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A Systematic Review of the Surgical and Ablative Management of Breast Cancer Liver Metastasis

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Abstract

Background: Systemic therapy is first line for Breast Cancer Liver Metastasis (BCLM), though interest in Surgical Resection (SR) and Ablation Therapy (AT) has increased. We assessed oncologic outcomes after SR and AT in BCLM.

Methods: A systematic review identified studies evaluating outcomes for SR and AT for BCLM. Selected studies reported the following outcomes: Disease-Free Survival (DFS), Overall Survival (OS), Overall Survival Rate (OSR), Local Recurrence (LR), Complication Rate (CR) and/or Mortality Rate (MR).

Results: Sixty- seven studies were included evaluating 2,259 patients with median age 49.7 years over follow-up 32.4 months. Median OS and DFS were 43.7 months and 22.8 months for SR and 40.6 and 23.4 months for AT. Local recurrence for SR was 51.4% versus 13.9% for AT. CR and MR were 8.8% and 0.04% for AT, versus 17.7% and 0.37% for SR. OSR at 1 and 5 years were 86.8% and 36.9% for SR, and 87.3% and 37.5% for AT.

Conclusion: This study is the largest literature review of SR and AT for BCLM, revealing both with favorable oncologic safety. While a clinical trial may not be feasible, SR and AT should be considered for BCLM patients.

Keywords: Ablation Therapy; Breast Cancer; Liver Metastasis; Surgical Resection

Introduction

Systemic and surgical management of primary Breast Cancer (BC) has continued to evolve over the past four decades, but for patients with metastatic breast cancer, treatment options are limited. Breast cancer most commonly metastasizes to the liver, lung, brain, bone and skin [1,2]. The liver is the third most common site for BC metastasis accounting for about 10% of patients, of which only 5-18% present with isolated Breast Cancer Liver Metastasis (BCLM) [1,3-9]. Metastatic BC is considered an incurable disease despite new therapies. Systemic chemotherapy is currently the mainstay for management of BCLM with a median survival of 1-25 months and a 5-year Overall Survival Rates (OSR) ranging from 8.5%-40% [10-14]. However, recent success

in Surgical Resection (SR) and Ablation Therapy (AT) reported for colorectal liver metastases have encouraged the development of similar protocols for management of BCLM [15,16].

Previous studies evaluating surgical and ablative techniques for management of BC patients with hepatic metastasis have suggested favorable oncologic outcomes with low morbidity. Only a few large-scale studies have evaluated survival, recurrence rates and other measures of oncologic safety for management of BCLM. The purpose of this systematic review is to summarize the totality of evidence that evaluates oncologic outcomes after SR and AT in the setting of breast cancer metastasis to the liver. We performed a systematic literature review to assess Overall Survival (OS), Disease-Free Survival (DFS), Local Recurrence (LR), Mortality Rates (MR), and Complication Rates (CR) among BCLM patients undergoing SR and AT.

Materials and Methods

Study Selection

A search was conducted of peer-reviewed articles through the MEDLINE database using PubMed. Our search terms included: "Breast Neoplasms", "Breast Cancer", "Liver Neoplasms", "Hepatectomy", "Resection of Liver", "Neoplasm Metastasis", or "Ablation Techniques" We filtered all articles from 1950 to 2016. A manual search of bibliographies of relevant articles was performed. All searches were conducted in September 2016. Abstracts were screened to identify studies that measured DFS, OS, OSR at 1, 2, 3 and/or 5 years, LR, MR and/or CR.

Data Extraction

Two investigators performed the search, independently screened articles pertaining to breast cancer liver metastasis using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and extracted data from each study [17]. Discrepancies in coding required agreement between authors to be considered resolved.

Definitions of Outcomes of Interest

Included studies reported at least one of the following outcomes:

Disease-Free Survival (DFS): Patients in the study who were alive from the time of surgery to date of last follow-up without the development of local or distant disease recurrence or a new breast tumor.

Overall Survival (OS): Patients in the study who were alive from the time of surgery to date of last follow-up.

Overall Survival Rate (OSR): at 1, 2, 3 and/or 5 years*:* Proportion of patients who were alive from the time of surgery to 1, 2, 3 and/or 5 years after surgery, respectively.

Complication Rate (CR): Proportion of patients who experienced a complication associated with surgery.

Mortality Rate (MR): Proportion of patients who died from time of surgery to date of post-operative follow-up.

Inclusion and Exclusion Criteria

Studies were selected based on the following inclusion criteria:

- Report on women undergoing SR or AT in the setting of BCLM
- Report on DFS, OS, OSR, LR, CR and/or MR

Studies were excluded by any one of the following criteria:

- Review articles
- Evaluated methods other than surgical resection or ablative therapy for management of BCLM
- Studies that included only patients with extrahepatic disease (EHD) from breast cancer or combined treatment modalities
- Evaluated fewer than 5 patients

Statistical Analysis

For all studies, we reported one or more of the primary outcomes of interest (DFS, OS, OSR at 1, 2, 3 and/or 5 years, LR, CR and/or MR). We further determined the weighted average of OS, DFS, OSR, LR, CR and/or MR among the SR and AT groups. We determined mean OS, median DFS, OSR, LR, CR and MR according to decade in which the studies ended (1990s versus 2000s versus 2010s for the SR group; 2000s versus 2010s for the AT group). The median age and mean follow-up time were also extracted, in addition to the proportion of people who had EHD. We determined the mean length of OS among patients with and without EHD.

We performed a one-way analysis of variance test to compare measures of oncologic safety (OS, DFS, OSR, LR, CR and MR) for studies that evaluated patients in the SR group through the 1990s versus 2000s versus 2010s in order to assess if a statistically significant difference exists among these outcomes of interest among patients treated with older versus more recent surgical techniques. We then performed an independent samples t-test to compare the same outcomes of interest among patients in studies continuing through the 2000s versus 2010s in the AT group to assess if a statistically significant difference exists among these outcomes of interest among patients treated with older versus more recent ablative techniques. We also performed an independent samples t-test among patients who underwent SR to determine if length of OS differed significantly for patients with and without EHD.

Results

The literature search yielded 3,028 articles (Figure 1). Sixty-seven studies published from 1988 to 2016 met inclusion and exclusion criteria and were selected for the systematic literature review. Table 1a and 1b provide baseline characteristics of studies selected for the systematic literature review reflecting patients undergoing SR. Table 2 provides baseline characteristics of studies selected for the systematic literature review reflecting patients undergoing AT.

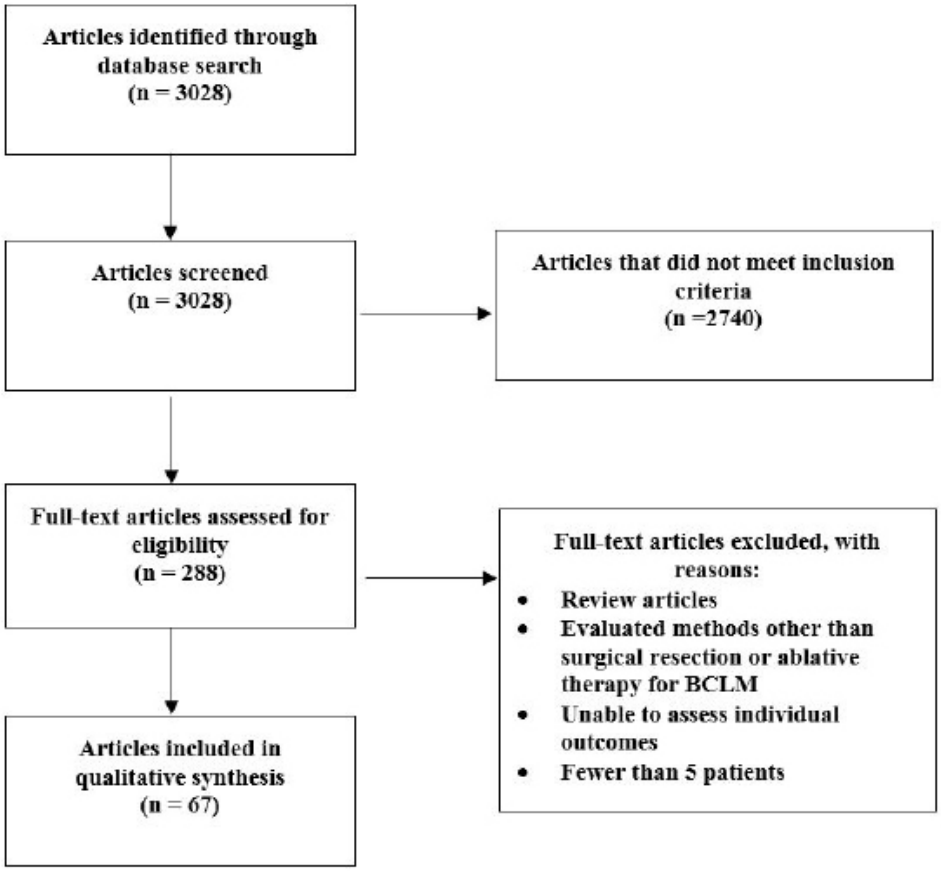

Figure 1: Flow Chart of the Literature.

Study (Year Published)	Study Years	No. of Cases (n)	Median Age (years)	Mean Follow-up (months)	EHD (n)	Primary Cancer IDC (n)	Mean Size of Liver Metastases (cm)	Mean No. of Liver Metastases (n)	Mean Time to Develop Liver Metastases (months)	Solitary Metastases (n)	Multiple Metastases (n)	Minor Hepatectomy <3cm (n)	Major Hepatectomy >3cm (n)	Adjuvant or Neo-Adjuvant Chemo (n)
Abbott [28] (2012)	1997-2010	20	-	62	18	73	-	-	-	-	-	-	-	-
Adam [29] (2006)	1984-2004	15	47	38	27	73	2.8	-	34	32	53	54	31	71
Arena [30] (2004)	-	17	48	-	0	-	-	2.2	-	-	-	3	14	-
Bacalbasa [31] (2014)	2002-2013	25	52	-	0	5	-	-	20.29	24	19	29	14	-
Belda [32] (2010)	1998-2008	108	47.8	31	0	-	-	1.75	34	-	-	5	7	8
Caralt [33] (2008)	1988-2006	17	58.4	35.9	1	-	-	-	39.1	-	-	7	6	8
Carlini [34] (2002)	-	21	55	-	-	15	-	-	35	15	2	15	2	13

Cordera[35] (2005)	1988-1998	10	-	-	-	-	-	-	-	-	-	-	-	-
D'Annibale [36] (2005)	1984-1999	12	56	-	-	15	-	-	-	-	-	-	-	9
Duan [37] (2012)	1996-2008	19	-	-	-	-	4.5	1.8	-	-	-	-	-	-
Elias [38] (2003)	1986-2000	54	49.2	32	3	-	-	4	39.1	-	-	20	34	54
Ercolani [39] (2005)	1990-2003	16	-	-	0	-	-	-	-	-	-	-	-	-
Furka [40] (2008)	-	26	-	-	-	-	-	-	-	-	-	16	1	17
Groeschl [41] (2012)	1990-2009	21	-	31	-	-	-	-	-	-	-	-	68	-
Hoffmann [42] (2010)	1999-2008	115	-	34	12	-	-	-	79	20	21	19	22	-
Kollmar [43] (2008)	-	41	-	-	-	-	-	-	-	-	-	-	-	-
Kondo[44] (2000)	1990-1999	27	-	-	-	-	7.7	-	-	-	-	-	-	-
Kostov [11] (2013)	2000-2006	6	58.2	60	20	37	-	-	-	-	-	12	29	42
Lang [45] (1999)	1983-1993	34	-	-	0	-	-	-	-	-	-	-	-	-
Lehner [46] (2009)	1994-2008	8	-	-	-	-	-	-	-	-	-	-	-	-
Lendoire [47] (2007)	1989-2006	42	54	28	-	-	-	-	-	-	-	-	-	-
Lorenz [48] (1995)	1982-1991	17	-	-	-	-	-	-	-	-	-	-	-	-
Lubrano [49] (2008)	1989-2004	19	54	28	0	-	-	-	54	-	-	7	9	-
Maksan [50] (2000)	1984-1998	16	44	29	-	-	-	2.6	42	-	-	-	-	3
EHD-Extrahepatic Disease; IDC-Invasive Ductal Carcinoma														

Table 1a: Study Characteristics-Surgical Resection.

Study (Year Published)	Study Years	No. of Cases (n)	Median Age (years)	Mean Follow-up (months)	EHD (n)	Primary Cancer IDC (n)	Mean Size of Liver Metastases (cm)	Mean No. of Liver Metastases (n)	Mean Time to Develop Liver Metastases (months)	Solitary Metastases (n)	Multiple Metastases (n)	Minor Hepatectomy <3cm (n)	Major Hepatectomy >3cm (n)	Adjuvant or Neo-Adjuvant Chemo (n)
Martinez [51] (2006)	1995-2004	24	55	39	-	18	2.7	-	-	-	-	-	-	-
Okaro [52] (2005)	1996-2002	9	45.8	-	-	-	-	-	-	-	-	1	5	-
Pocard [53] (2001)	1988-1999	54	47.1	41	13	58	3.8	-	60	44	21	34	31	65

Polistina [54] (2013)	2004-2011	32	62.5	22.5	0	-	-	-	-	-	-	-	-	-
Raab [55] (1998)	1983-1994	86	47	-	-	-	-	-	-	20	14	-	-	-
Reddy [56] (2007)	1995-2005	57	-	-	-	-	-	-	36	-	-	13	5	17
Rubino [57] (2010)	-	20	-	-	-	-	-	-	35	-	-	-	-	-
Sadot [58] (2016)	1991-2014	69	52	31	0	65	3	1	53	44	-	27	24	-
Sakamoto [59] (2005)	1985-2003	65	51	72	9	-	-	-	-	-	-	-	15	-
Santoro [60] (2000)	1990-1998	8	-	-	-	-	-	-	-	13	2	13	2	11
Schneebaum [61] (1994)	-	8	-	-	-	-	-	-	-	-	-	-	-	-
Seifert [62] (1999)	1985-1997	34	-	12	-	-	5.3	3.3	-	-	-	10	5	-
Selzner [63] (2000)	1987-1999	15	48	17	3	17	-	-	30	-	-	11	6	10
Stehlin [26] (1988)	-	20	-	-	5	-	-	-	-	-	-	6	3	-
Thelen [64] (2008)	1988-2006	22	-	-	13	-	-	-	-	14	12	19	20	-
Treska [65] (2014)	2000-2013	9	-	-	-	-	-	-	-	-	-	-	-	-
Van Walsum [66] (2012)	1994-2010	39	50	26	5	20	-	-	-	22	10	19	13	-
Vlastos [67] (2004)	1991-2002	19	46	-	-	25	2.9	1.7	34.9	20	11	17	14	27
Weinrich [68] (2014)	2001-2007	25	53.3	22	-	-	-	-	55	6	-	-	-	26
Weitz [69] (2005)	1981-2002	32	-	-	-	-	-	-	-	-	-	-	-	-
Ye [70] (2015)	2003-2013	167	42	54	4	-	-	-	-	-	-	-	-	-

Yedibela [71] (2005)	1978-2001	29	-	-	-	-	-	-	-	-	-	-	-	-
Yoshimoto [72] (2000)	1985-1998	24	-	-	8	-	-	-	-	14	11	-	-	25
Zegarac [73] (2013)	2006-2009	43	-	37	-	-	-	-	-	-	-	-	-	-
EHD-Extrahepatic Disease; IDC-Invasive Ductal Carcinoma														

Table 1b: Study Characteristics (Continued)-Surgical Resection.

Study (Year Published)	Study Years	No. of Cases (n)	Median Age (years)	Mean Follow-up (months)	EHD (n)	Primary Cancer IDC (n)	Mean size of Liver Metastases (cm)	Mean No. of Liver Metastases (n)	Mean Time to Develop Liver Metastases (months)	ER+	PR+	HER2+	Adjuvant or Neo-Adjuvant Chemo (n)	Adjuvant or Neo-Adjuvant Hormonal Therapy (n)
Abe [74] (2005)	2000-2004	8	49	29.5	4	-	2.24	-	-	-	-	-	-	-
Barral [75] (2016)	2000-2014	79	53.2	18.4	29	-	2.89	1.44	45.5	-	-	-	79	-
Carrafiello [76] (2011)	2003-2007	13	54.5	12.9	8	10	3.5	1.66	87	-	-	-	13	-
Colle ttini [77] (2012)	2008-2010	37	58.6	11.6	39	-	2.6	2.16	-	-	-	-	-	-
Gunabushanan [78] (2007)	2002-2005	14	45.2	18	4	-	1.9	-	-	10	-	-	-	-
Iannitti [79] (2007)	2004-2006	11	-	19	-	-	3.6	-	-	-	-	-	-	-
Jakobs [27] (2009)	1999-2006	43	57	37	18	-	2.09	2.6	-	-	-	11	21	2
Kumler [80] (2015)		32	54	37.2	15	-	-	-	-	26	-	4	19	26
Lawes [81] (2006)	1994-2004	19	52	-	11	-	3	2.9	-	-	-	-	2	-
Lee [82] (2013)	2002-2011	10	46.5	29	4	-	2.4	-	-	5	5	3	6	-
Livraghi [83] (2001)	1996-1999	24	51.5	11.8	8	-	1.9	-	-	-	-	-	-	-
Mack [84] (2004)	1993-2002	232	54.4	10	72	-	-	2.5	45.6	-	-	-	-	-
Meloni [85] (2009)	1996-2008	52	55	31.2	-	22	2.5	1.7	-	-	-	-	-	-

Seidensticker [86] (2015)		59	57.4	16.14	29	-	4.9	13	26.5	49	-	20	40	22
Sofocleous [87] (2007)	1999-2005	12	55	29.4	10	9	-	-	83	3	2	4	-	-
Tasci [88] (2013)	1996-2011	24	51	24	-	22	3.7	2.4	26.5	6	4	6	19	-
Veltri [89] (2014)	1998-2011	45	56	-	18	-	2.3	1.9	-	-	-	-	-	-
Wieners [90] (2011)	-	41	55	18	19	-	4.4	-	-	23	18	14	14	-
Zhang [91] (2014)	2009-2012	17	-	15	7	14	3.5	2.3	30	10	6	8	11	8
EHD-Extrahepatic Disease; IDC-Invasive Ductal Carcinoma														

Table 2: Study Characteristics-Ablative Therapy.

Data were extracted from the 67 studies that collectively evaluated 2,269 patients with median age 49.6 years (range 45.2-62.5). Follow-up time ranged from 10-62 months with a mean of 32.5 months. Most common tumor histology was invasive ductal carcinoma (74.5%). Extrahepatic disease was present in 32.0% of patients overall. Table 3a and 3b describe the primary outcomes of interest among the SR group, while Table 4 describes the primary outcomes of interest among the AT group.

Study (Year Published)	Study Years	No. of Cases (n)	Mean Follow-up (months)	Median Disease-free Survival (months)	Median Overall Survival (months)	1-year OSR (%)	2-year OSR (%)	3-year OSR (%)	5-year OSR (%)	Local Recurrence (%)	Complication Rate (%)	Mortality Rate (%)
Abbott [28] (2012)	1997-2010	86	62	14	57	-	-	-	-	0	20.93	0
Adam [29] (2006)	1984-2004	108	38	15	-	-	-	-	37	48	19.44	0
Arena[30] (2004)	-	17	-	-	43	92	85	52	41	53	35.29	0
Bacalbasa[31] (2014)	2002-2013	43	-	-	32.2	93.02	-	74.42	58.14	-	16.28	0
Belda[32] (2010)	1998-2008	21	31	-	-	67	-	-	23	-	0	4.76
Caralt[33] (2008)	1988-2006	12	35.9	-	35.9	100	-	79	33	58.3	16.67	0
Carlini[34] (2002)	-	19	-	-	53	-	-	-	46	-	10.53	0
Cordera[35] (2005)	1988-1998	10	-	-	-	-	-	-	-	-	-	2
D'Annibale[36] (2005)	1984-1999	26	-	-	36	-	-	-	30	-	19.23	0
Duan[37] (2012)	1996-2008	16	-	-	67	-	-	53.3	43.8	-	-	-

Elias[38] (2003)	1986-2000	54	32	-	34	-	-	50	34	-	12.96	0
Ercolani[39] (2005)	1990-2003	21	-	-	41	-	-	53.9	24.6	-	19.05	0
Furka[40] (2008)	-	17	-	-	-	-	-	-	-	-	11.76	0
Groeschl [41] (2012)	1990-2009	115	31	22	52	79	-	52	27	64	-	-
Hoffmann[42] (2010)	1999-2008	41	34	34	58	-	-	-	48	21.9	43.9	0
Kollmar [43] (2008)	-	27	-	-	-	-	-	-	50	-	0	0
Kondo [44] (2000)	1990-1999	6	-	-	36	-	-	60	40	-	0	0
Kostov [11] (2013)	2000-2006	42	60	29.4	43	84.6	-	64.1	38.5	41	0	2.38
Lang[45] (1999)	1983-1993	34	-	-	20	-	-	-	29	-	-	-
Lehner[46] (2009)	1994-2008	57	-	-	36	-	-	52	30	-	-	-
Lendoire [47] (2007)	1989-2006	19	28	-	-	-	-	-	53	-	-	-
Lorenz [48] (1995)	1982-1991	8	-	-	15	-	-	-	12	-	-	-
Lubrano [49] (2008)	1989-2004	16	28	-	42	94	-	61	33	56	-	-
Maksan [50] (2000)	1984-1998	9	29	-	-	-	-	-	51	55.5	0	0
OSR-Overall Survival Rate												

Table 3a: Oncologic Outcomes-Surgical Resection.

Study (Year Published)	Study Years	No. of Cases (n)	Mean Follow-up (months)	Median Disease-free Survival (months)	Median Overall Survival (months)	1-year OSR (%)	2-year OSR (%)	3-year OSR (%)	5-year OSR (%)	Local Recurrence (%)	Complication Rate (%)	Mortality Rate (%)
Martinez[51] (2006)	1995-2004	20	39	-	32	-	61	-	33	-	-	0
Okaro[52] (2005)	1996-2002	8	-	-	31	-	-	-	-	-	0	0
Pocard[53] (2001)	1988-1999	65	41	-	36	90	-	71	-	29.2	9.23	0
Polistina[54] (2013)	2004-2011	26	22.5	-	15.5	80.7	57	-	31	-	15.38	0
Raab[55] (1998)	1983-1994	34	-	-	27	-	-	50	18.4	-	-	2.94
Reddy[56] (2007)	1995-2005	20	-	24	67	-	-	-	-	-	40	-
Rubino[57] (2010)	-	20	-	66	74	88	88	76	60	55.5	10	-
Sadot[58] (2016)	1991-2014	167	31	-	50	-	-	-	38	-	23	0
Sakamoto[59] (2005)	1985-2003	34	72	-	36	96	-	52	21	76.5	-	-
Santoro[60] (2000)	1990-1998	15	-	-	44	-	-	-	38.3	-	-	-
Schneebaum[61] (1994)	-	8	-	-	42	-	-	-	-	-	-	-

Seifert[62] (1999)	1985-1997	15	12	-	57	100	71	53.6	-	40	20	0
Selzner[63] (2000)	1987-1999	19	17	-	24	-	-	35	22	70.6	5.26	5.26
Stehlin[26] (1988)	-	9	--	-	28	-	-	-	11	-	-	-
Thelen[64] (2008)	1988-2006	39	-	-	74	92	-	68	61	-	12.82	0
Treska[65] (2014)	2000-2013	22	-	-		-	-	-	34	-	-	-
Van Walsum[66] (2012)	1994-2010	32	26	-	55	-	-	-	37	59.3	34.38	0
Vlastos [67] (2004)	1991-2002	31	-	-	63	-	86	-	61	-	-	0
Weinrich [68] (2014)	2001-2007	24	22	-	53	-	81	-	33	-	12.5	0
Weitz [69] (2005)	1981-2002	29	-	-	48	-	-	-	-	-	10.34	0
Ye[70] (2015)	2003-2013	28	54	-		-	-	-	53	-	42.86	0
Yedibela [71] (2005)	1978-2001	24	-	-	33	-	58	-	43	-	-	-
Yoshimoto[72] (2000)	1985-1998	25	-	24	34.3	-	71	-	27	-	0	0
Zegarac [73] (2013)	2006-2009	32	37	22.5	37	-	-	-	-	-	-	-
Weighted Average			**35.6**	**22.8**	**43.7**	**86.8**	**70.6**	**58.3**	**36.8**	**51.4**	**17.7**	**0.37**
OSR-Overall Survival Rate												

Table 3b: Oncologic Outcomes (Continued)-Surgical Resection.

Study (Year Published)	Study Years	No. of Cases (n)	Mean Follow-up (months)	Median Disease-free Survival (months)	Median Overall Survival (months)	1-year OSR (%)	2-year OSR (%)	3-year OSR (%)	5-year OSR (%)	Local Recurrence (%)	Complication Rate (%)	Mortality Rate (%)
Abe[74] (2005)	2000-2004	8	29.5	-	-	-	62.5	-	-	-	0	0
Barral[75] (2016)	2000-2014	79	18.4	14.2	-	98.3	95.5	-	-	-	15.2	0
Carrafiello [76] (2011)	2003-2007	13	12.9	16.6	10.9	-	-	67		-	0	0
Collettini [77] (2012)	2008-2010	37	11.6	8	18	-	-	-	-	2.6	2.7	0
Gunabushanan[78] (2007)	2002-2005	14	18	19	-	64	-	-	-	14	-	-
Iannitti[79] (2007)	2004-2006	11	19	-	-	45	-	-	-	2.7	0	2.3
Jakobs[27] (2009)	1999-2006	43	37	-	58.6	-	-	-	38	16.3	6.9	0
Kumler[80](2015)		32	-	45	33.5	87	68	48	-	22	-	-
Lawes[81] (2006)	1994-2004	19	29	9	-	-	-	41	-	-	0	0
Lee[82] (2013)	2002-2011	10	11.8	48	16	-	-	-	-	20	-	-
Livraghi[83] (2001)	1996-1999	24	10	-	-	63	-	-	-	41	0	0
Mack[84] (2004)	1993-2002	232	31.2	-	50	96	80	63	41	6.5	3	0
Meloni[85] (2009)	1996-2008	52	37.2	-	29.9	68	-	43	27	-	9.6	0
Seidensticker[86] (2015)		59	16.14	45	21.9	-	-	-	-	-	-	-
Sofocleous [87] (2007)	1999-2005	12	29.4	12	60	-	-	70	30	41	0	0
Tasci [88] (2013)	1996-2011	24	24	9	48	-	-	-	29	41.6	-	-
Veltri[89] (2014)	1998-2011	45	-	-	-	90	58	43.9	-	18	20	0
Wieners[90] (2011)	-	41	18	-	-	79	-	-	-	-	-	-
Zhang[91] (2014)	2009-2012	17	15	-	-	70.6	-	-	-	-	88.2	0
Weighted Average			**21.7**	**23.4**	**40.6**	**87.3**	**79.3**	**56.4**	**37.5**	**13.9**	**8.8**	**0.04**
OSR-Overall Survival Rate												

Table 4: Oncologic Outcomes-Ablative Therapy.

Results of Patients Undergoing Surgical Resection

Forty-eight studies evaluated 1,497 patients undergoing SR for BCLM with median age 49.3 years. Mean follow-up time ranged from 12-60 months with a mean of 35.6 months. Twenty-five studies reported on the presence or absence of EHD in 901 patients undergoing SR, with 17.2% of patients with demonstrated evidence of EHD. Weighted-averages for median length of OS and DFS were 43.2 and 22.8 months, respectively, among the SR group. Local recurrence was 51.4%, while CR and MR were 17.7% and 0.37%, respectively. OSR at 1, 2, 3 and 5 years were 86.8%, 70.6%, 58.3% and 36.8%, respectively. Among SR patients, the weighted-average for length of OS among patients with EHD was 43.2 months compared to 37.6 months among patients without EHD (p=0.68).

For studies evaluating patients undergoing surgical resection through the 1990s, 2000s and 2010s, median length of OS and DFS was 47.2, 36.6 and 47.5 years (p=0.104), and 24.0, 24.6 and 14.0 years (p=0.399), respectively; LR was 53.3%, 52.6%, 53.1% (p=0.959); CR was 14.3%, 13.0% and 15.6% (p=0.370); and MR was 0.3%, 0.17% and 0.0% (p=0.514). OSR for studies ending in the 1990s, 2000s and 2010s was 94.7%, 86.4% and 86.9% at 1 year (p=0.541), 66.7%, 76.0% and 57.0% at 2 years (p=0.362); 54.7%, 59.0%, 74.4% at 3 years (p=0.250); and 31.3%, 37.9% and 42.8%, respectively (p=0.160).

Results of Patients Undergoing Ablative Therapy

Nineteen studies evaluated 772 patients undergoing AT for BCLM with median age 53.3 years and mean follow-up time 21.7 years (range 10-29.5 months). Fifteen studies reported on the presence or absence of EHD in 648 patients undergoing AT, with 39.5% of patients having evidence of EHD. Weighted-averages for median length of OS and DFS were 40.6 months and 23.4 months among the AT group. Local recurrence was 13.9%, while CR and MR were 8.8% and 0.04%, respectively. OSR at 1, 2, 3 and 5 years were 87.3%, 79.3%, 56.4% and 37.5%.

For studies evaluating patients undergoing ablative therapy through the 2000s versus 2010s, median length of OS and DFS was 41.9 versus 27.5 months (p=0.233) and 14.2 versus 27.5 months (p=0.142), respectively; LR was 16.1% versus 20.8% (p=0.618); CR was 3.87% versus 37.0% (p=0.332); and MR was 0.26% versus 0.0% (p=0.230), respectively. OSR for studies ending in the 2000s versus 2010s was 74.3% versus 82.5% at 1 year (p=0.581); 79.3% versus 63.0% at 2 years (p=0.294); 56.8% versus 46.0% at 3 years (p=0.159), and 34.0% versus 29.0% at 5 years (p=546), respectively.

Discussion

Metastatic BC treatment is usually palliative with the goal to improve quality of life and prolong survival. Between 60-95% of BCLM patients have disease progression while on systemic therapy with multiple chemotherapeutic agents [18]. Metastatic BC treatment has historically involved 5-fluorouracil or anthracycline-based regimens as first-line or adjuvant chemotherapy [19]. Other agents such as taxanes and vinorelbine have been added with significant benefit. Currently taxanes and anthracyclines are used by many as first-line treatment, with response rates up to 40% when used alone and up to 80% when used in combination regimens in selected patient populations [20-22].

A phase III multicenter European Organization for Research and Treatment of Cancer (EORTC) trial previously examined the efficacy of paclitaxel vs doxorubicin, as well as doxorubicin/paclitaxel vs doxorubicin/cyclophosphamide as first-line chemotherapy regimens for management of patients with metastatic BC. The median OS for BCLM patients without EHD ranged from 22.7-27.1 months, while the median OS for BCLM patients with EHD ranged from 14.2-16.8 months from these trials.[18] Another recent study evaluating patients with advanced HER2/neu-negative BC undergoing systemic chemotherapy still found a relatively low median OS of 20 months for BCLM patients [23].

Similarly, the CLEOPATRA trial evaluated pertuzumab/trastuzumab/docetaxel compared to placebo/trastuzumab/docetaxel in patients with HER2-positive metastatic BC [24]. Median progression-free survival was 12.4 months in the placebo group and 18.7 months in the pertuzumab group [24]. More recently, the PALOMA-3 trial looking at palbociclib/fulvestran found a significant and consistent improvement in progression-free survival compared with fulvestrant/placebo. The reported median progression-free survival was 9.5 months in the fulvestrant/palbociclib group versus 4.6 months in the fulvestrant/placebo group (p<0·0001) [25]. Although occasional high response rates with such chemotherapy regimens have been reported, the duration of response demonstrated in the aforementioned studies has been consistently short-lived, and prognosis remains poor. The outcome for non-responders with BCLM is considered much worse. Previous studies have reported an OS of non-responders as low as three months with no patients surviving longer than eighteen months [26].

Given that BC is the most common malignancy affecting women worldwide and liver metastases develop in up to half of all women with metastatic BC, patients may benefit clinically from a more aggressive multimodality treatment approach. Our review aims to specifically examine the current literature on outcomes data for surgical and ablative management of BCLM.

Among all studies, we found relatively high rates of DFS and OS, including high OSR at 1, 2, 3 and 5 years for both SR and AT. The median OS of 43.2 months and 40.6 months found among patients undergoing SR and AT, respectively, in our systematic review is nearly twice, or more than twice, that of patients going systematic therapy alone in the aforementioned trials. Among 5 studies in the SR group that reported a mean OS greater than or equal to 5 years, the majority of breast cancer patients had invasive ductal carcinoma, solitary metastasis, size of primary tumor less than or equal to 5 cm, size of the largest metastasis less than 5 cm, time to liver metastases greater than 12 months, and negative liver resection margins. In the one study in the AT group that reported mean OS greater than or equal to 5 years, the majority of patients had invasive ductal carcinoma, size of liver metastases less than 4cm, and time to liver metastases greater than 12 months. In

studies with mean OS greater than or equal to 5 years in both the SR and AT groups, the majority of patients had undergone systemic adjuvant chemotherapy.

Similar to OS, the median DFS, 22.8 and 23.4 months, among patients in our systematic review undergoing SR and AT, respectively, are longer than the progression-free survival times found in the aforementioned studies. Of note, the mean time to the development of liver metastasis among patients undergoing SR was 42.2 months, while mean time to the development of liver metastasis among patients undergoing AT was 48.5 months. Therefore, we demonstrate SR and AT offer BCLM patients the opportunity for alternative therapies that prolong survival and improve their prognosis longer than available chemotherapy regimens currently offer them.

Complication rates in our systematic review are also lower than in previously reported studies of patients undergoing systemic chemotherapy. In the CLEOPATRA trial, complications were reported in 29% who received placebo versus 36% in the pertuzumab group [24]. The PALOMA-3 trial reported a 73% adverse event rate in the palbociclib/fulvestrant group [25]. In comparison, we report a lower CR of 17.7% and 8.8% for patients undergoing SR and AT, respectively. Complication rates such as bile leak/injury, pleural effusion and bleeding were among the most commonly reported. The mortality rate was also low in both treatment groups. The results of our study suggest that hepatectomy and/or ablation are beneficial and safe in patients with BCLM either alone or as adjuncts to systemic therapy, leading to improved oncologic outcomes, as compared to those who undergo systemic treatments alone.

Our systematic review demonstrates lower LR rates for AT compared to SR. The implications of this difference remain unclear, although it may be attributable to the significant number of SR patients in the included studies that did not achieve R0 on resection. However, OSR for SR and AT were ultimately comparable. Regardless, both treatment modalities demonstrated relatively low morbidity and mortality thus encouraging the utility of SR and AT treatment options for BCLM.

Despite advances in management of breast cancer in the last 5 to 10 years, our study did not show a statistically significant difference in any of the measures of oncologic safety studied (OS, DFS, LR, CR, MR) between studies examining patients through the 1990s versus 2000s versus 2010s for the SR or AT groups. This finding could be due to the fact that many of the studies recruited and collectively reported on patients over a 10 to 20-year time period spanning multiple decades from the 1980s to 2010s, and thus we do not have an effective means to compare measures of oncologic safety among patients treated by older versus more recent techniques in this systematic review.

With regard to SR specifically, although some studies included cases without EHD, a significant proportion of the reviewed studies included cases with EHD. The presence of EHD complicates the decision process for whether surgical resection for curative intent is the most appropriate management for BCLM. In the past, the presence of multiple lesions may have been considered a limiting factor to SR. However, many studies selected for our systematic review included patients with multiple lesions, and many required major hepatectomy with resection of greater than three segments. Our analysis, however, did not show a statistically significant difference for OS between those undergoing SR with and without EHD. As a result, the presence of EHD should not be a limiting factor preventing patients from undergoing SR. In addition, the median age of patients undergoing SR in our review was 49.3 years, demonstrating the fairly young age of the studied population in which aggressive surgical treatment for curative purposes should most certainly be offered.

Few studies specified the appropriate candidates for surgical resection and ablative therapy. Among studies that commented on patient selection criteria, appropriate SR candidates were described as patients with good performance status, patients in whom feasibly complete and safe resection of liver tumour could be achieved with most patients. Tumour size was not mentioned as a specific criterion and most studies did not report it. Among studies that did comment on tumour size, the mean size ranged from 1-4cm. Patients who underwent AT were those deemed surgically unresectable either technically or due to impaired patient tolerance for major liver surgery. The mean tumor size for the AT group was not much larger than those in the SR group with a range from 1-4.9cm. AT procedures were performed usually using expandable electrodes that were placed under CT-fluoroscopy guidance, although other methodologies have also been described and are not uniformly performed [27].

There were few studies that examined the prognostic factors for longer survival for those undergoing surgical and ablative management of breast cancer liver metastases. These factors included the following: hormone-receptor positivity (i.e. estrogen receptor and/or progesterone receptor), complete oncologic resection, longer disease-free interval, solitary liver metastasis, no tumor recurrence, tumor size < 3 cm, negative axillary lymph node status and a period to metastases development ≥ 24 months and the use of adjuvant chemotherapy and/or radiation. While these factors were individually reported to be associated with longer survival in each study, there was no consensus amongst these few studies on these factors except for two variables: estrogen receptor positive breast cancers and solitary liver metastasis were uniformly reported to be the prognostic factors for longer survival for patients undergoing surgical and/or ablative management of breast cancer liver metastases.

Our study has some limitations. Many studies had missing data with respect to tumor characteristics and use of adjuvant therapy that may impact the reported oncologic outcomes. The use of observational data also introduces confounding factors, including patient demographics, genetic predisposition, tumor size, specimen weight, nodal status, hormonal status, and neoadjuvant and/or adjuvant therapy, that may bias oncologic outcomes in certain studies, but cannot be accounted for in a systematic review. Finally, the methodology utilized in a systematic review includes many retrospective studies. As a result, our systematic review is

not adequate to determine causality. Large randomized controlled trials are necessary to further evaluate the oncologic safety of SR and AT for patients with BCLM versus standard systemic therapy alone.

Despite the limitations described above, our study has specific strengths. Through a rigorous and transparent literature review, we have identified, synthesized and assessed all available evidence to demonstrate the oncologic safety of SR and AT for breast cancer liver metastasis. As a result, our study is the largest comprehensive literature review on the surgical and ablative management of BCLM to date. The large representative sample of 2,269 patients in 67 studies enhances our study's external validity. Our results are likely generalizable to women with breast cancer with isolated liver metastasis highlighting the importance of careful patient selection.

Conclusion

Historically, patients with BCLM undergoing systemic therapy have had a poor prognosis with fairly short survival times. Surgical and ablative therapies for BCLM provide alternative modalities to improve prognosis, as demonstrated by the relatively favorable overall and disease-free survival with low morbidity and mortality among the SR and AT groups in our study. The integration of localized surgical and ablative therapies with previously established options for management of BCLM, namely systemic chemotherapy, promises encouraging results in terms of overall and disease-free survival. While a clinical trial would provide a higher level of evidence for support of SR and AT for localized management of BCLM, a clinical trial may not be feasible and surgery and ablative therapy should still be highly considered for select patients with BCLM.

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Synopsis: A systematic literature review reveals both surgical and ablative management of breast cancer liver metastasis yield favorable overall and disease-free survival with low morbidity and mortality.

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