapy the CyberKnife system at the Neurological Institute of Colombia.