Stereotactic Body Radiation Therapy (SBRT) for Liver Oligometastases: outcomes and safety

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Research

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Abstract

Background: The aim of this study was to investigate adverse effects, progression free survival (PFS), one-year local control (LC) and one-year overall survival (OS) of patients with liver oligometastases treated with stereotactic body radiotherapy (SBRT), and whether there is a significant difference in these parameters in patients with primary colorectal cancer compared to other tumor localizations.

Methods: Patients were simulated using four-dimensional computed tomography (4DCT). Using volumetric modulated arc therapy (VMAT) technique, SBRT was performed on 16 patients with <3 liver metastases. The prescribed dose was 60 Gy in 8 fractions (BED 105 Gy). Cone beam CT (CBCT) was used for image guidance before each fraction with online correction.

Results: There were no adverse effects. Mean PFS for all patients, patients with primary colorectal cancer, and patients with primary non-colorectal cancer was 12.2 months (SD 8.3), 16.3 months (SD 7.9), 8.1 months (SD 6.8), respectively. There was a significant difference in the mean PFS for these two observed groups ($p = 0.023$). The one-year LC was 62.5%. Patients with primary colorectal cancer had the one-year LC of 87.5%, while the group of patients with primary non-colorectal cancer had the one-year LC of 37.5% ($p = 0.014$). The total one-year OS was 87.5%. In the group of patients with primary colorectal cancer, the one-year OS was 100%, while in the group of patients with primary non-colorectal cancer, the one-year OS was 75% ($p = 0.147$).

Conclusion: SBRT is a safe and effective method of treating liver oligometastases.

Background

Metastases in the liver cause significant morbidity, causing pain and anorexia, among others, while significant liver dysfunction worsens the general condition of the patient and is one of the significant causes of mortality in patients with malignant diseases [1]. The liver is one of the most common sites for metastatic spread. The largest number of liver metastases are of colorectal cancer origin [2,3]. Although it is a metastatic disease, if it is limited in number and localization only to the liver, these patients are candidates for local therapy [4,5]. Surgery is the first option for local treatment, with long-term good results in the control of oligometastatic liver disease [6-8]. Unfortunately, only 10-20% of metastases in the liver are resectable, which is why most patients are treated with systemic therapy. Although new combinations of chemotherapeutic agents and targeted drugs lead to better results, they do not do so without significant toxicity. Other methods of local ablative therapies that have shown benefit are stereotactic body radiotherapy (SBRT), radiofrequency and microwave ablation, transarterial chemoembolization, cryoablation and alcohol injection [9-11]. Radiotherapy is a proven palliative treatment method, and in patients with painful metastases in the liver, even one fraction of irradiation of the whole liver could achieve a significant reduction in symptoms and lead to improved quality of life in most patients [12,13].

Due to the low tolerance of the liver parenchyma to radiation, the standard form of external radiotherapy to a larger volume of liver tissue is not an option for treating liver metastases due to the high risk of damage to the healthy liver parenchyma (RILD, Radiation Induced Liver Damage) [14-16]. Technological advances have improved planning systems and imaging methods which made it possible to apply high doses of radiation in a smaller number of fractions to a limited volume in the liver parenchyma while maximally sparing the surrounding healthy parenchyma [17-21]. By increasing the dose that can be safely applied to the tumor, the ability to control the tumor also increases. Numerous studies investigated and continue investigating the possibilities of application, efficiency and safety of stereotactic radiation of liver metastases.

The aim of this study is to investigate adverse effects, period up to disease progression (Progression Free Survival, PFS), one-year local control (LC) and one-year overall survival (OS) of patients with liver oligometastases treated with SBRT, as well as whether there is a significant difference in these parameters in patients with primary colorectal cancer compared to other tumor localizations.

Methods

Patients

This prospective study included patients who were treated consecutively in the period from August 2016 to June 2019. At the time of analysis, each patient had a follow-up time of at least one year. Inclusion factors for SBRT of liver metastases are: liver metastases that are unresectable or medically inoperable due to comorbidities and which are verified by biopsy or CT / MR / PET imaging with an increase in tumor markers, <3 size metastases, size ≤ 6cm, stable primary tumor, good liver function, in good general condition (ECOG 0-2). Exclusion factors are observed and later confirmed, through diagnostic tests, disease progression at the time of CT simulation and crossing the dose constraints on healthy tissues.

Methods

Patients were simulated using four-dimensional computed tomography (4DCT, GE LightSpeed, 16 slice, slice thickness 1.25mm) in supine position using abdominal compression (Macromedics), with or without intravenous contrast [22]. For more accurate visualization and delineation, available pre-therapeutic diagnostic tests were registered (contrast-enhanced CT, MR, PET/CT). The target volume was contoured at the following phases of 4DCT: fb (free breathing), 0, 50, 90 and Min-IP (Minimal Intensity Projection) in the ARIA radiotherapy system (Varian Medical Systems Inc, Palo Alto, CA, USA), with target volume position check on all available diagnostic and 4DCT simulation images. By combining the contours in the mentioned phases, ITV (Internal Tumor Volume) was defined, which was named iGTV, and then PTV with a margin of 3-5 mm. Organs at risk were contoured according to the RTOG atlas and include: liver (liver contoured on fb series and Avg (Average) series, oesophagus, small intestine, large intestine, stomach, kidneys, spinal cord, spinal cord PRV, ribs and skin.

The prescribed dose was 60 Gy in 8 fractions (7.5 Gy daily; BED 105 Gy, $\alpha/\beta = 10$), every other day. Planning was done using the Eclipse planning system, and the Accuros XB algorithm was used to calculate the dose. The two half-arc volumetric modulated arc therapy (VMAT) technique with a treatment couch rotation of ± 10° was used. The treatment was performed on a Varian Clinac DHX linear accelerator. Before each fraction, cone beam CT (CBCT) and online verification and correction of the patient's position and metastasis or metastases were performed. Checking the position of the target volume was controlled so that the liver contour on the obtained CBCT image overlapped with the liver contour obtained on the Avg series of simulation 4DCT, which was considered a surrogate for the liver position during treatment if metastases were not clearly visible [23,24].

Patients were monitored prospectively at quarterly intervals with control laboratory tests (blood count, liver biochemical tests) and radiological imaging. Radiographic response assessment was performed according to RECIST 1.1 criteria and was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR is defined as the total radiographic disappearance of all lesions. PR is defined as at least a 30% reduction in the amount of diameter of the target lesions. PD is defined as at least a 20% increase in the diameter of the target lesions. In addition to a relative increase of 20%, the lesion also had to show an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. SD is defined as neither a sufficient decrease to qualify for PR, nor a sufficient increase to qualify for PD [25].

Progression of the disease is considered to be the progression of the treated lesion, the appearance of new metastases in the liver, in the distant organs and/or lymph nodes. One-year local control is met if the treated lesion is without signs of disease progression. Patients were followed for local control for up to a year in case of disease progression which was not a consequence of the progression of the treated lesion. In case the patient would die within one year from the beginning of the treatment, it was considered that the local control was not met. One-year overall survival was measured from the day of commencement of the stereotactic radiotherapy treatment.

Statistical analysis

Standard descriptive methods (arithmetic mean with standard deviation, range of numerical feature from minimum to maximum value) were used in statistical data analysis. Student t-test was used to examine statistical significance. The difference was considered significant if $p<0.05$. StatsDirect Statistical Software (ver. 3.2.10) was used for statistical analysis.

Results

There were no treatment side effects or changes in blood counts and liver biochemical parameters. The mean age for the 16 patients analysed (Table 1. Patients characteristics) was 63 years (standard deviation 15.64, minimum 17, maximum 78). The most numerous were the patients with primary colorectal cancer (8 patients). Four patients had primary breast cancer, 2 had primary cancer of the hepatobiliary tract, 1 had primary lung cancer and one had hepatocellular carcinoma. The total number of

treated metastases was 21. Ten patients received HT due to liver metastases before treatment with SBRT, while in 6 patients SBRT was the first therapy for oligometastatic liver disease.

The PFS for all patients was 12.2 months (standard deviation 8.3, minimum 3 months, maximum 28 months). In the group of patients with primary colorectal cancer, the PFS was 16.3 months (standard deviation 7.9, minimum 3 months, maximum 28 months). In the group of patients with primary non-colorectal cancer, the PFS was 8.1 months (standard deviation 6.8, minimum 3 months, maximum 24 months). There is a significant difference in the mean time to disease progression for these two observed groups ($p = 0.023$) (Figure 1. Progression Free Survival (PFS) plot).

The one-year LC was 62.5%. In the group of patients with primary colorectal cancer, the one-year LC was 87.5%, while in the group of patients with primary non-colorectal cancer, the one-year LC was 37.5%. There is a significant difference in one-year LC for patients with colorectal cancer compared to patients with primary tumor of other localizations ($p = 0.014$).

The total one-year OS was 87.5% (14 of 16 patients). In the group of patients with primary colorectal cancer, the one-year OS was 100%, while in the group of patients with primary non-colorectal cancer, the one-year OS was 75%. There is no significant difference in the one-year OS for these two observed groups ($p = 0.147$).

Discussion

This study investigated the safety and efficacy of stereotactic body radiotherapy in the treatment of patients with oligometastatic liver disease and it examined whether there was a difference in prognosis if the patient had primary colorectal cancer compared to other primary tumors. The duration of the study was determined so that each patient had follow-up of at least one year, and care was taken to ensure that in both groups (colorectal cancer vs. other primary) there was a sufficient number of patients to conduct an adequate statistical analysis.

This study shows a significant difference in PFS for patients with colorectal cancer compared to other primary tumors (16.3 months vs 8.1 months, $p=0.023$). Compared to other studies (Rusthoven et al. PFS 6.1 months; Lee et al. PFS 3.9 months, Nicosia et al. PFS 7 months), an enviable mean time to disease progression was achieved, especially for the group of patients with colorectal cancer [26-28].

The achieved one-year LC of 62.5% is slightly lower, while the one-year LC of 87.5% for patients with colorectal cancer is in line with the results of local control from other studies, ranging from 71 to 95% [26,27,29-31]. This study showed that there was a significant difference in local control in patients with colorectal cancer compared to other histologies (87.5% vs 37.5%, $p=0.014$). An explanation of the results of one-year local control can be found in the prescribed dose and size of treated metastases. The higher the dose, the greater the possibility of local control, as the study by Rule et al. shows that there is a significant difference in the two-year control between 30 Gy in 3 fractions and 60 Gy in 5 fractions (56% vs 100%, $p=0.009$) [32]. One-year local control is 94% and 95% for the prescribed doses of 75 Gy in 3

fractions and 60 Gy in 3 fractions [26,31]. Dose escalation in these studies is safe in terms of tolerance and toxicity, if dose volume limits and liver volume are to be spared. According to the study by Rusthoven et al. 100% two-year control was achieved for metastases of size <3cm, while for metastases >3cm it was 77% (p=0.015) [26]. In the group of patients this study analysed, only one third of patients had metastases <2cm, while other metastases were >2cm, which potentially affected somewhat lower total local control.

The one-year OS for all patients, patients with colorectal cancer, and patients with other primary tumors is 87.5%, 100%, and 75%, respectively. No significant difference in one-year survival was achieved between the observed groups (p=0.147). The results of other studies range from 68.6% to 83.5% [28-31]. Rusthoven et al. showed that there was a group of favorable histologies, which include colorectal cancer, breast and kidney cancer, carcinoids, GIST and sarcomas, which has a significantly longer mean survival of 32 months compared to other adverse histologies with a mean survival of 12 months (p=0.001) [26].

The difference in PFS and one-year LC shows that in patients with olimetastatic liver disease, primary colorectal cancer has a good prognosis, which is confirmed by the study of Andratschke et al. [29].

The disadvantage of this study is the relatively small number of patients, which led to the formation of a group with combined patients with primary tumors other than colorectal cancer. That prevented individual comparison of outcomes between different primary tumors. The small sample also affected the result of one-year OS, i.e. the inability to obtain a significant difference between the observed groups.

In conclusion, 8 x 7.5 Gy SBRT is a safe and effective method of local ablative treatment of oligometastatic liver disease.

Declarations

Ethics approval and consent to participate

Decision to be treated with SBRT for liver oligometastases was made on tumor board for all patients. Before the treatment, every patient signed standardised consent form.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

Conception and design: DC, GM; Acquisition, analysis and interpretation of data: DC, GM; Drafting the article: DC, GM, Revising it critically for important intellectual content: DC, GM.

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Table

Table 1. Patients characteristics

	All patients	Male	Female
Number of patients	16	6 (37.5%)	10 (62.5%)
Age (years)			
<65	7 (43.7%)	1 (6.3%)	6 (37.5%)
≥ 65	9 (56.3%)	5 (31.2%)	4 (25%)
Median age	63	73	56
Primary tumor			
Colorectal cancer	8 (50%)	5 (31.2%)	3 (18.8%)
Breast cancer	4 (25%)	-	4 (25%)
Lung cancer	1 (6.3%)	1 (6.3%)	-
Hepatobiliary tract cancer	2 (12.5%)	-	2 (12.5%)
Primary liver cancer	1 (6.3%)	-	1 (6.3%)
Number of liver metastases per patient			
1	11 (68.8%)	3 (18.8%)	8 (50%)
2	5 (31.3%)	3 (18.8%)	2 (12.5%)
Size of the metastases			
<2 cm	7		
2-4 cm	8		
4-6 cm	6		

References

1. Costi R, Leonardi F, Zanoni D, Violi V, Roncoroni L. Palliative care and endstage colorectal cancer management: the surgeon meets the oncologist. World J Gastroenterol 2014;20(24):7602–21. doi:10.3748/wjg.v20.i24.7602
2. Kemeny NE, Ron IG. Liver Metastases. Curr Treat Options Gastroenterol 1999;2(1):49–57. doi:10.1007/s11938-999-0018-1
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(1):7–30. doi:10.3322/caac.21387
4. Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, et al. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. J Pathol 1986;150(3):195–203.

doi:10.1002/path.1711500308

5. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13(1):8–10. doi:10.1200/JCO.1995.13.1.8
6. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14(12):1208–15. doi:10.1016/S1470-2045(13)70447-9
7. Smith JJ, Angelica D MI. Surgical management of hepatic metastases of colorectal cancer. Hematol Oncol Clin North Am 2015;29(1):61–84. doi:10.1200/JOP.2015.009407
8. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol Off J Am Soc Clin Oncol 2007;25(29):4575–80. doi:10.1200/JCO.2007.11.0833
9. Bekaii-Saab T, Wu C. Seeing the forest through the trees: a systematic review of the safety and efficacy of combination chemotherapies used in the treatment of metastatic colorectal cancer. Crit Rev Oncol Hematol 2014;91(1):9–34. doi:10.1016/j.critrevonc.2014.01.001
10. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240(4):644–58. doi:10.1097/01.sla.0000141198.92114.f6
11. Hellman S, Weichselbaum RR. Importance of local control in an era of systemic therapy. Nat Clin Pract Oncol 2005;2(2):60–1. doi:10.1038/ncponc0075
12. Borgelt BB, Gelber R, Brady LW, Griffin T, Hendrickson FR. The palliation of hepatic metastases: results of the radiation therapy oncology group pilot study. Int J Radiat Oncol Biol Phys 1981;7(5):587–91. doi:10.1016/0360-3016(81)90370-9
13. Soliman H, Ringash J, Jiang H, Singh K, Kim J, Dinniwell R, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. J Clin Oncol Off J Am Soc Clin Oncol 2013;31(31):3980–6. doi:10.1200/JCO.2013.49.9202
14. Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, et al. Radiation associated liver injury. Int J Radiat Oncol Biol Phys 2010;76(3):S94–100. doi:10.1016/j.ijrobp.2009.06.092
15. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31(5):1237–48. doi:10.1016/0360-3016(94)00418-K
16. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002;53(4):810–21. doi:10.1016/s0360-3016(02)02846-8
17. Kini VR, Vedam SS, Keall PJ, Patil S, Chen C, Mohan R. Patient training in respiratory-gated radiotherapy. Med Dosim off J am Assoc. Med Dosim 2003;28(1):7–11. doi:10.1016/S0958-3947(02)00136-X

18. Brock KK, McShan DL, Ten Haken RK, Hollister SJ, Dawson LA, Balter JM. Inclusion of organ deformation in dose calculations. Med Phys 2003;30(3):290–5. doi:10.1118/1.1539039
19. Dawson LA, Balter JM. Interventions to reduce organ motion effects in radiation delivery. Semin Radiat Oncol 2004;14(1):76–80. doi:10.1053/j.semradonc.2003.10.010
20. Dawson LA, Brock KK, Kazanjian S, Fitch D, McGinn CJ, Lawrence TS, et al. The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. Int J Radiat Oncol Biol Phys 2001;51(5):1410–21. doi:10.1016/s0360-3016(01)02653-0
21. Hara W, Soltys SG, Gibbs IC. CyberKnife robotic radiosurgery system for tumor treatment. Expert Rev Anticancer Ther 2007;7(11):1507–15. doi:10.1586/14737140.7.11.1507
22. Wunderink W, Méndez Romero A, de Kruijf W, de Boer H, Levendag P, Heijmen B. Reduction of respiratory liver tumor motion by abdominal compression in stereotactic body frame, analyzed by tracking fiducial markers implanted in liver. Int J Radiat Oncol Biol Phys 2008;71(3):907-15. doi:10.1016/j.ijrobp.2008.03.010
23. Case RB, Sonke JJ, Moseley DJ, Kim J, Brock KK, Dawson LA. Inter- and intrafraction variability in liver position in non-breath-hold stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2009;75(1):302-8. doi:10.1016/j.ijrobp.2009.03.058
24. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37(8):4078-101. [published correction appears in Med Phys 2012;39(1):563. Dosage error in article text] doi:10.1118/1.3438081
25. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2):228-47. doi:10.1016/j.ejca.2008.10.026
26. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27(10):1572–8. doi:10.1200/JCO.2008.19.6329
27. Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 2009;27(10):1585–91. doi:10.1200/JCO.2008.20.0600
28. Nicosia L, Cuccia F, Mazzola R, Figlia V, Giaj-Levra N, Ricchetti F, et al. Stereotactic Body Radiotherapy (SBRT) Can Delay Polymetastatic Conversion in Patients Affected by Liver Oligometastases. J Cancer Res Clin Oncol 2020;10.1007/s00432-020-03223-9. (Online, ahead of print)
29. Andratschke N, Alheid H, Allgäuer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer 2018; 18(1):283. doi:10.1186/s12885-018-4191-2
30. Mahadevan A, Blanck O, Lanciano R, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. Radiat Oncol 2018;13(1):26. doi:10.1186/s13014-018-0969-2

31. Scorsetti M, Arcangeli S, Tozzi A, Comito T, Alongi F, Navarria P, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys 2013;86(2):336–42. doi:10.1016/j.ijrobp.2012.12.021
32. Rule W, Timmerman R, Tong L, Abdulrahman R, Meyer J, Boike T, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol 2011;18(4):1081–7. doi:10.1245/s10434-010-1405-5

Figures

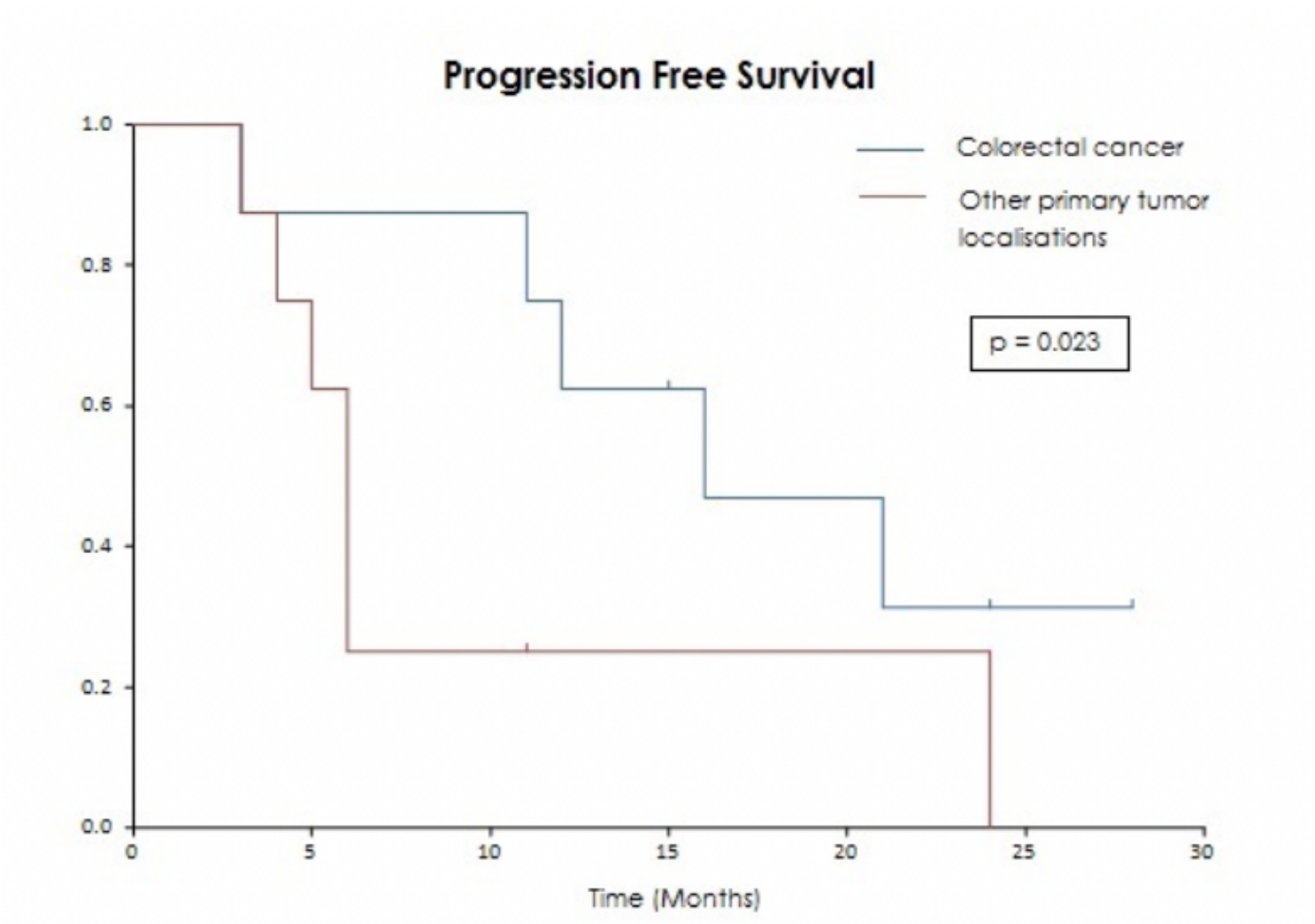

Figure 1

Progression Free Survival (PFS) plot