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Review

Clinical outcome of breast cancer patients with liver metastases alone in the anthracycline-taxane era: a retrospective analysis of two prospective, randomised metastatic breast cancer trials

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Abstract

Liver metastases have long been known to indicate an unfavourable disease course in breast cancer (BC). However, a small subset of patients with liver metastases alone who were treated with pre-taxane chemotherapy regimens was reported to have longer survival compared with patients with liver and metastases at other sites. In the present study, we examined the clinical outcome of breast cancer patients with liver metastases alone in the context of two phase III European Organisation for Research and Treatment of Cancer (EORTC) trials which compared the efficacy of doxorubicin (A) versus paclitaxel (T) (trial 10923) and of AC (cyclophosphamide) versus AT (trial 10961), given as first-line chemotherapy in metastatic BC patients. The median follow-up for the patients with liver metastases was 90.5 months in trial 10923 and 56.6 months in trial 10961. Patients with liver metastases alone comprised 18% of all patients with liver metastases, in both the 10923 and 10961 trials. The median survival of patients with liver metastases alone and liver plus other sites of metastases were 22.7 and 14.2 months (log rank test, $P=0.002$) in trial 10923 and 27.1 and 16.8 months (log rank test, $P=0.19$) in trial 10961. The median TTP (time to progression) for patients with liver metastases alone was also longer compared with the liver plus other sites of metastases group in both trials: 10.2 versus 8.8 months (log rank test, $P=0.02$) in trial 10923 and 8.3 versus 6.7 months (log rank test, $P=0.37$) in trial 10961. Most patients with liver metastases alone have progression of their disease in their liver again (96 and 60% of patients in trials 10923 and 10961, respectively). Given the high prevalence of breast cancer, improved detection of liver metastases, encouraging survival achieved with currently available cytotoxic agents and the fact that a significant portion of patients with liver metastases alone have progression of their tumour in the liver again, a more aggressive multimodality treatment approach through prospective clinical trials seems worth exploring in this specific subset of women.
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1. Introduction

Metastatic breast cancer (MBC) is generally considered an incurable disease with a median survival of 18–24 months [1,2]. Therefore, treatment is palliative in intent, and its goals include improving quality of life

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and prolonging survival. Although transient responses are possible with conventional treatment modalities (chemotherapy, endocrine manipulations or local radiotherapy), most patients develop progressive disease within 1–2 years of initiating therapy [3–6]. However, a small number of patients remain disease-free for long periods of time, challenging the traditional belief that MBC is a universally fatal, incurable disease [7,8]. Indeed, due to the prognostic heterogeneity of metastatic disease, significant variations between the eventual outcomes of these patients are not surprising.

Apart from the patient's preference, the decision about the optimal therapeutic management of an individual metastatic patient is largely dependent on the prognostic and/or predictive models that have been established through the evaluation of multiple patient-, tumour- and disease-related factors [9–11]. A short disease-free interval (DFI), young age, negative receptor status, lack of response to prior therapy, presence of visceral involvement, multiple sites of disease and Her-2-positivity are among the prognostic factors indicating an unfavourable disease course [12]. It has long been reported that the development of visceral metastases, particularly in the liver, is an ominous sign indicating a poor disease outcome and a poor response to chemotherapy, endocrine therapy, or both [13–17]. Moreover, even with high dose and intensive chemotherapy supported by stem cell support, liver metastases were shown to retain their poor prognosis [18–20]. This dire reputation of liver metastases is partly attributed to the other unfavourable prognostic and/or predictive factors that are reported to be commonly associated with the presence of liver metastases (a shorter DFI, negative oestrogen receptors, young age, node-positive disease) [21–25]. Available data suggest that the liver is not a common initial site of distant metastases in breast cancer, observed in 5–20% of MBC patients; however, more than half of the patients develop liver metastases at some point in their clinical course [26–28].

Despite the fact that the management of breast cancer (BC) patients with liver metastases represents a tough situation, only a few reviews have investigated the clinical outcome of this group and a median survival in the range of 3–14 months has been reported [27–29]. Interestingly, with the diagnostic and therapeutic facilities available in the 1970s–1980s, a subgroup of patients with liver metastases alone has been reported to survive significantly longer compared with patients with liver plus other site(s) of metastases (19 months versus 14 months, respectively). In other words, our understanding of the clinical outcome of this subset of BC patients with liver metastases alone is limited to retrospective data dating back to two decades ago.

Starting from the 1990s, our therapeutic armamentarium against MBC has been widened to include more potent endocrine agents (e.g. third generation aromatase inhibitors), newer cytotoxic drugs (e.g. taxanes), and molecularly targeted biological agents (e.g. trastuzumab). Furthermore, surgical resection of isolated liver metastases and local ablation of selected liver metastases have been shown to be feasible in small series with very low morbidity and mortality. Additionally, in comparison to the 1970s and 1980s, the detection of liver metastases is now improved by modern imaging techniques including axial computed tomography (CAT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

The objective of the present study was to investigate the clinical outcome of patients with liver metastases alone in the context of two prospective randomised MBC trials involving anthracyclines and taxanes. It was assumed that the clinical outcome of these patients would be indicative of what can be achieved nowadays with our best cytotoxic agents. The present evaluation was also done with the intention to plan and develop improved therapeutic strategies for this specific subset of women.

2. Patients and methods

The efficacy of paclitaxel (T) versus doxorubicin (A) and of AT (doxorubicin/paclitaxel) versus AC (doxorubicin/cyclophosphamide) given as first-line chemotherapy in MBC patients has recently been compared in two phase III multicentre European Organisation for Research and Treatment of Cancer (EORTC) trials [26,27]. The first trial (10923) randomised 331 patients between August 1993 and May 1996 to either seven cycles of paclitaxel (200 mg/m^2 as a 3-h intravenous (i.v.) infusion every 3 weeks) or seven cycles of doxorubicin (75 mg/m^2 i.v. every 3 weeks) with crossover at progression [30]. The second trial (10961) randomised 275 patients between November 1996 and February 1999 to either AT (doxorubicin 60 mg/m^2 i.v., paclitaxel 175 mg/m^2 as a 3-h i.v. infusion) or AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 i.v.) every 3 weeks for a maximum of six cycles [31].

Anthracycline and taxane-naïve MBC patients with uni- or bidimensionally measurable lesions were eligible for both trials, and no prior chemotherapy for metastatic disease was permitted. Patients were centrally randomised at the EORTC Data Center, and the stratification factors for randomisation included centre and prior adjuvant treatment in both trials and, in trial 10961 performance status and presence of bone metastases as well. Baseline diagnostic work-up consisted of laboratory studies, and radiological evaluation (chest X-ray, CAT scan or MRI if abdominal ultrasound was abnormal and bone scan) in addition to a medical history and a physical examination in both studies. Adequate hepatic function for eligibility was defined as

having a total bilirubin level <1.25 times the upper normal limit in trial 10923. Patients were required to have total bilirubin levels $\leqslant 1.25$ times the upper normal limit and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leqslant 2.5$ times the upper normal limit in trial 10961. The primary endpoints were progression-free survival (PFS) with first-line chemotherapy and response rate (RR) with second-line chemotherapy in trial 10923 (secondary endpoints included the RR to first-line chemotherapy, quality of life (QoL) assessment and overall survival). PFS was the primary endpoint of trial 10961 (secondary endpoints included RR, safety, overall survival and QoL assessment). In trial 10923, seven courses of treatment were planned unless progression or unacceptable toxicity occurred before the seven courses were completed. Tumour response was assessed according to Union Internationale Contre le Cancer (UICC) criteria every 2 months, and a full re-evaluation of disease status was performed within 2 weeks of crossover. An early crossover was allowed at the time of documented progression while on first-line therapy, unless contraindicated or refused by the patients, while a delayed crossover was optional for the rest of the patients at the time of disease progression. In trial 10961, both treatments were administered for a maximum of six cycles, and crossover to taxane in the AC group was allowed only after progression. A dose escalation for paclitaxel and cyclophosphamide was planned at cycle 2 if no $\geqslant$grade 3 neutropenia had occurred in cycle 1. Tumour measurements were performed every 6 weeks until disease progression, and patients who received at least two cycles of therapy were evaluated for tumour response according to the World Heath Organization (WHO) criteria.

The results were analysed according to the intention-to-treat principle. QoL was assessed by the EORTC QoL Questionnaire C30 in both trials. Patient characteristics were well balanced between the two arms, with more than 75% of the patients having visceral disease in both trials.

The reported efficacy results were as follows: in trial 10923, the objective response rate (ORR) and median PFS were significantly better ($P=0.003$ and $P<0.001$, respectively) in the doxorubicin arm compared with the paclitaxel arm, but no significant median survival difference was observed; in trial 10961, no significant differences were observed between the AT and the AC arms in terms of ORR, median PFS and median survival. In a univariate analysis, the number of disease sites was found to be the only factor with a significant impact on PFS in trial 10961.

We retrospectively identified all patients with liver metastases enrolled in these two trials and then further classified those patients as having liver metastases alone or liver plus other sites of metastases. A total of 274 (160 patients from trial 10923 and 114 patients from trial 10961) patients with liver metastases were identified. The number of patients with liver metastases alone was 29 in trial 10923 and 20 in trial 10961. The records of 274 patients with liver metastases alone were reviewed, and the following information was obtained for each patient: disease-free interval, oestrogen receptor status, performance status, prior adjuvant chemotherapy, prior adjuvant endocrine therapy and overall response to the assigned study treatment. The first site of progression following enrolment in these two trials was also noted for those patients with liver metastases alone. The primary objective of this retrospective study was to analyse the clinical outcome (overall survival duration and time to progression) of patients with liver metastases alone. Survival was defined as the time elapsed between the date of randomisation and the date of death or last contact. Time to progression was defined as the time elapsed between the date of randomisation and the date of the first documented progression or death (if it occurred without documented progression) or the date of last contact if the patient was alive and did not progress. Survival and TTP curves were estimated by the Kaplan–Meier method and compared using the log-rank test. A multivariate analysis using the Cox regression model were performed for both endpoints, TTP and OS, in order to analyse the impact of liver involvement (alone or with other sites of metastases) when adjusting for covariates: treatment (taxane versus not), study (10961 versus 10923) and prognostic factors such as DFI ($\geqslant$24 months or <24 months), prior chemotherapy (yes versus no), performance status (0, 1 versus 2). Receptor status was not included in the analysis because ER status was unknown in 28 and 36% of the patients in trials 10961 and 10923, respectively. The aim of this multivariate analysis was not to identify parsimonious prognostic models on the basis of the variables analysed, but to assess whether the type of liver involvement (alone or with other sites of metastases) maintained a significant value when its impact, measured through the Cox regression coefficient, was adjusted for the known prognostic variables. All these variables were therefore included in the model without taking into account their statistical significance. The P value that was used to assess the independent prognostic value of the type of liver involvement was <0.05.

3. Results

The median follow-up of the patients with liver metastases was 90.5 months in trial 10923 and 56.6 months in trial 10961. The number of patients with liver metastases alone/liver plus other sites metastases who progressed or died before evaluation of progression was 27/127 in trial 10923 and 20/91 in trial 10961. 22

patients with liver metastases alone and 122 patients with liver plus other sites metastases died in trial 10923, while 15 patients with liver metastases alone and 82 patients with liver plus other site metastases died in trial 10961. Their median age was 54 years in both studies. Table 1 shows the relative proportions of patients with liver metastases alone and liver metastases, while Table 2 presents the pretreatment characteristics of the patients with liver metastases alone and liver plus other sites metastases per treatment arm in both trials. The response rates achieved in the liver metastases alone and liver plus other sites metastases groups in both trials are shown in Table 3. In trial 10923, the patients in the liver metastases alone subset had somewhat higher RRs compared with those in the liver plus other site metastases group in the A arm (44% in the liver metastases alone subset and 29% in the liver plus other sites metastases group) and the RRs in the liver metastases alone and liver plus other sites metastases groups were 23 and 30% in the T arm. In trial 10961, the objective response rates in the liver metastases alone and liver plus other sites metastases groups were 45% versus 51% in the AT arm and 67% versus 58% in the AC arm, respectively.

Median time to progression for the liver metastases alone and liver plus other sites metastases groups were 10.2 and 8.8 months (log rank test, $P=0.02$) in trial 10923 and, 8.3 and 6.7 months (log rank test, $P=0.37$) in trial 10961. The TTP curves are shown in Figs. 1 and 2. The median survival of the liver metastases alone and liver plus other sites metastases groups were 22.7 versus 14.2 months (log rank test, $P=0.002$) in trial 10923 and, 27.1 versus 16.8 months (log rank test, $P=0.19$) in trial 10961. Fig. 3 shows the survival curve of the patients with liver metastases alone ($n=49$) and liver plus other sites metastases ($n=226$) pooled from both trials ($P=0.002$).

Table 1
Patient population

Ratio	Trial 10923 ($n=331$)	Trial 10961 ($n=275$)
LM/all MBC patients	160/331 (48%)	115/275 (42%)
LMA/LM	29/160 (18%)	20/115 (17%)
LMA/all MBC patients	29/331 (9%)	20/275 (7%)

n, number of patients; LM, liver metastases; LMA, liver metastases alone; MBC, metastatic breast cancer.

Table 2
Patient characteristics (LMA and LPO groups)

Patients with LMA				
Patient and disease characteristics	EORTC 10923 (A versus T)		EORTC 10961 (AT versus AC)	
	A ($n=16$)	T ($n=13$)	AT ($n=11$)	AC ($n=9$)
DFI (median) months (range)	19.7 (0–117)	12.1 (0.5–90)	22.4 (0–60)	40.1 (0–74)
ER				
Positive	9	4	8	6
Negative	6	6	1	2
Unknown	1	3	2	1
Performance status				
0	9	7	6	6
1	7	6	5	3
Prior adj. CT	2	4	2	3
Prior adj. HT	6	5	7	5
Patients with LPO				
Patient and disease characteristics	EORTC 10923 (A versus T)		EORTC 10961 (AT versus AC)	
	A ($n=68$)	T ($n=63$)	AT ($n=47$)	AC ($n=48$)
DFI (median) months (range)	32.5 (0–205)	29 (0–189)	28 (0–256)	31 (0–166)
ER				
Positive	24	31	18	23
Negative	18	7	14	13
Unknown	26	25	15	12
Performance status				
0	26	23	19	15
1	39	33	26	24
2	3	7	2	9
Prior adj. CT	27	16	17	14
Prior adj. HT	54	50	29	29

LMA, liver metastases alone; LPO, liver plus other sites of metastases; *n*, number of patients; A, Doxorubicin; C, cyclophosphamide; T, paclitaxel; ER, oestrogen receptor; DFI, disease-free interval; CT, chemotherapy; HT, endocrine therapy; adj., adjuvant.

Table 3
Responses to CT in the LMA and LPO groups

Response to study treatment in the LMA group ($n=49$)				
	Trial 10923 ($n=29$)		Trial 10961($n=20$)	
	A ($n=16$)	T ($n=13$)	AT ($n=11$)	AC ($n=9$)
PR	7	3	5	6
NC	6	4	3	2
NE	1	2	3	-
PD	2	4	-	1
Response to study treatment in patients with LPO ($n=226$)				
	Trial 10923 ($n=131$)		Trial 10961 ($n=95$)	
	A ($n=68$)	T ($n=63$)	AT ($n=47$)	AC ($n=48$)
PR	20	19	24	28
NC	20	28	10	9
NE	5	2	4	3
PD	23	14	9	8

n, number of patients; A, doxorubicin; C, cyclophosphamide; *T*, paclitaxel; LPO, liver plus other sites of metastases; LMA, liver metastases alone; PR, partial remission; NC, no change; NE, non-evaluable; PD, progressive disease.

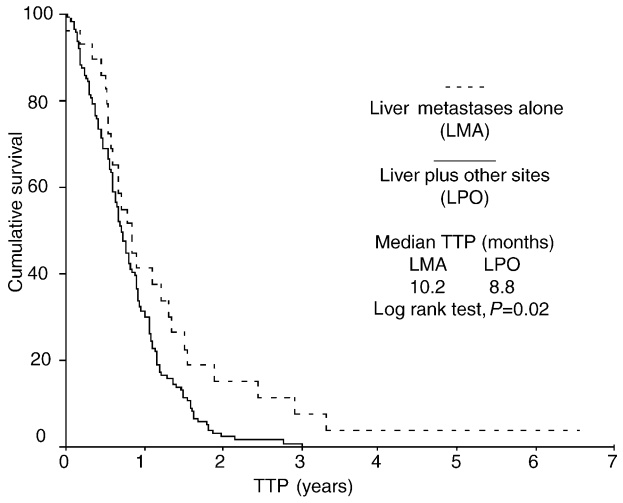

Fig. 1. Trial 10923 (LPO/LMA groups). Kaplan–Meier curve of TTP. TTP, time to progression.

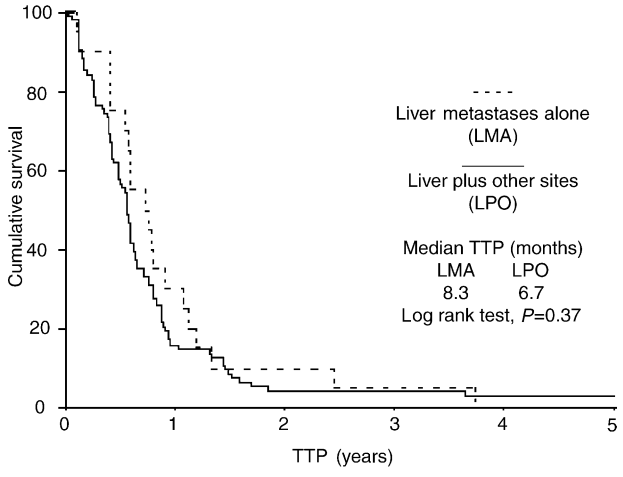

Fig. 2. Trial 10961 (LPO/LMA groups). Kaplan–Meier curve of TTP. TTP, time to progression.

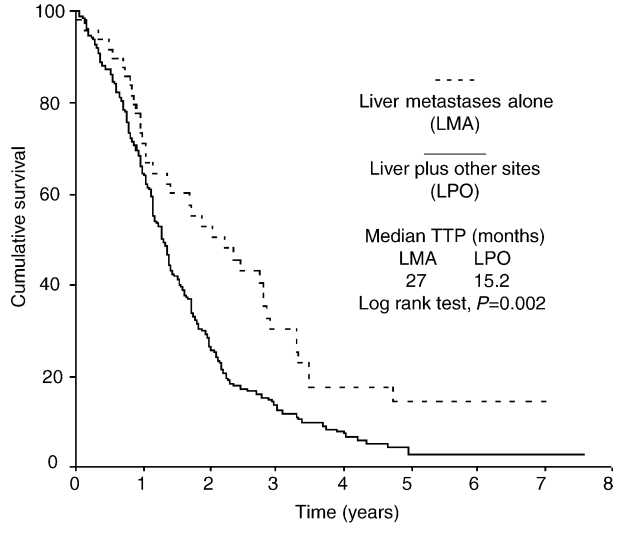

Fig. 3. Kaplan–Meier curve for overall survival (pooled data from trials 10923 and 10961). TTP, time to progression.

In the multivariate analysis, the liver plus other sites metastases group has a significantly worse overall survival with a Hazard Ratio (HR) of 1.82 (95% Confidence Interval (CI): 1.27–2.62) ($P=0.001$) and a shorter TTP with a HR of 1.39 (95% CI: 1.00–1.92) ($P=0.04$) when adjusting for all covariates described in Section 2 (Table 4). When the impact of potential prognostic factors on TTP and overall survival in the pooled population (10961 and 10923) were analysed, absence of prior chemotherapy was significantly associated with a longer TTP and better overall survival. Other factors, which were significantly associated with an improved overall survival, included a PS of 0–1, a DFI of $\geqslant 24$ months and the administration of combination chemotherapy instead of monotherapy (Table 4).

Table 5 shows the first sites of progression in the liver metastases alone subset. The first site of progression was the liver again in 28 of the 29 (97%) patients with live metastases alone in trial 10923 and 12 of the 20 (60%) patients with liver metastases alone in trial 10961.

4. Discussion

This retrospective analysis confirms that following treatment with today's commonly used cytotoxic agents, BC patients with liver metastases alone survive longer than patients with liver plus other sites of metastases and that their subsequent disease progression occurs mostly in the liver. So far, only a few retrospective studies have analysed the clinical outcome of patients with liver metastases (Table 6). Zinser and colleagues compared 233 BC patients with liver metastases treated between 1973 and 1980 with doxorubicin-containing chemotherapy with another group of 58 BC patients with liver metastases, treated with endocrine manipulation and/or single agents fluorouracil or thiotepa in the 1950s at the MD Anderson Hospital [27]. Those 233 patients with liver metastases were identified from a group of 1171 MBC patients (20%), and their median survival was reported as 14 months. The median survival of this second group of 58 patients was reported as 5 months. In the 1950s, liver metastases were detected on the basis of clinical and biochemical criteria and in the 1970s the imaging technique for detecting liver metastases was the technetium-99 sulphur colloid scan. All patients were symptomatic, postmenopausal and had no prior exposure to anthracyclines. The overall Response Rate (RR) to combination chemotherapy was 57%, with 20% of patients achieving a Complete Remission (CR). 29 out of 233 patients (12%) were reported to have liver metastases alone. In the 1950s, more patients presented with liver metastases at their initial diagnosis and only 5% of the 58 patients had liver metastases alone. An analysis of survival based on the extent of metastatic disease (patients with liver metastases alone;

Table 4
Multivariate analysis for trials 10961 and 10923 (pooled population)

	TTP			OS		
	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Groups (LMA versus LPO)	1.39	1.00–1.92	0.04	1.82	1.27–2.62	0.001
Study treatment (10961 versus 10923)	1.21	0.94–1.55	0.13	0.68	0.52–0.88	0.004
Taxane versus non-taxane treatment	1.07	0.83–1.37	0.58	1.16	0.90–1.50	0.24
Performance status (0, 1 versus 2)	1.06	0.65–1.74	0.78	2.02	1.23–3.32	0.005
Prior CT (no versus yes)	1.33	1.00–1.76	0.04	1.52	1.14–2.04	0.005
DFI ($\geqslant$or $<$24 months)	1.24	0.95–1.61	0.10	1.57	1.19–2.07	0.001

LMA, liver metastases alone; LPO, liver plus other sites of metastases; DFI, disease-free interval; CT, chemotherapy; TTP, time to progression: OS, overall survival; HR, hazard ratio; CI, confidence interval.

liver and bone metastases; and liver metastases plus $>$ 3 sites) showed that patients with liver metastases alone experienced an extended survival compared with the latter two groups (median survivals were 19, 17 and 12 months, respectively). In the MD Anderson study, the median survival of all patients with liver metastases was 14 months, and it was shorter than the median survival of 619 MBC patients (21 months) treated between 1973 and 1976 in the same institution with four similar protocols, all containing a combination of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) ± immunotherapy or other cytotoxic agents [9]. Nevertheless, Zinser and colleagues concluded that despite the poor outcome of liver metastases from breast cancer, most patients did respond to chemotherapy and a longer survival was possible for several prognostic groups, including the patients with liver metastases alone, and those who had no prior chemotherapy, had a good performance status, normal bilirubin, lactate dehydrogenase (LDH) and AST levels and no ascites.

A subsequent study investigated the relationship between the clinical, biochemical and pathological features and survival in 312 BC patients with liver metastases who were followed between 1974 and 1986 [28]. Ultrasound (US) or radionuclide scans were used to detect liver metastases at that time. A very poor median survival of less than 4 months was reported here, and clinical outcome was not associated with the clinical pattern of disease before the development of liver metastases. The apparent reduction in the survival of these patients compared with the ones from the MD Anderson review is explained by differences in the initial diagnostic work-up and the use of doxorubicin in only a few of the patients. In addition, the proportions of patients with high levels of AST, which was shown to be the strongest independent predictor of survival after the diagnosis of liver metastases in a multivariate analysis, and of those who were not fit to receive chemotherapy were higher in the second report.

Another study analysed the incidence of liver metastases in BC patients treated between 1982 and 1987 and their clinical outcome [29]. 47 out of 912 BC patients developed (5.2%) liver metastases, detected by US, and 10 out of the 47 (21%) patients were identified with liver metastases alone. Most patients were symptomatic and had abnormal liver function tests. 70% of the patients with liver metastases were treated with both chemotherapy and endocrine therapy, and the median survival was reported as 4 months. Absence of jaundice, objective response to treatment, and liver involvement only were associated with a significantly better survival in a univariate analysis. The median survival of the patients with liver metastases alone in this report was 8.5 months.

Table 5
First progression sites in patients with LMA

10961 ($n=20$)		10923 ($n=29$)	
First progression site	*n*	First progression site	*n*
Liver	12	Liver	28
Brain + liver	1	Bone	1
Brain + bone + lung	1		
Bone	2		
Not reported[a]	4		

n, number of patients; LMA, liver metastases alone.

[a] One patient withdrew her consent, 1 patient is lost to follow-up and 1 patient had an early death due to rapid deterioration of her status following randomisation and an elevation of serum markers was accepted as progression for the fourth patient.

In the last decade, the new cytotoxic agents, particularly the taxanes, have been shown to produce encouraging response rates in BC patients with liver metastases (Table 7). The analysis of five multicentre phase II studies evaluating the efficacy of single agent docetaxel as first-line treatment for MBC with respect to the presence or absence of liver metastases revealed that the response rates to docetaxel 75–100 mg/m^2 were maintained in the presence of liver metastases which were identified in 73 of the 209 patients. The median survival of patients with liver metastases was reported to be 14.7 months compared with 16.4 months median survival for all of the MBC patients [32]. These encouraging results led to a prospective open-label

Table 6
Retrospective studies investigating the clinical outcome of BC patients with LM

Reference study	Zinser and colleagues [27]		O'Reilly and colleagues [28]	Hoe and colleagues [29]	Present analysis	
					Paridaens and colleagues [30] (Trial 10923)	Biganzoli and colleagues [31] (Trial 10961)
The period during which pts were treated	1955–1957	1973–1980	1974–1986	1982–1987	1993–1996	1996–1999
Total number of MBC pts reviewed	NR	1171	NR	912	331	275
Number of pts with LM/LMA	58/3	233/29	312/NR	47/10	160/29	115/20
Treatment administered	ET or single-agent thiotepa or 5-FU	A-containing combination CT	ET or CT	70% received both ET and CT	A versus T	AT versus AC
Diagnostic methods used to detect LM	Clinical and biochemical criteria	Tc 99m sulphur colloid scan*	US and Rn scan (94%)	US (74.7%)	CAT	CAT
Response rate						
All pts	NR	NR	NR	NR	41% versus 25% (A versus T) ($P = 0.003$)	58% versus 54% (AT versus AC) ($P =$ NS)
Pts with LM	NR	57% (20% with CR)	20% (16% for CMF and 39% for single-agent A)	13%	31%	55%
Pts with LMA	NR	NR	NR	NR	34%	55%
Median TTP						
All pts	NR	NR	NR		7.5 mo versus 3.9 mo[b] (A versus T) ($P < 0.001$)	6 mo versus 6 mo[b] (AT versus AC) ($P =$ NS)
Pts with LM	NR	NR	NR	NR	8.8 mo[a]	6.7 mo[a]
Pts with LMA	NR	NR	NR	NR	10.2 mo	8.3 mo
Median survival						
All pts	NR	21 mo	NR	NR	18.5 mo versus 15.6 mo (A versus T) ($P =$ NS)	20.6 mo versus 20.5 mo (AT versus AC) ($P =$ NS)
Pts with LM	5 mo	14 mo	3.8 mo (4.6 mo for CMF and 9.6 mo for single-agent A)	4 mo	14.2 mo[a]	16.8 mo[a]
Pts with LMA	NR	19 mo	NR	8.5 mo	22.7 mo	27.1 mo

pts, patients; LM, liver metastases; LMA, liver metastases alone; TTP, time to progression; NR, not reported; Rn, radionuclide; CMF, cyclophosphamide/methotrexate/5-fluorouracil; A, doxorubicin; T, paclitaxel; C, cyclophosphamide; US, ultrasound; CAT, computed axial tomography; ET, endocrine therapy; NS, non-significant; mo, months; MBC, metastatic breast cancer.

[a] Includes patients with liver plus other sites of metastases, patients with LMA are not included.

[b] Denotes progression-free survival, not time to progression.

phase II study in order to investigate the activity of docetaxel (100 mg/m^2 i.v. as a 1-h infusion every 3 weeks for up to seven cycles) specifically in 47 BC patients with liver metastases [33]. The best overall response for evaluable patients was reported as 64.3%, and the estimated median overall survival was 335 days. Docetaxel was compared with doxorubicin in 326 patients previously exposed to alkylating agents in a phase III trial. In the subgroup with liver metastases ($n = 136$), a RR of 54.3% was achieved in the docetaxel arm compared with a RR of 25.8% in the other arm [34]. Docetaxel-containing combination chemotherapies were investigated in two randomised phase III trials. The first one compared doxorubicin/docetaxel (AD) with AC in 429 MBC patients, and the other compared DAC (docetaxel/doxorubicin/cyclophosphamide) with FAC in 484 MBC patients as first-line chemotherapy in the metastatic setting. The response rates in the AD/AC and DAC/FAC arms were 62%/43% and 55%/47% in patients with liver metastases [35,36]. Indeed, these higher response rates are not surprising when one considers that the patients in all these taxane studies were highly selected and in particular had good liver function tests.

The present analysis shows an increased incidence of liver metastases compared with two decades ago. In total, 45% (275/606) patients presented with liver metastases in the 10923 and 10961 studies (48% in trial 10923 and 42% in trial 10961). Furthermore, in both trials approximately 18% of patients with liver metastases were reported to have liver involvement only. Collectively then, 8% of patients had liver metastases alone. These figures most likely result from the contribution of modern imaging techniques (CT, MRI and PET scan) to improve the detection of liver metastases. However, it might be argued that the percentage of the breast cancer patients with liver metastases alone is an overestimate, not reflecting the truth, since these patients were not evaluated with the rigour that would normally be used while planning a potential surgical intervention for hepatic metastases. Almost certainly many of them would have had small volume extrahepatic/peritoneal disease in such circumstances. It should also be noted that the limited diagnostic facilities and the conservative investigation policies for detection of liver metastases (e.g. imaging only in the case of abnormal liver function tests or palpable hepatomegaly) could explain the fewer breast cancer patients with liver metastases and their very poor clinical outcome in the historical case series.

The response rates achieved with doxorubicin or paclitaxel given as monotherapy (trial 10923) were lower than those achieved with an anthracyline-containing combination chemotherapy or an anthracycline/taxane combination (trial 10961). Overall, in the liver metastases alone subset, objective response rates were 10/29 (34%) and 11/20 (55%) in trials 10923 and 10961, respectively. The patients with liver metastases and liver plus other site metastases had similar response rates; 30% in trial 10923 and 55% in trial 10961 (Table 3). Indeed, the response rates in the 10961 trial were not different from the RRs obtained in Zinser's review with doxorubicin-containing combination regimens; however, the median survival exceeded the one reported in Zinser's report by 3–8 months in the liver metastases alone group and by almost 3 months in patients with liver metastases. This could probably be explained by the impact of subsequent treatments on survival. O'Reilly and colleagues reported an objective RR of 39% in patients with liver metastases treated with single-agent anthracycline between 1974 and 1986 [28]. Later on, in the early 1990s, the response rates to first-line single agent chemotherapy with anthracyclines (doxorubicin, epirubicin or mitoxantrone) were reported in the range of 20–80% in breast cancer patients with liver metastases, but all these trials included very few patients with liver metastases [37]. In the present analysis, 32 and 29% of patients with liver metastases responded to doxorubicin and paclitaxel, respectively, in trial 10923.

Keeping in mind the limitations of retrospective analyses, the present analysis suggests that MBC patients with liver metastases, and especially those with liver metastases alone, achieve a somewhat improved survival with the currently available cytotoxic regimens, in spite of today's more extensive use of adjuvant chemotherapy. It is possible that the impact of the study treatments on survival may be better reflected by TTP since this surrogate is not influenced by subsequent therapies, as in the case of median survival. A median TTP up to 10 months and a median survival up to 27 months are now possible in BC patients with liver metastases alone treated with anthracyclines and taxanes, administered either sequentially or in combination. This improved survival outcome in the liver metastases alone group, consistent with the data from previous reviews, can be explained by a lower tumour burden in this subset. At the same time, however, it highlights the need to explore a different therapeutic approach for these patients, who may be more likely to benefit from multimodality treatment than others.

An interesting finding in this analysis is the observation that most patients with liver metastases alone had further progression of their tumour in the liver (28/29 and 12/20 patients in trials 10923 and 10961, respectively). This indicates that, perhaps, an additional therapeutic modality following an excellent response to chemotherapy might be useful in maintaining the disease-free status and in delaying further progression in the liver.

In addition to chemotherapy, the surgical resection of isolated liver metastases, the application of recently developed, less invasive thermal ablation techniques, and the use of regional chemotherapy via the hepatic

Table 7
ORRs to taxanes (either as monotherapy or in combination with anthracyclines) in patients with LM, reported in first-line CT trials in the late 1990s

Phase II Trials							
Reference	Trial treatment	Number of pts with LM/all pts	Results	Comments			
Coleman and colleagues [33]	Docetaxel (100 mg/m^2 q3 wks)	47/NA	ORR = 64.3% (17% CR) (95% CI: 48–78.5%) median survival = 335 days (95% CI: 227–568 days)	A prospective, open-label multicentre trial involving BC patients with LM			
Fumoleau and colleagues [32]	Docetaxel (75–100 mg/m^2 q3 wks)	73/209	ORR = 60% (pts with LM) ORR = 61% (all pts) median TTP (pts with LM) = 14.7 months median TTP (all pts) = 16.4 months	Results from five phase II trials for MBC are pooled			
Phase III trials							
Reference	Period during which pts were treated	Number of pts with LM/ all MBC pts	Treatment arms	ORR (all pts)		ORR in pts with LM	
Chan and colleagues [34]	1994–1997	136/326 (42%)	A versus D	D 47.8%	A 33.3%	D 54.3%	A 25.8%
Nabholtz and colleagues [35]	1996–1998	NR/429	AD versus AC	AD 60%	AC 47%	AD 62%	AC 43%
Nabholtz and colleagues [36]	1998–1999	NR/484	DAC versus FAC	DAC 55%	FAC 44%	DAC 55%	FAC 47%

pts, patients; MBC, metastatic breast cancer; LM, liver metastases; A, doxorubicin; D, docetaxel; C, cyclophosphamide; F, 5-Fluorouracil; ORR, objective response rate; NA, not applicable; NR, not reported; q, every; wks, weeks; CR, complete response; CI, confidence interval.

artery have all been investigated for the management of liver metastases from BC with promising results [38–43]. However, their potential role in the management of liver metastases from BC is based solely on the reports from small, heterogeneous single-institution series, and the lack of prospective randomised trials demonstrating that these regional treatment modalities add further benefit to conventional treatment hampers their integration into routine clinical practice. Finally, an increasing number of molecularly targeted biological agents are being developed in parallel to our improved understanding of the biological mechanisms underlying the process of tumour angiogenesis, metastases and invasion. These agents may provide substantial consolidation in stage IV breast cancer by delaying disease progression following the removal of liver metastases either by surgery or local ablative techniques.

In summary, the results of our study point to the need for a revision of the 'optimal' management of BC patients with liver metastases alone, given that the detection of this small subset of BC patients is now facilitated and that a median survival of more than 2 years can be achieved with modern chemotherapy. Optimism is fed by the fact that there is level III evidence supporting the hypothesis that MBC might be curable with a multidisciplinary approach in highly selected patients with limited metastases [44–46]. Moreover, there is ample room to improve the survival of BC patients with liver metastases alone, who may indeed represent the population deserving a more aggressive therapeutic approach, including chemotherapy, surgical resection or local ablation, and perhaps biological agents for consolidation of response. This hypothesis needs to be tested prospectively through well-designed clinical trials. However, given the small percentage of patients with liver metastases alone and the paucity of centres experienced in the surgical removal or the local ablation of liver metastases from breast cancer, a large, multicentre, international collaboration seems mandatory to accomplish this ambitious task.

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