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Adult primary liver sarcoma: systematic review

Sarcoma primário de fígado em adultos: revisão sistemática

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ABSTRACT

Introduction: primary liver sarcoma is a rare type of tumor, more common in children. Among adults, it represents a spectrum of neoplasms with reserved prognosis. There is no consensus on the treatment of choice of these lesions, justifying a systematic review of the literature on treatment options, prognostic factors, and survival. **Material/Methods:** a systematic review of articles published in Pubmed, Medline, LiLacs e SciElo, from 1966 to March/2019, presenting the keywords: primary-liver-sarcoma and primary-hepatic-sarcoma was undertaken. Studies including patients older than 18 years, and published in English, Portuguese and Spanish were included. Case reports, metastatic tumors and multiple oncologic diagnosis were excluded. The initial search listed 1,318 articles. 1,206 did not meet the inclusion criteria. After reviewing 112 eligible articles, 15 were selected (14 case series and 1 retrospective-cohort). **Results:** proposed treatment modalities for primary liver sarcoma included surgery and/or chemotherapy and/or radiotherapy or liver transplantation. The most common histological types were angiosarcoma (32%), leiomyosarcoma (29%), epithelioid hemangioendothelioma (15%) and embryonal sarcoma (7%). Histology, degree of differentiation and R0 resection were mentioned positive prognostic factors. Median survival ranged from two to 23 months. Five-year survival rate varied from 0% to 64%, on average 21%. **Conclusion:** surgical resection (R0 resection) is the main treatment for primary liver sarcomas. Development of effective systemic therapies are required to improve prognosis of patients harboring this type of tumor.

Keywords: Liver. Sarcoma. Liver Neoplasms. Systematic Review.

INTRODUCTION

Primary liver sarcoma (PLS) is a rare tumor, most common in childhood[1], and represents between 0.1% and 2% of total liver tumors[1-6]. The natural history is of rapid growth, with short survival, with or without treatment[2,3,5-10]. In adults, it represents a spectrum of neoplasms, among which stand out angiosarcoma (AS), leiomyosarcoma (LMS), undifferentiated embryonic sarcoma (UES), epithelioid hemangioendothelioma (EHH), and malignant fibrous histiocytoma (MFH)[1-15].

The main signs and symptoms of these neoplasms are nonspecific[1,2,4-6], including abdominal pain, palpable mass, fever, bleeding/rupture (mainly, but not exclusively in angiosarcomas), and weight loss[1-15]. No known tumor marker rises in cases of PLS[1,7], which makes the identification of these neoplasms difficult and late[1-3,7,10,16,17]. Currently, there is no consensus on the treatment of choice for these neoplasms[1].

This systematic review aims to list therapeutic options, prognostic factors, and results in this category of patients.

METHODS

We searched the databases Pubmed, Medline, LiLacs, and SciElo, between 1966 and March 2019, using the keywords "primary liver sarcoma" and "primary hepatic sarcoma". We included articles in English, Portuguese, and Spanish that studied patients aged 18 years and older, diagnosed with primary liver sarcoma, and who received some type of treatment. We excluded case reports, metastatic tumors, and cases of patients with multiple oncological diagnoses (Figure 1).

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Three authors independently carried out the search, reading the title and abstract of all articles obtained in the databases. After that, they analyzed the complete texts. Disagreements were resolved by debate between the authors and by the senior author's final judgment.

We found 1,318 articles, of which we excluded 1,206 for not meeting the inclusion criteria. Of the 112 articles analyzed and discussed, we included 15 in this work (14 case series and 1 retrospective cohort study) (Figure 1).

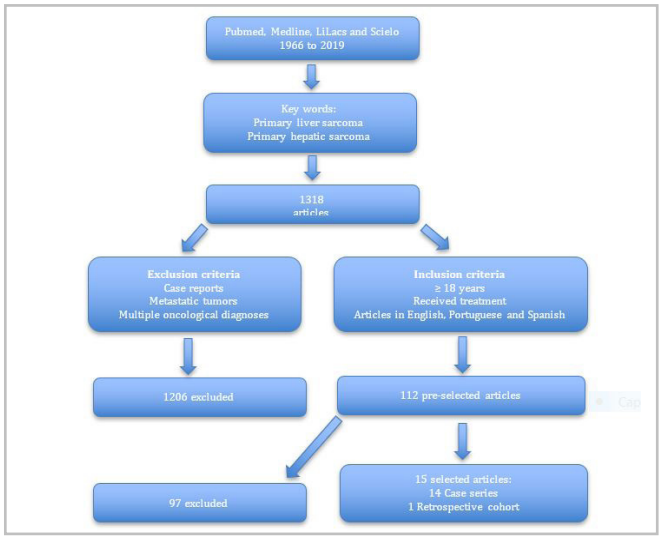

Figure 1. *Flowchart of the Systematic Review.*

RESULTS

Of the 15 articles on PLS included[1-15], six are from specific angiosarcomas case series. These publications covered a wide spectrum of sarcomas and different treatments. Table 1 presents a summary with the main data of each article.

In total, 569 cases were reported, 52% being male (294) and 48% female (272). The main signs and symptoms were abdominal pain (57%), palpable mass in the right hypochondrium (27%), weight loss (18%), and fever (10%). Other findings included anemia and anorexia. Intralesional bleeding, with or without rupture, was found in up to 26.6% of angiosarcomas. We also observed 8% of asymptomatic patients (Table 2).

The most common histological type was angiosarcoma, found in 32% of patients, followed by leiomyosarcoma (29%) and eptelioid hemangioendothelioma (15%)[15]. Embryonic sarcoma occurred in 7%, rhabdomyosarcoma in 5%, carcinosarcoma in 3%, and malignant histiocytoma in 2% of the reported patients.

Surgical resection was indicated in 78% of patients, 66% as monotherapy[1-11,13-15], and, in 17%, combined with adjuvant chemotherapy[1-5,8,9,11,13,14].

Chemotherapy (QT) was used in 31% of patients. Doxorubicin, adriamycin, etoposide, ifosfamide, and cyclophosphamide were the most used drugs[1-5,8,13]. Neoadjuvancy was not used in any case. Only two articles cited the use of radiotherapy (RXT), whether adjuvant or isolated[2,3].

Other types of treatments were employed. Liver transplantation (TX) was mentioned by some articles[1,3,4,7,9,15], and used in up to 17.3% of cases in the largest retrospective cohort[15].

Transcatheter arterial chemoembolization (TACE) and/or selective hepatic transarterial embolization (TAE) were used in 15% of patients, mainly in the case series of angiosarcomas, and were used as monotherapy or in combination with chemotherapy or surgery[1,2,9,10,12,14]. In these articles, the choice for these therapies was clearly associated with the presence of rupture and/or bleeding.

The median survival ranged from two to 23 months. Five year survival ranged between 0% and 64%[6,12], with an average of 21%. The best results were achieved in patients with epithelioid hemangioendothelioma treated with R0 resection.

R0 resection, combined or not with adjuvancy, was the only curative therapy, being the most important prognostic factor[4-6,9-11]. In addition, there was an inverse relationship between tumor size and patient survival[9]. The most aggressive histological type was angiosarcoma. The degree of differentiation was directly related to prognosis[4,6,13,15] (Table 3).

DISCUSSION

Primary liver sarcomas are rare diseases[1-5,10,18,19] of heterogeneous spectrum[2,4] and variable[1,3], generally dismal[2,3,5-10] prognosis. Most of these neoplasms are of idiopathic cause[8,10]. However, in angiosarcomas[1,8] there is an association with exposure to thorotrast[1,2,4,8,10,12,20-23], vinyl chloride, arsenic, and use of androgenic steroids[13].

Table 1. *Summary of included articles.*

Authors	Sex	Average age	Nº Cases	Signs / symptoms	Histology	Therapy	Predicting Factors	Survival
Poggio JL et al[4] (2000)	13 ♂ 7 ♀	56	20	Abdominal mass: 10 Pain in RUQ: 10 Weight loss: 8 Fever: 8 Bleeding: Ø	Leiomyosarcoma: 5 Malignant fibrous histiocytoma: 4 Angiosarcoma: 3 Epithelioid hemangioendothelioma: 3 Carcinosarcoma: 2 Embryonic: 1 Liposarcoma: 1 Fibrosarcoma: 1	Resection R0: 19 R2: 1 TX: 1 QT: 6 (Ifosfamide, Doxorubicin, Etoposide)	Worse prognosis: Poorly differentiated (5y: 18%)	1y: 79% 3y: 37% 5y: 37%
Molina E et al[8] (2003)	4 ♂ 1 ♀	53	5	Abdominal mass: 1 Pain in RUQ: 4 Weight loss: 1 Fever: 2 Bleeding: 2	Angiosarcoma	Surgery + Chemo: 2 Surgery: 1 Biopsy: 2		Average 6 months
Almogy G et al[2] (2004)	6 ♂ 2 ♀	52	8	Pain in RUQ: 50% Asymptomatic: 25% Fever: 37.5% Bleeding: 25% (angiosarcoma)	Angiosarcoma: 2 Leiomyosarcoma: 2 Embryonic: 2 Epithelioid hemangioendothelioma: 1 Neural sheath sarcoma: 1	Resection R0: 3 RXT: 2 QT: 5 TACE: 2	Worst prognosis: Positive margins	2 patients without cancer returned at 47 mo. The others died within a year.
Weitz J et al[6] (2007)	14 ♂ 16 ♀	52	30	Pain in RUQ: 19 (63%) Asymptomatic: 6	Epithelioid hemangioendothelioma: 10 Embryonic: 5 Angiosarcoma: 5 Malignant fibrous histiocytoma: 1 Leiomyosarcoma: 2 Others: 7	Resection R0: 11 R1 & R2: 13	Worse prognosis: Poorly differentiated Resections R1 or R2.	Angiosarcoma Low average survival (11 months) R0: 64% (5 y) R1 or R2: 0% (3y)
Li Y et al[7] (2008)	21 ♂ 13 ♀	58	7 cases + 27 reviewed cases	Abdominal mass: 0/7 Pain: 6/7 Weight loss: 4/7 Fever: 1/7 Bleeding: 0/7	Malignant fibrous histiocytoma	Surgery: 4/7 & 20/27 TX:1/27		Average survival - 4 months, 6 cases:>2y
Park YS et al[12] (2009)	5 ♂ 1 ♀	52	6	Abdominal mass: 2 Pain in RUQ: 4 Weight loss: 0/7 Fever– 1 Bleeding: 3	Angiosarcoma	TACE: 4 TAE: 2		Responsive to TACE: 8-12 months Non-responsive: 2 months

Matthaei N et al[5] (2009)	14 ♂ 8 ♀	54	22	Abdominal mass: 2 Pain in RUQ: 3 Weight loss: 2 Incidental finding: 15	Leiomyosarcoma: 7 Rhabdomyosarcoma: 5 Angiosarcoma: 5 Fibrous malignant histiocytoma: 1 Others: 4	All surgical QT: 8 (Cyclophosphamide Doxorubicin Etoposide and / or ifosfamide)	Worse prognosis: Angiosarcoma	Average survival 153 months 2y: 85.2% 3y: 70.2% 5y: 65.2%
Zhou Y et al[10] (2010)	5 ♂ 1 ♀	55	6	Abdominal mass: 1 Pain in RUQ: 4 Weight loss: 4 Asymptomatic: 1 Fever: 0/7 Bleeding: 0/7	Angiosarcoma	Resection R0: 5 TACE: 5 (Lipiodol + adriamycin + carboplatin)		5 recurrences within 2 years.
Chi M et al[3] (2012)	60 ♂ 49 ♀	58	109	Abdominal mass: 56.8% Pain in RUQ: 50.5% Weight loss: 34.7% Fever: 12.6% Bleeding: 7.4%	Leiomyosarcoma	Surgery: 61% QT: 13.7% TX : 5.3% RXT: 2.1%		Average survival 19 months 1y: 100%, 2y: 41.1% 5y: 14.5%
Duan XF et al[11] (2012)	5 ♂ 1 ♀	49	6	Abdominal mass: 1 Pain in RUQ: 2 Weight loss: 1 Fever: 2 Bleeding: 0/7	Angiosarcoma	Resection R0: 5 R2: 1 QT: 1		R0: 1y: 100% 3y: 80% 5y: 40%
Zheng Y et al[9] (2014)	49 ♂ 15 ♀	59	64	Rupture 26.6%	Angiosarcoma	Surgery: 30 Palliative: 15 TACE: 10 TX: 5 QT: 4		Average survival: 5 months Surgery + QT: 17 months
Lin YH et al[1] (2015)	8 ♂ 5 ♀	48	13	Pain in RUQ: 9 Anemia: 7 Thrombocytopenia: 2	Angiosarcoma: 6 Undifferentiated Sarcoma: 4 Epithelioid Hemangioendothelioma: 1 Embryonic sarcoma: 1 Leiomyosarcoma: 1	Surgery + QT: 4 Surgery: 4 TAE + Surgery: 3 TX: 2 Resection: R0: 9 R1: 1	Non-angiosarcoma longer survival than angiosarcoma: 1y: 85.7% x 33.3%; 3y: 71.4% x 16.7%; 5y: 57.1% x 0%	Average survival: 1y: 61.5%, 2y: 53.8%, 5y: 30.8%; Surgical patients: 1y: 72.7%, 2y: 63.6%, 5y: 36.4%

Konstantinidis et al[15] (2019)	93 ♂ 144♀	52	237		Angiosarcoma: 64 Undifferentiated sarcoma: 4 Epithelioid Hemangioendothelioma: 67 Embryonic sarcoma: 31 Leiomyosarcoma: 33	Resection: 40.9% TX: 17.3%	R0 Well-differentiated Epithelioid hemangioendothelioma	5 years: 25% Angiosarcoma: <1 year
Tripke et al[13] (2019)	5♂ 4♀	61	9	5 symptomatic (pain)	Angiosarcoma	Resection R0: 8 R1 + QT: 1 (Doxorubicin + Ifosfamide)	Poorly differentiated	Overall survival: 18 months R0: 59 months Disease free survival: 10 months , R0: 11months
Zhou et al[14] (2019)	12♂ 5♀	57	17	Pain: 9 Palpable mass: 7 Anorexia: 4	Liposarcoma: 6 Leiomyosarcoma: 4 Epithelioid hemangioendothelioma: 3 Fibrosarcoma: 2 Hepatoblastoma: 2	Biopsy: 5, Surgery: 12 (R0: 10), TACE: 5, QT: 17 (All)	R0	Overall 5y: 12% (R0: 20%)

Table 2. *Clinical and pathological characteristics of 569 patients with primary liver sarcoma.*

Variable	Average (range)	N	(%)
Age years	54 (18-86)		
Male		294	(52%)
Signs and symptoms			
Abdominal pain		324	(57%)
Palpable mass		154	(27%)
Weight loss		102	(18%)
Fever		57	(10%)
Asymptomatic		48	(8%)
Histology			
Angiosarcoma		181	(32%)
Leiomyosarcoma		163	(29%)
Epithelioid hemangioendothelioma		85	(15%)
Embryonic sarcoma		43	(7%)
Rhabdomyosarcoma		36	(6%)
Carcinosarcoma		18	(3%)
Malignant histiocytoma		13	(2%)
Liposarcoma		7	(1%)
Others (Neural Sheath, Undifferentiated, Fibrosarcoma, etc.)		23	(5%)

Table 3. *Prognostic factors.*

Prognosis	Factor	References (N)
Favorable	R0 resection	15
	Degree of differentiation	13
	Epithelioid Hemangioendothelioma	6
Unfavorable	R1/R2 resection	10
	Angiosarcoma	9
	Size > 10 cm	8
	Affected lymph nodes	5
	Tumor bleeding / rupture	2

In the last three years, at the Professor Fernando Figueira Institute of Integral Medicine (IMIP), there were four cases of primary liver sarcomas, justifying this search for treatment options. We found limited literature, basically composed of case reports. The case series, in addition to being scarce, are short and non uniform, addressing numerous types of sarcoma and different therapeutic approaches. In this scenario, this study aimed to gather evidence about the disease and thus collaborate to standardize it.

Due to the rarity and non specific symptoms, the diagnosis of PLS is difficult and late, usually occurring in advanced stages[1-3,7,10,16,17]. Nonetheless, this neoplasm requires immediate diagnosis and treatment[8]. Preoperative diagnostic suspicion is necessary in order to infer the histological type[1,2,11,24] and to assess staging and resectability. Imaging with large masses that are not compatible with hepatocarcinoma or cholangiocarcinoma is what raises the suspicion of this diagnosis[2,3]. Ruptured tumors or intra lesional bleeding also warn of this condition. Preoperative biopsy may be unnecessary and be associated, in angiosarcomas and fibrous histiocytomas, with serious complications, such as massive bleeding and death[1,2,7,8,10,20,25]. In therapeutic planning, TAE should be considered beforehand in bleeding/ruptured tumors or in the event of biopsy accidents[2,8 -10,12,25,26].

Together, epithelioid hemangioendothelioma, leiomyosarcoma, and angiosarcoma account for 75% of the cases and, in this study, represented 429 cases. We discuss below the four most common types of primary liver sarcoma.

Epithelioid hemangioendothelioma

Epithelioid hemangioendothelioma is recognized as a low grade angiosarcoma[15,27,28], with indolent behavior, even in the presence of lymph node disease and metastases.

Leiomyosarcoma

The most common clinical presentation of leiomyosarcoma was hepatomegaly, large abdominal mass, and epigastric pain[3,29]. This tumor occurs in middle aged people and the distribution between the sexes is similar[3,29]. In this survey, the average age of patients with this neoplasm was 57 years, and there was no predilection for sex, 52% of whom were men.

The prognosis of leiomyosarcoma is reasonable, with a median survival of 19 months and survival at one, two and five years of approximately 61%, 41% and 14%, respectively, ranging from 0.5 to 141 months. The factors of unfavorable prognosis in this group were compromised surgical margin and large tumors (greater than 10 cm3)[30-34].

Leimomyosarcoma has been described in computed tomography (CT) as a large, well defined, heterogeneous, and hypodense mass, with contrast enhancing of internal and peripheral areas[1,35]. It was also described as a large hypervascular mass with hemorrhage or liquefactive necrosis[1,35]. In magnetic resonance imaging (MRI), in T1 sequence, the tumor was described with homogeneous or heterogeneous hypo intensity, and in T2, with hyper intensity and occasional observation of encapsulation[29].

Metastases were common in these patients, occurring in approximately 43% of cases during the course of treatment. The main site was the lung, followed, in descending order, by pleura/chest wall/diaphragm, kidney, and bones[3].

The treatment of leiomyosarcoma was surgical, aiming at complete resection of the primary tumor. Schemes of systemic therapy with chemotherapy or radiotherapy have not been established and, when used, do not appear to increase survival[3].

Angiosarcoma

Angiosarcoma accounts for approximately 2% to 3% of soft tissue sarcomas in adults[9] and has an

etiology associated with exposure to thorotrast[1,2,4,8,10,12,20 23,26,28], vinyl chloride, and arsenic[1,8,23]. The disease develops between nine and 35 years after contact with these agents[9]. This exposure causes mutations in the p53 and K-ras genes, which leads to the development of cancer[9]. This sarcoma is more common in men (76%) and, in general, affects patients between 50 and 60 years of age[9].

The main symptoms of angiosarcoma are abdominal pain[1,9], fatigue, weakness, and weight loss[8,10,26]; the main signs are hepatosplenomegaly, ascites, jaundice, and anemia[9]. In addition, 17% to 27% of the cases present with rupture of the tumor and hemoperitoneum[1,8,9,29 31].

The diagnosis is difficult: the main tumor markers, CA 19.9 and alpha fetoprotein, do not increase during the development of the disease[1,5]. In addition, biopsy in suspected cases is contraindicated due to the high risk of massive bleeding during the procedure[8-11]. Some image characteristics can help at this moment: At CT, angiosarcoma is hypoattenuating when compared to the normal liver, and the contrast can highlight central or peripheral areas in an unusual way[1,32]. In MRI, T1 sequences show focal areas of high signal intensity and those in T2 show the heterogeneous architecture of the tumor[1,32].

The treatment of this primary sarcomas is basically surgical (R0 resection), being the only curative one[10]. There is no specific standardization for any neoadjuvant or adjuvant treatment with chemotherapy or radiotherapy[26]. However, recent studies have associated chemotherapy with prolonged survival of patients with advanced angiosarcoma[26,33,34].

Among all primary liver sarcomas, angiosarcoma has the worst prognosis. The median survival is approximately six months[1]. The main factors of poor prognosis for this tumor are spontaneous bleeding and tumor rupture[9].

In a recent study (2018) using the National Cancer Database (2004-2014), 17.3% of patients underwent liver transplantation, the majority (97.6%) having angiosarcoma or epithelioid hemangioendothelioma. When evaluating the 131 cases separately, we observed that those undergoing transplantation were younger, had larger tumors, and had more lymph node involvement. The overall mean survival was similar when compared with transplantation with resection, but when analyzed separately, angiosarcomas tended to display longer survival with resection compared with transplantation (16.6 vs. 6 months, $p = 0.07$)[15].

Undifferentiated embryonic sarcoma

Undifferentiated embryonic sarcoma of the liver is an even rarer entity, affecting mainly children over the age of five. These children usually have a palpable and painful abdominal mass. Fever, weight loss, and gastrointestinal symptoms may also be present[1,2,4,6,15]. Macroscopically, the tumor contains a larger solid component and some cystic areas. Interestingly, CT overestimates the cystic component of the lesion, ultrasonography (US) being the most reliable test for assessing tumor consistency. Imaging studies help to rule out non neoplastic diseases, such as liver abscesses and hematomas, and assess the extent of the lesion, which is essential when planning therapy. The diagnosis of embryonic sarcoma can be correctly assumed when considering imaging findings in conjunction with the patient's age and alpha fetoprotein level[1,2,4,6,15].

Histologically, it is a tumor composed of undifferentiated spindle cells interspersed with an abundant myxoid matrix. Some evidence suggests that this sarcoma is derived from the malignant transformation of mesenchymal hamartoma. Some reports describe the identification of both histological types in the same patient[36]. When they occur in adults, undifferentiated embryonic sarcomas of the liver affect women, aged between 40 and 55 years.

CONCLUSION

Few specific articles and low levels of evidence characterize the current literature related to primary liver sarcomas. In this scenario, the treatment of choice is R0 resection, which presents itself as the only curative modality[4-6,9-11,23,26,37,38]. We could not establish the usefulness of systematic use of chemotherapy or radiotherapy[2-5,9,11,23,37,39 41].

Early diagnosis and treatment are essential. Factors associated with an unfavorable prognosis are

histological type, lymph node involvement, tumor rupture, and R1/R2 resections. Factors of favorable prognosis and increased survival are R0 resection, degree of differentiation, and small tumors.

RESUMO

Introdução: *o sarcoma primário do fígado é uma neoplasia rara, que acomete mais frequentemente crianças. Nos adultos, representa espectro de neoplasias de prognóstico reservado. Entretanto, em nenhuma faixa etária há consenso sobre a terapêutica de escolha dessas lesões, motivando revisão sistemática com objetivo de elencar opções de tratamento, fatores prognósticos e sobrevida.* **Material/Método:** *realizamos revisão sistemática dos artigos publicados nas bases de dados Pubmed, Medline, LiLacs e Scielo, de 1966 a março/2019, contendo as palavras-chaves: primary-liver-sarcoma e primary-hepatic-sarcoma. Foram incluídos estudos que incluíram pacientes com idade a partir de 18 anos e publicados em inglês, português e espanhol. Relatos de caso, tumores metastáticos e pacientes com múltiplos diagnósticos oncológicos foram excluídos. Foram encontrados inicialmente 1.318 artigos, desses, 1.206 foram excluídos por estarem fora dos critérios de inclusão. Dos 112 artigos analisados e discutidos, 15 foram incluídos nesse artigo (14 séries de casos e 1 estudo de coorte retrospectivo).* **Resultado:** *os tratamentos propostos para o sarcoma primário do fígado em adultos incluíram cirurgia e/ou quimioterapia e/ou radioterapia ou transplante hepático. Os tipos histológicos mais frequentemente relados foram angiossarcoma (32%), leiomiossarcoma (29%), hemangioendotelioma epitelioide (15%) e sarcoma embrionário (7%). Tipo histológico, grau de diferenciação e resseção R0 foram os principais fatores de bom prognóstico. A sobrevida média total variou de dois a 23 meses. A sobrevida em cinco anos variou entre 0 e 64%, em média 21%*. **Conclusão:** *ressecção cirúrgica R0 é a base do tratamento dos sarcomas primários do fígado. Esse grupo heterogêneo de tumores requer desenvolvimento de terapias sistêmicas efetivas para melhoria do prognóstico.*

Palavras chave: *Fígado. Sarcoma. Neoplasias Hepáticas. Revisão Sistemática.*

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