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Liver resection and local ablation of breast cancer liver metastases--a systematic review. — Source link

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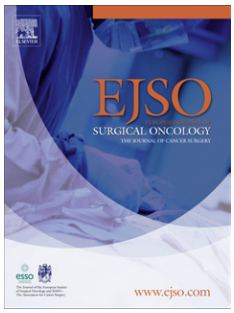

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Liver resection and local ablation of breast cancer liver metastases – a systematic review.

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Conflicts of interest : none

Abstract

Aim : To analyze surgical treatment of breast cancer liver metastases (BCLM) regarding selection criteria, outcome and prognostic parameters.

Methods : We searched Embase and Medline for all studies published 1999-2010.

Results : Resection was associated with a median survival (MOS) of 20-67 months and 5-year survival of 21-61%. Local ablation also had a favourable outcome; MOS was 30-60 months and and 5-year survival 27-41%. Regarding selection, no specific limits regarding the number and size of BCLM can be given. Features of the primary breast cancer (BC) was not significant for the prognosis. Microscopically radical (R0) resection is a positive prognostic factor, while the effects of disease interval, hormone receptor status and response to preoperative chemotherapy were divergent. The presence of EHD had a negative effect on survival in some studies, but failed to have so in other studies.

Conclusions: Surgical therapy may benefit a subset of patients with BCLM. Resection may be indicated, if an RO-resection can be done with a low risk of mortality. Liver resection in the presence of extrahepatic disease remains controversial, while patients with BCLM and bone metastases could possibly be managed differently than other EHD.

Introduction

The liver is the primary metastatic site in 12-15 % of patients with metastatic breast cancer (BC) [1,2]. Systemic hormone and/or chemotherapy will be indicated in these patients, but nearly all patients will die despite treatment. Liver resection and local ablation techniques have evolved into safe and efficient therapy for isolated colorectal liver metastases (CRLM) [3-6]. Although liver resection of BCLM was previously regarded with much skepticism, it has been argued that surgery may be useful also for the selected subset (<5%) of patients presenting with isolated BCLM [1,2,7-10]. During the last decade, several series with liver resection and/or local ablation of BCLM have been published, and this paper aims at a systematic review of all papers published 1999-2010 concerning selection criteria, outcome and prognostic parameters.

Methods

Search strategy. We searched Embase and Medline without language restriction for all human studies published 1999-2010 using the search terms: 1) liver OR hepatic AND metastases; 2) liver OR hepatic AND resection 3) hepatectomy OR radiofrequency OR ablation OR microwave OR cryotherapy OR cryosurgery OR laser; 4) cancer OR carcinoma AND breast; 5) non-colorectal OR noncolorectal OR non-neuroendocrine OR nonneuroendocrine. The complete search combined #1 AND (#2 OR #3) AND (#4 OR #5). Finally, we cross-searched all retrieved papers.

Inclusion criteria. 1) original studies reporting ≥10 patients; 2) studies reporting post-surgical outcome, either survival rate after at least two years or median overall survival (MOS); 3) studies of "non-colorectal, non-neuroendocrine" (NCRNNE) liver metastases were included only if the results with BCLM could be extracted separately; 4) we selected the most recent study, if there were sequential upgradings by the same research group.

Literature survey. The two senior authors (M.B., D.N.) independently surveyed the literature. In case of unclarity or disagreement, the complete paper was analyzed and a verdict was reached by consensus. The study quality was graded as "randomized controlled trial" (RCT), "non-randomised controlled trial" (with control group), "prospective study" (a priori fixed selection criteria) or "retrospective study" (of register data, medical charts etc).

Literature study. The included studies were analyzed regarding number of patients, rate of synchronous BCLM, rate of major liver resections (>2 liver segments), rate of microscopically radical (R0-) resections, and median follow-up (months) as well as the "liver status" (number and size of BCLM accepted). The acceptance of patients with extrahepatic disease (EHD) was classified as : "EHD 0" : EHD contraindicated, "EHD 1" : no EHD, except stable bone metastases; and "EHD 2" : resectable EHD or EHD stable on therapy accepted.

Answers were sought to the following questions: 1) recurrence rate (RR), median overall survival (MOS), and 2, 3- and 5-year survivals (table 1); 2) prognostic factors after surgical resection (table 2); 3) selection criteria for surgical treatment of BCLM (table 3). Assesment of the risk of bias was done graphically by plotting MOS and 5-year survivals, respectively, in relation to study size (patient number) in the singlecentre studies (fig. 1A-B). Likewise, RR was analyzed in relation to the mean follow-up time (fig. 2).

Results

Results of literature search.

The complete search yielded 285 papers. We excluded 134 studies as irrelevant (without BCLM or surgery), 14 incomplete reports (no outcome data), 63 reviews and 36 "small studies" (<10 patients). We further excluded 8 papers because a more recent "upgrading" was available [11-17]. No RCT, NRCT or prospective studies were found. Thus, 32 retrospective studies were analyzed [18-49]; two of which were found in the cross-search [30,45].

Studies of liver resection (N=25).

25 studies concerned mainly liver resection alone [18-42], although three of the studies included a small group which had additional local ablation [26,31,32] (table 1). Three of the studies were multicentre efforts [32,33,42]. The 22 single-centre studies contained 694 patients, i.e. median 27 (12-85) patients (table 1). The studies were collected during 9-21 years (median 14 years). The mean, annual number of operations was 0.7 – 7.4 (median 2). Only one institution had an annual average exceeding five [11,13,20].

The rate of synchronous metastases were 0-26% (reported in 12/25 studies). Major liver resection was done in 6-82% of cases (reported in 16/25 studies), and the reported rates of R0-resection were 65-100 % (reported in 10/25 studies).

Postoperative MOS was 20-67 months. The studies had 2-, 3- and 5-year survivals of 58-86%, 35-79% and 21-61%, respectively. The largest series (N=454), a multicentre study by Adam et al. [32], reported MOS 45 months, and 5-year survival 41%. Regarding RR after resection of BCLM, intra- and/or extrahepatic recurrence occurred in 53-78% of the patients (reported in 12/18 studies). There was a correlation between RR and the length of follow-up (fig 2).

Prognostic factors after resection of BCLM.

In the different series, several potential, prognostic factors were analyzed by univariate and multivariate techniques. The factors may be classified as related to: i) primary breast cancer (BC); ii) BCLM; iii) EHD; or iv) therapeutic factors (table 2).

Factors related to the primary BC-operation (site, procedure, grade, TN-stage, presence of axillary glands) were of no significance in most studies (table 2). Interval between primary BC and BCLM was a positive factor in the studies by Selzner, Pocard, and Caralt [20,22,37] but not so in several other studies [21, 24,26,27,31, 35, 36]. Size, site or number of BCLM were not generally found to be of significance, except that >1 BCLM was a negative factor in one study [23] (table 2). In the study by Elias [24], hormone receptor status was a positive factor, but this was refuted by several other studies [20,26,31,35]. In contrast, presence of hormone receptors in the primary BC as well as in BCLM had a negative influence in the study by Lubrano [36].

Patient age was generally without significance, except in the study by Lubrano, where patients < 50 had a poor prognosis (table 2). Presence of EHD had a negative effect in the studies by Sakamoto and Thelen [27,35], but was not significant in other studies [20,21,31].

RO-resection was a positive prognostic factor in some studies [18,31,35], but failed be so in the study by Elias [24]. Except for one study [36], the execution of liver surgery in terms of major vs. minor resections was generally not of significance [20,22,26,27,31](table 2). Repeat hepatectomy was found to be a positive factor for survival by Adam [31]. Response to preoperative chemotherapy was a positive factor according to Adam [31], but failed to be so in two other studies [22,26].

Studies of local ablation (N=7)

We found seven studies [43-49] with totally 390 patients using mainly local ablation therapy, although one study included a group of patients treated by liver resection alone [49] (table 1). The studies were collected during 6-12 years (median 8 years). Thus, the annual average was 1 – 23 treatments (median 2). Three institutions had an annual average exceeding four [43,47,48]. The rate of synchronous metastases were 0-19% (reported in 3/7 studies). Six studies used RF [44-49], but

the largest study used Laser-induced interstitial thermotherapy (LITT) in 232 patients (corresponding to 59% of total) [43]. Post-treatment MOS was 30-60 months. The studies had 2-, 3- and 5-year survivals of 42-80%, 43-75% and 27-41%, respectively. The LITT-study reported MOS 52 months MOS, and 2-, 3-, and 5-year survivals were 80%, 63% and 41%, respectively, although this study included patients 1) unresectable, 2) unfit for or refusing resection; 3) with recurrent BCLM; 4) with bilateral BCLM; 5) with stable bone metastases. 6) with multiple (up til 13) BCLM. The second largest study (N=52) had 30 months MOS, and the 3- and 5-year survivals were 43% and 27%, respectively. [47].The third largest study (N=43) showed similar figures, i.e. MOS 59 months; and 3- and 5-year survivals were 75% and 38%, respectively [48].

Patient selection for surgical treatment of BCLM.

Most studies accepted ≥5 BCLM, although the maximum number of metastases accepted varied widely (reported in 18 studies). Most studies also included BCLM > 5 cm, although four studies were restricted to < 5 cm; two of them were RF-studies. Five studies reported that they used a positive response to preoperative chemotherapy to select patients [18,22,24,27,36].

Seven studies did not include patients with EHD [18,19,23,25,26,36,40], while stable, isolated bone metastases were accepted in four studies [22,24,37]. Various other EHD was accepted in 9 studies of liver resection, as long as EHD was resectable or stable on therapy[20,21,27,28,29,31,32,35,42], and in four studies of local ablation [45-48](table 3).

Studies of potential biases. There are several, potential problems with the available studies, which represent heterogenous, uncontrolled, and retrospective series. Most studies were also small, which gives a a risk of statistical bias (i.e. type I and II errors). Further, results may be skewed by the fact, that some of the prognostic factors analyzed were - explicitly or not – already used in the preoperative selection of patients. Obviously, this kind of selection will skew the statistical analysis of prognosis regarding the same factor.

We estimated the risk of publication bias by analyzing MOS and 5-year survivals, respectively, in relation to patient numbers in the studies. Figure 1 shows that larger studies gravitate around a 5-year survival of 30-40%, while several smaller studies report a more favourable outcome. Publication bias is a plausible explanation [50]. Studies of the relation between RR and median follow-up time reveal showed a positive association between the two (fig. 2), i.e. a short follow-up may cause under-estimation of the risk of recurrence.

Discussion

Liver resection. BCLM is usually part of generalized metastatic disease, and carries a grave prognosis. New drugs such as anthracyclines, taxanes and monoclonal antibodies against growth receptors (i.e. trastzumab) have improved the prognosis, but MOS was 5-14 months only also in some recent studies [51,52]. For the selected subset (<5%) of patients presenting with isolated BCLM, surgery has been proposed as a useful adjunct to medical oncological therapy [1,2,7-10]. We identified 25 studies concerning resection of BCLM published in 1999-2010. As shown in table 1, surgical resection resulted in MOS 20-57 months, and 2-, 3- and 5-year survivals ranged 58-94%, 35-65% and 21-61%, respectively. . As described above, we found that smaller studies reported longer MOS and higher 5-year survivals than larger series (fig. 1A-B). Considering studies with N>25 will result in more conservative estimates of MOS and 5-year survival around 30-45 months and 25-42%, respectively. The figures compare well with outcome after resection of CRLM, which indicates that resection may be worthwhile also for selected patients with BCLM.
Prognostic factors after liver resection were analyzed in several studies. General features of the primary BC did not influence the prognosis, and were not among the stated selection criteria (tables 2,3). Hormone receptor status were analyzed by several authors [20,24,26,27,31,35,36]. Most studies found them to be without significance [20,26,27,31,35,], but there were divergent results [24,46](table 2). Further work is needed to clarify this issue, as hormone drugs are an important part of BC therapy and hormone receptor status has been associated with a good prognosis in previous studies of metastatic (non-resectable) BC [51,52]. The anticipated possibility to do an R0-resection was a selection criterion in many studies, and consequently the final rates of R0-resection ranged 65-100% (table 1). It was also a positive prognostic factor in three studies [18,31,35]; only Elias et al. found it to be without significance (although they had 81% RO-resections) [24]. Most studies accepted patients with > 5 metastases and maximum sizes > 5cm for treatment (table 3), and numbers and sizes do not seem to influence the prognosis (table 2). Furthermore, the type of liver resection (major vs. minor) seems to be without significance [20,22,26,27,31], although one study found that major hepatectomy was associated with a poor prognosis [36]. The fact that repeat hepatectomy was associated with better survival in two studies does support not using larger than necessary resections [15,20].

Response to preoperative oncologic treatment was a selection criterion in several studies [18,22, 24, 27,36]. However, in the analyses of prognostic factors, the importance of an objective response varied. While it was a positive, prognostic factor in the study by Adam et al. [20], it failed to be so in two other studies [16,26]. However, a clear-cut disease progression on preoperative chemotherapy was an adverse factor in two studies [16,20], which agrees also with a previous study by Elias [10]. Taken together, data indicate that the response to preoperative therapy is important, and the response may also serve as a guide for further, postoperative therapy. In fact, although liver resection was associated with a good outcome *qou ad vitam*, many patients suffer develop recurrent disease. As shown in figure 2, there was a positive association between RR and median follow-up time - or in other words : there is a risk of under-estimating the risk of recurrence with a short follow-up. Thus, the cumulated RR could well exceed 70 % . Obviously, liver resection is rarely "curative", and it has been previously described as an "adjuvant" to medical oncological therapy [56]. Development of more efficient medical oncological therapy for palliative and adjuvant use is needed, and RCT including surgery also needs to be done.

Selection of patients. Few patients with BCLM are currently candidates for surgery, and two authors report that they made liver resection in < 1% of a breast cancer cohort [20,27]. Thus, nearly all studies in this review were accumulated over more than a decade. One institution only performed more than (average) five resections per year, and most of them considerably less (median 2) (table 1). Obviously, BCLM are heavily selected for liver resection, but which criteria should be used ? This question is difficult to answer. The studies were retrospective, heterogenous, and the stated selection criteria were not always respected. Most women had metachronous BCLM, although this was usually not mentioned as an inclusion criterion (table 1). In a previous study of metastatic BC [52], the interval between primary BC and metastases was a positive prognostic factor , and it is generally believed to reflect tumour biology. Consequently, "disease interval" was analyzed by several authors [20-22, 24,26,27,31,35-37]. It was a positive prognostic factor in three studies [20,22,37]. In one study, patients with a disease interval ≥ 12 months had MOS 27 months, while them with < 12 months had MOS 9 months [20]. Likewise, Caralt et al. found that an interval >24 months resulted in significantly longer survival [37]. Using a cut-off at 48 months, Pocard et al. found that these patients had MOS 82 months vs. 45 months for patients with an interval ≤ 48 months [22]. However, the disease interval was not significant in several other studies, which used

cut-offs at 12 months [24,26,31] or 24 months [21,27,35,36]. The reason for these differences is not obvious, and should be studied further.

Extrahepatic disease was handled very differently in the studies. Some centres excluded patients with EHD [18,19,23,25,26,36,40], while others accepted patients even with widespread EHD [20,21,27,28,29,31,35,42,]. A third party accepted patients with bone metastases stable on therapy [22,24,37]. In the multivariance analyses, EHD had a negative effect on survival in some studies [27,35], but failed to have so in other studies [20,21,31]. Also, we found no obvious differences in long-term survival after liver resection between the groups with different EHD-status (table 1). Although, some studies including EHD had good results, the series are small, and the rate of patients with EHD was generally low also in studies accepting such patients. To conclude, liver resection in the presence of widespread EHD remains an unsettled issue. Bone metastases of BC may represent a special situation. They are generally believed to have a more indolent course [57-60], which could indicate that they should be managed differently than other EHD.

Local ablation of BCLM. RF is established treatment for hepatocellular carcinoma and CRLM, and it is associated with a low complication rate and a good long-term outcome [61-63]. Local ablation of BCLM also had a favourable outcome with MOS 30-60 months, and 3- and 5-year survivals of 43-75% and 27-41%, respectively (table 1). As shown also in figure 1, local ablation compares well with resection , especially as most studies of local ablation included patients with extrahepatic disease (table 1). However, RF should not be used for large BCLM as typically the induced necrosis is not larger than 3cm. It has previously been shown, that RF of CRLM confers a higher risk of local recurrence than does resection [62]. By the same token, RF of BCLM >2.5 cm increased the risk of death by a factor 2.1 in a recent report [47]. We conclude that RF is a relevant therapeutic alternative for small BCLM, but there is a need for RCT comparing different surgical therapies. So far, most studies of local ablation have used RF, although the largest study concerns LITT [43] (table 1).

In conclusion, the present systematic review indicates that liver resection may be indicated in a selected subset of patients with BCLM, if an RO-resection is possible and the procedure can be done with acceptable morbidity and mortality. Also local ablation was associated with a good long-term outcome and may be a relevant alternative for small metastases. There is a need for RCT

comparing the two modalities. We found a high risk of recurrent disease after liver resection, and data indicate that patients should be given further adjuvant chemo- and/or hormone therapy. Several studies analyzed different prognostic factors, such as hormon receptor status, disease interval and objective response to preoperative chemotherapy, but further work is needed to clarify their significance. Liver resection in the presence of EHD remains controversial. Bone metastases of BC are believed to have a more indolent course, and should possibly be managed differently than other EHD.

Table 1. Surgical therapy of Breast Cancer Liver Metastases.

Author (Period), Type of surgery	Number of Patients (N)	Rate of syn-chr. BCLM (%)	Major liver resection (%)	RO-resection (%)	RR (median follow-up)	MOS (mo.)	Actuarial survival (%)		
							2-year	3-year	5-year
Lang[18] (1983-93), LR	34*	-	-	86	n.r.	20	-	-	29
Seifert[19] (1985-97), LR	15	13	47	-	RR 53% (12 mo.)	57	71	54	-
Selzner[20] (1987-99), LR	17	6	35	94	RR75% (17 mo)	24	-	35	22
Yoshimoto[21] (1985-98), LR	25	16	44	-	RR 72%	34	71	-	27
Pocard [22] (1988-97), LR	65	-	48	-	RR 67% (41 mo)	41	-	71	-
Carlini [23] LR	17	-	6	-	-	53	-	-	46
Elias [24] (1986-2000), LR	54	22	63	81	RR 78% (32 mo)	34	-	50	34
Arena [25] LR	17	-	82	-	RR 53%	36	85	52	41
Vlastos [26] (1991-2000), LR+ RF	31	26	45	-	RR 70% (25 mo)	25	86	-	61
Sakamoto [27] (1985-2003), LR	31	13	44	-	RR 76% (72 mo)	36	-	52	21
Yedibela [28] (1978-2001), LR	24*	-	-	67	-	33	58	-	43
Weitz [29] (1981-2002), LR	29*	-	-	-	-	48	-	-	-
D´Annibale [30] (1984-99), LR	18	-	-	-	-	-	-	-	30
Adam [31] (1984-2004), LR+RF+ Cryo	85	11	64	65	RR 69% (38 mo)	32	-	-	37
Adam [32] (1983-2004), LR+RF+ Cryo	454*#	-	-	-	- (31 mo)	45	-	-	41
Lendoire[33] (1989-2006), LR	19*#	-	-	-	-	-	-	-	53

Reddy [34] (1995-2005), LR	20*	-	-	-	-	67	-	-	-
Thelen [35] (1988-2006), LR	39	15	51	72	RR 59% (24 mo)	36	-	50	42
Lubrano [36] (1989-2004), LR	16	0	56	100	RR 56% (28 mo)	42	-	61	33
Caralt [37] (1988-2006), LR	12	17	50	92	RR 58% (36 mo)	36	-	79	33
Kollmar [38] (2000-07), LR	27*	7	25	85	-	52	-	-	50
Furka [39] LR	17	-	6	-	-	-	-	-	30
Ercolani [40] (1990-2007), LR	44*	-	-	-	-	41	-	63	36
Lehner [41] (1994-2008), LR	57*	-	-	-	-	36	-	52	30
Hoffman[42] (1999-2008), LR	41#	10	54	78	RR 69% (34 mo)	58	-	68	48
Mack [43] 1993-2002 (LITT)	232	19	-	-	- (28 mo)	50	80	63	41
Berber [44] 1996-2005 (RF)	10	-	-	-	-	51	-	-	-
Lawes [45] 1998-2004 (RF)	19	-	-	-	- (29 mo)	-	42	-	-
Sofocleous [46] 1999-2005 (RF)	12	0	-	-	- (22 mo)	60	-	70	30
Meloni[47] 1996-2008 (RF)	52	15	-	-	53% (19 mo)	30	-	43	27
Jakobs[48] 1999-2006 (RF)	43	-	-	-	(37 mo)	59	-	75	38
Treska[49] (RF /LR)	22	-	-	-	-	-	-	-	34

(*) data extracted from larger study of "non-colorectal, non-neuroendocrine" liver metastases.
(#) multicentre study
LR: liver resection; RF: radiofrequency ablation; LITT: laser-induced thermotherapy; Cryo : cryotherapy;
RR: recurrence rate; MOS : median overall survival;

Table 2. Factors influencing survival after surgical resection.

Prognostic factor	Influence on prognosis		
	positive	negative	no influence
1.Features of primary BC			
Anatomic site			27
Surgical procedure			27, 31,35
Stage (TN-stage)			20- 22, 24, 27, 31, 35,36
Histology :grade/ differentiation			27, 31, 35,36
Presence of hormone receptors		36	27,31
2.Features of BCLM			
Interval between BC and BCLM	20,22,37		21,24,26,27,31,35,36
Number and size		36	20-22,24,26,27,31,35
Presence of hormone receptors	24	36	20, 26,31, 35
Invasion of liver vasculature			35
3.Extrahepatic factors			
Patient age (high vs. low)	36		24,26,27, 31,35
Presence of extrahepatic disease		27,35	20,21,31
Presence of hilar gland metastases			20, 27, 31
Presence of abdominal gland metastases			21
4. Therapeutic factors			
R0-resection	18, 31,35		24
Type of resection (minor vs. major)	36		20,22,26,27,31
Repeat hepatectomy	31		
Response to preoperative chemotherapy	31		22,26
Blood or plasma transfusion			36

Numbers correspond to reference list.

Table 3. Patient selection for surgical treatment of BCLM.

Author, (Type of study)	**Number of Patients (N)**	**Response to preop. therapy**	**Status of BCLM**		**Inclusion of patients with extrahepatic disease 0 = no EHD 1 = stable bone metastases 2 = EHD, if stable/resectable**
			Max. number	Max size (cm)	
Lang[18] (LR)	34*	yes	>5	>5	0
Seifert[19] (LR)	15	-	9	11	0
Selzner[20] (LR)	17	-	2	≤ 5	2
Yoshimoto[21] (LR)	25	-	Multiple	7	2
Pocard [22] (LR)	65	Yes	≥ 3	12	1
Carlini [23] (LR)	17	-	-	-	0
Elias [24] (LR)	54	Yes	-	-	1
Arena [25] (LR)	17	-	Multiple	-	0
Vlastos [26] (LR+ RFA)	31	-	7	8	0
Sakamoto [27] (LR)	31	Yes	> 4	8	2
Yedibela [28] (LR)	24*	-	-	-	2
Weitz [29] (LR)	29*	-	> 1	> 5	2
Adam [31] (LR+RFA+ Cryo)	85	-	> 3	19	2
Thelen [35] (LR)	39	-	> 4	> 5	2
Lubrano [36] 1989-2004 (LR)	16	Yes	4	10	0
Caralt [37] (LR)	12	-	-	-	1
Ercolani[40] 1990-2007 (LR)	44*	-	-	-	0
Hoffman 2010[42] (LR,multicentre)	41	-	≤ 5	> 5	2
Mack[43] 1993-2002 (LITT)	232	-	13	≤ 5	1

Lawes[45] 1998-2004 (RF)	19	-	8	7	2
Sofocleus[46] 1999-2005 (RF)	12	-	≤ 3	7	2
Meloni[47] 1996-2008 (RF)	52	-	< 5	< 5	2
Jakobs[48] 1999-2006 (RF)	43	-	≤ 5	≤ 5	2
(*) data extracted from larger study of "non-colorectal, non-neuroendocrine" liver metastases. Type of study : LR: liver resection; RF: radiofrequency ablation; LITT: laser-induced thermotherapy; Cryo : cryotherapy;					

Legends

Figure 1A and 1B. Patient number (N) in relation to median overall survival (months) and 5-year survival, respectively, for different single-centre studies. Smaller studies had a greater variation in outcome. As shown, a disproportionately large number of smaller studies reported a long survival when compared with larger studies. (dots = series with liver resection; triangles = series with local ablation)

Figure 2. Recurrence rate (RR) vs. mean length of follow-up (months) for the different series of liver resection. Most studies in fig. 2 had RR $\geq$60%. Studies with a long mean follow-up time tended to report a higher RR. (The stippled line showes the computed linear correlation between the two variables.)

Fig 1A

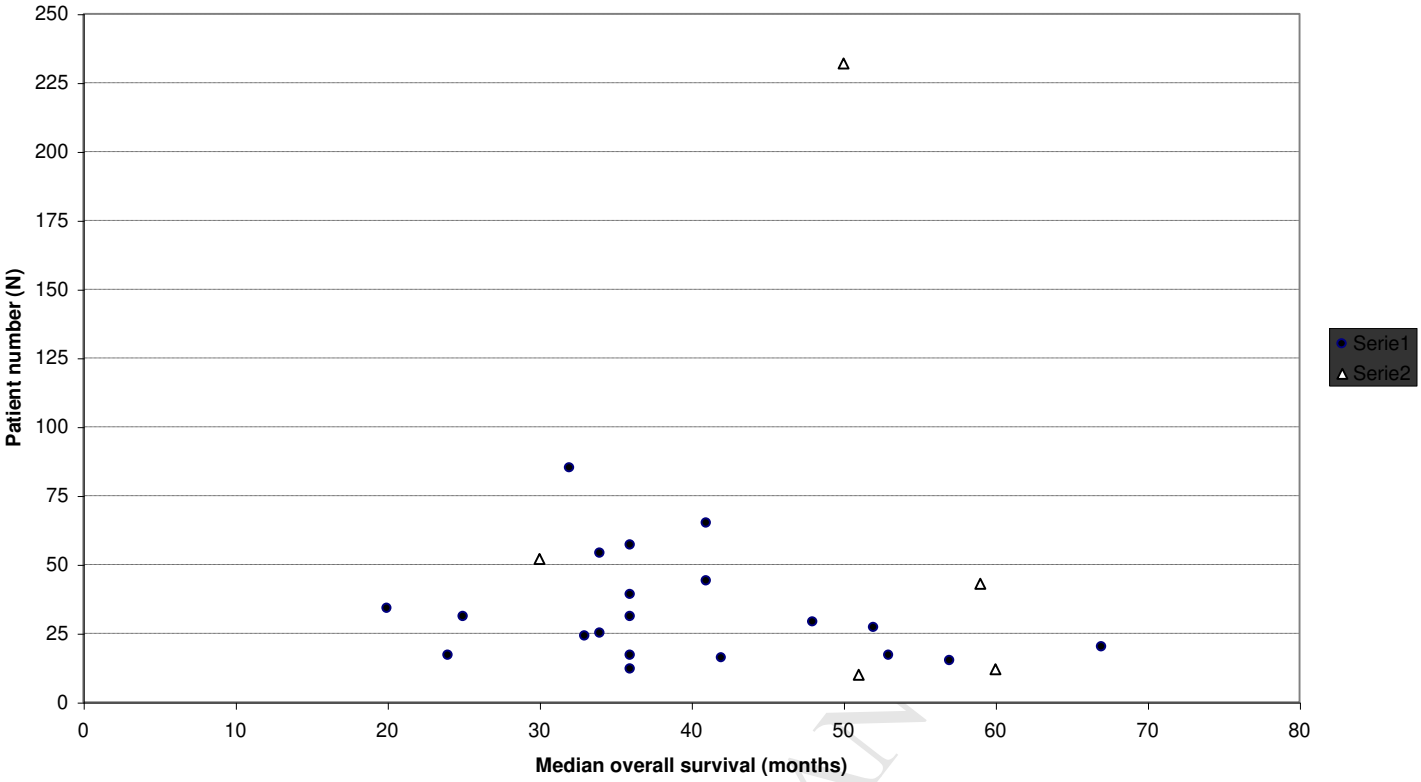


Fig 1B.

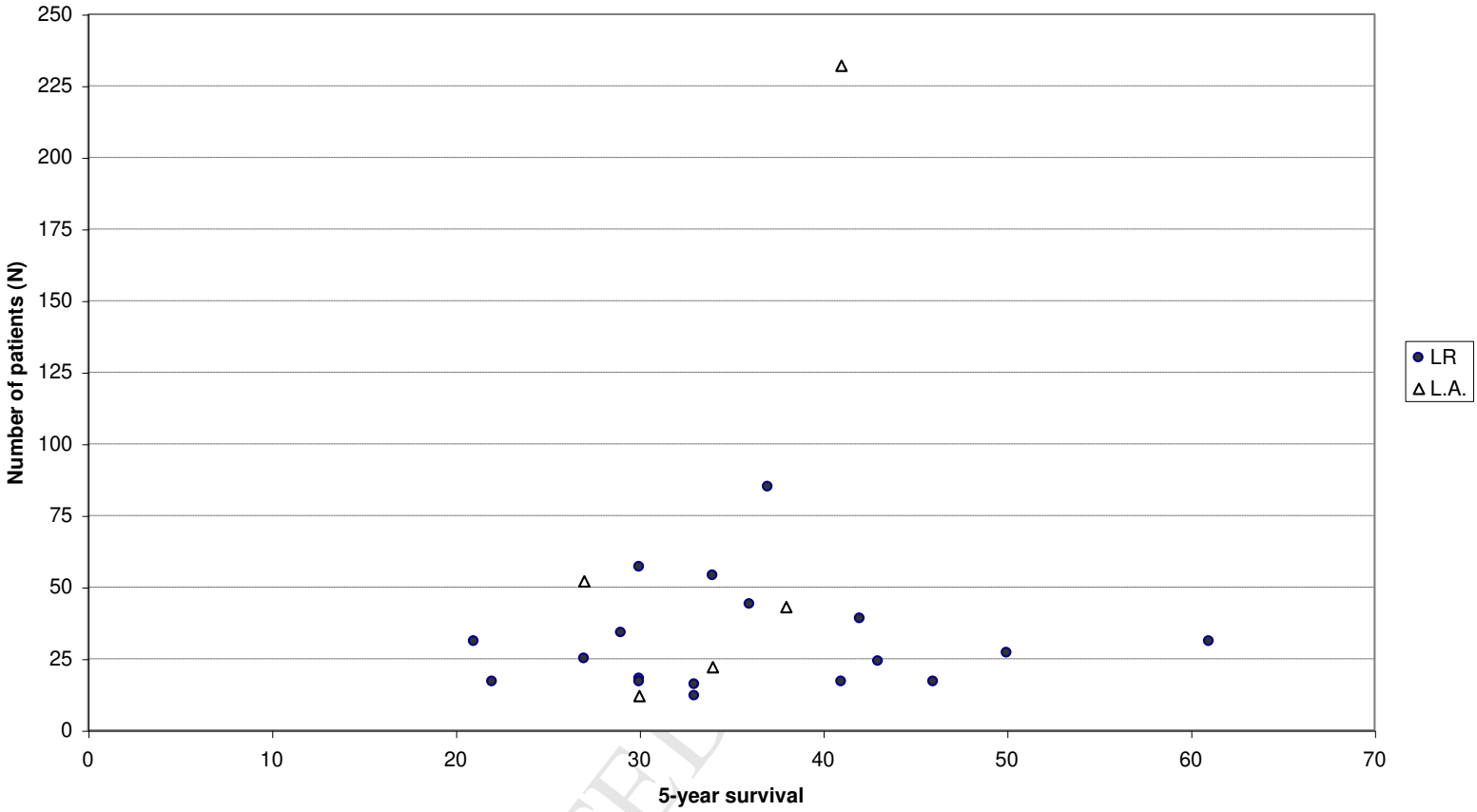
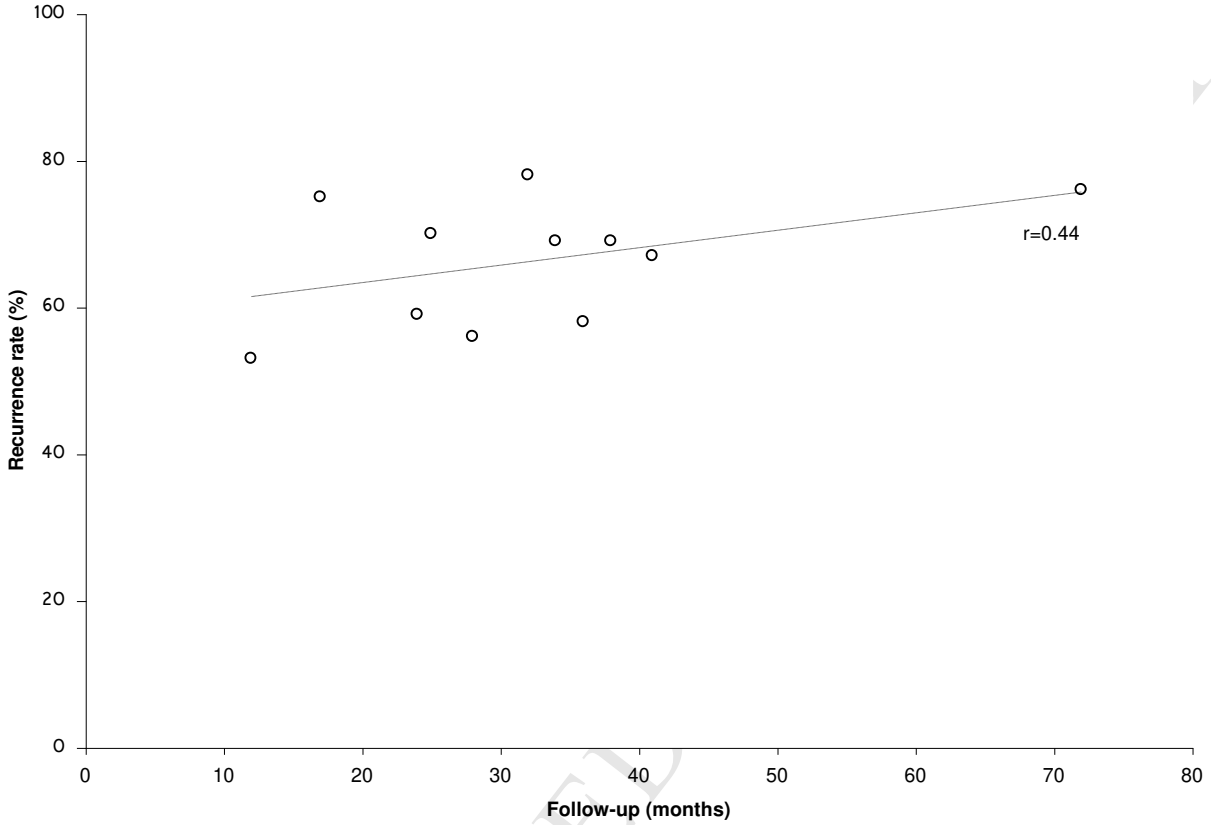


Fig 2.



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