



# Patterns and kinetics of hepatocellular carcinoma relapse post-liver transplantation: oligorecurrence and role of local therapies

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**Background:** Amongst patients with recurrent hepatocellular carcinoma (HCC) post-liver transplantation, systemic therapy options may be limited by immunosuppression or poor performance status. Thus, we aimed to assess the impact of metastasis-directed therapy to all sites of disease (MDT-All) in HCC patients with limited disease recurrence [i.e., oligorecurrence (oligoM1)] post-transplantation and characterize pre-transplant characteristics associated with oligoM1.

**Methods:** In this retrospective cohort study, patients at a single institution with recurrent HCC post-liver transplantation were identified. OligoM1 disease was defined as  $\leq 3$  lesions at recurrence, while polyrecurrent (polyM1) disease was defined as  $> 3$  lesions. Outcomes were compared in patients with oligoM1 disease by receipt of MDT-All. Regression analyses were used to identify predictors of polyM1 disease and characteristics associated with post-recurrence outcomes.

**Results:** Forty-three patients with recurrent HCC post-liver transplantation from 2005–2022 were identified. Twenty-seven (63%) patients had oligoM1. Microvascular invasion was independently associated with polyM1 [odds ratio (OR): 14.64; 95% confidence interval (CI): 1.48–144.77;  $P=0.022$ ]. Elevated alpha-fetoprotein (AFP)  $\geq 400$  ng/mL [hazard ratio (HR): 2.44; 95% CI: 1.08, 5.52;  $P=0.033$ ] at recurrence was independently associated with inferior overall survival (OS), while oligoM1 (HR: 0.42; 95% CI: 0.21, 0.87;  $P=0.018$ ) was independently associated with favorable OS. Amongst patients with oligoM1 who received MDT-All ( $n=15$ ) median OS was 38.4 *vs.* 16.1 months for those who did not receive MDT-All (log-rank  $P=0.021$ ). There was a non-significant improvement in polyprogression-free survival (polyPFS) (median 14.0 *vs.* 10.7 months,  $P=0.1$ ) amongst oligoM1 patients who received MDT-All compared to those who did not.

**Conclusions:** Receipt of MDT-All was associated with improved OS amongst patients with limited HCC disease recurrence following liver transplantation.

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**Keywords:** Hepatocellular carcinoma (HCC); oligometastatic; metastasis-directed therapy (MDT); radiotherapy; liver transplantation; patterns of failure

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## Introduction

Liver transplant is a potentially curative procedure for patients with hepatocellular carcinoma (HCC). Despite use of bridging and downstaging therapies and strict selection criteria, HCC relapse can occur following transplant. Systemic therapy options for patients with relapsed HCC following liver transplantation are limited by functional status and treatment-related toxicity. Immune checkpoint inhibition is infrequently administered to the immunosuppressed, transplanted patient. The benefits of local therapy, also called metastasis-directed therapy (MDT), in the setting of oligometastatic cancer have been studied in prospective, randomized controlled trials in a number of settings, with results from trials conducted in prostate (1,2), lung (3), and mixed disease sites (4) demonstrating that MDT may improve progression-free survival (PFS) or

overall survival (OS). In aggregate, these studies of MDT provide significant evidence of the benefit of MDT across multiple disease sites, but the benefit of MDT may still depend in part upon both the disease site being treated and how the oligometastatic state is defined (5). Thus, there is value in assessing the benefit of local therapies in metastatic disease based upon specific disease sites and specific biological scenarios, such as the post-transplant immunosuppressed state.

No single definition of oligometastatic cancer has been applied across trials or disease sites, although studies commonly restrict the definition to a limited number of grossly evident metastases, (e.g., fewer than 3 to 5 lesions), and often with a requirement that all sites of disease may be treated with local therapies (6). Within the realm of HCC, a number of retrospective studies have attempted to identify cohorts of patients with metastatic HCC who may benefit from local therapies (7-10), which commonly take the form of surgery, radiation therapy, transarterial chemoembolization (TACE), or thermal ablative therapies. To our knowledge, however, no report has attempted to define the oligorecurrent (oligoM1)/oligometastatic state specifically in patients with post-transplant recurrence and to quantify the impact of MDT in this context.

Hence, we aimed to (I) characterize the patterns of HCC recurrence and progression following liver transplantation at a high-volume transplant center, (II) identify pre-transplant characteristics associated with oligoM1 *vs.* polyrecurrence (polyM1); (III) identify clinical characteristics associated with differential outcomes; and (IV) evaluate the impact of MDT on outcomes in patients with limited disease at the time of initial recurrence. We present this article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-541/rc>).

## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Johns Hopkins University institutional

### Highlight box

#### Key findings

- Patients with recurrent hepatocellular carcinoma (HCC) following liver transplantation with  $\leq 3$  foci of recurrence [i.e., oligorecurrence (oligoM1)] had favorable overall survival (OS) outcomes compared to patients with  $\geq 4$  metastases (polyrecurrence). Moreover, amongst oligoM1 patients, receipt of local metastasis-directed therapy to all sites of disease (MDT-All) was associated with improved OS.

#### What is known and what is new?

- Randomized trial data supports the benefit of MDT in patients with limited metastatic cancer (i.e., oligometastasis/oligoM1), but benefit may depend upon patient- and disease-specific characteristics. Patients with HCC recurrence post-transplant have limited systemic therapy options owing to the need for immunosuppression.
- This study is among the first to characterize the potential benefit of MDT in HCC patients with oligoM1 specifically following liver transplantation.

#### What is the implication, and what should change now?

- MDT-All may prolong survival of patients with HCC recurrence post-transplant, providing impetus for prospective study.

review board (No. IRB00344985) and individual consent for this retrospective analysis was waived. A single-institution retrospective review was conducted to identify patients with HCC who received liver transplantation and subsequently experienced disease recurrence. Eligibility for liver transplant was determined using Milan criteria. Following transplant, surveillance involved imaging scans every 2 months for 2 years, then every 6 months thereafter. Imaging scans typically consisted of magnetic resonance imaging (MRI) or computed tomography (CT) of the abdomen and pelvis, and CT chest every 6 months. Baseline demographic and clinical characteristics were recorded. CT, positron emission tomography, and MRI were reviewed to determine radiographic recurrence and subsequent disease progression, which was characterized using RECIST criteria. Any site of recurrence was considered a metastatic lesion. Patients with three or fewer metastases were classified as having oligoM1 disease at the time of recurrence, while patients with more than three metastases were considered to have polyM1 disease. Progression was defined as progression of a previously detected metastasis, including ones previously treated with local or systemic therapy, or the appearance of new metastases. In patients with initial oligoM1 disease, polyPFS was defined as the time from initial recurrence to the polyM1 state or death. OS was the time from initial recurrence to death. Patients who did not experience an event of interest were censored at the time of last clinical follow-up.

Sites of recurrence were categorized into the following anatomical regions: liver, abdominal nodes, lungs, mediastinal nodes, adrenal glands, bone, brain, and peritoneal cavity. Any other recurrences that did not correspond to one of the pre-defined regions were classified as “other”.

MDT was defined as any locally directed therapy administered with the intention of eradication of the site of metastatic disease. For example, surgical resection, stereotactic ablative radiation therapy, radioembolization of metastatic disease were considered MDT, while palliative-intent radiotherapy alone was not considered MDT. In some cases, however, MDT could have both a therapeutic and palliative rationale.

### Statistical analysis

Pre- and post-transplant categorical data are presented as the number and percentage, and continuous data as the median and range. Patients with missing data were excluded from the analysis related to the data in question.

The relationship between clinical variables among the two groups was evaluated using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables, where appropriate. Univariable and multivariable logistic regressions were used to assess the predictive performance of various clinical variables on oligoM1 *vs.* polyM1 recurrence following liver transplantation. Predictive performance was evaluated using the Hosmer-Lemeshow goodness-of-fit test and receiver operating characteristic (ROC) analysis.

Time-to-event outcomes including polyPFS and OS were compared between patients with initial oligoM1 *vs.* polyM1 disease at the time of recurrence using the Kaplan-Meier method. Univariable Cox regression was performed to identify clinical prognostic factors. A multivariable model was constructed based upon statistically significant and clinically relevant covariates in univariable analysis. Model fitness was assessed via chi-square goodness-of-fit test. Further subgroup analysis of patients with oligoM1 disease stratified by receipt of MDT to all sites of disease (MDT-All) was also conducted using the Kaplan-Meier method. In all multivariable regressions collinearity and dependency were examined and variables showing a high level of correlation and dependency were removed from the final model. Statistical analyses were performed using IBM SPSS Statistics (version 28.0) and Stata Statistical Software: Release 17 (StataCorp LLC, College Station, TX, USA). A *P* value <0.05 was set as the threshold for statistical significance in all analyses.

## Results

Three hundred and ninety-seven patients with HCC who underwent liver transplantation at our institution were reviewed, of whom 43 (11%) patients experienced HCC recurrence between 2005 and 2022. The median follow-up time was 8.4 (range, 1.6–173.5) months. At the time of recurrence, 16 (37%) patients presented with >3 metastases (polyM1 disease), while 27 (63%) presented with ≤3 metastases (oligoM1 disease). *Table 1* shows baseline demographic and clinical characteristics of the two groups. There was no significant difference in the time to recurrence between patients with oligoM1 and polyM1 disease (median 10.6 *vs.* 11.3 months, *P*=0.9). The regions of first recurrence were liver (*n*=14), abdominal nodes (*n*=14), lungs (*n*=11), mediastinal nodes (*n*=4), adrenals (*n*=3), brain (*n*=1), and peritoneal cavity (*n*=1). Eighteen (42%) patients received systemic therapy after recurrence, consisting of

**Table 1** Baseline demographic and clinical characteristics in the overall cohort (n=43) and stratified by polyM1 (>3 metastases; n=16) and oligoM1 (≤3 metastases; n=27) disease at initial recurrence

| Characteristics                            | PolyM1 (n=16)     | OligoM1 (n=27)    | Overall (n=43)    | P value |
|--|-------------------|-------------------|-------------------|---------|
| Age (years)                                | 58.9 [44.3, 70.7] | 63.2 [46.6, 72.4] | 61.7 [44.3, 72.4] | 0.34    |
| Sex  |                   |                   |                   | 0.688   |
| Male                                       | 14 (87.5)         | 21 (77.8)         | 35 (81.4)         |         |
| Female                                     | 2 (12.5)          | 6 (22.2)          | 8 (18.6)          |         |
| Race                                       |                   |                   |                   | 0.648   |
| White                                      | 12 (75.0)         | 17 (63.0)         | 29 (67.4)         |         |
| Black                                      | 4 (25.0)          | 8 (29.6)          | 12 (27.9)         |         |
| Asian                                      | 0 (0.0)           | 2 (7.4)           | 2 (4.7)           |         |
| ECOG PS at recurrence                      |                   |                   |                   | 0.739   |
| 0 to 1                                     | 10 (62.5)         | 19 (70.4)         | 29 (67.4)         |         |
| 2 and above                                | 6 (37.5)          | 8 (29.6)          | 14 (32.6)         |         |
| Number of metastatic lesions at recurrence | 8 [4, 47]         | 1 [1, 3]          | 2 [1, 47]         | <0.001  |
| Number of metastatic sites at recurrence   |                   |                   |                   | 0.002   |
| 1  | 5 (31.3)          | 22 (81.5)         | 27 (62.8)         |         |
| 2  | 8 (50.0)          | 5 (18.5)          | 13 (30.2)         |         |
| 3  | 2 (12.5)          | 0 (0.0)           | 2 (4.7)           |         |
| 4  | 1 (6.3)           | 0 (0.0)           | 1 (2.3)           |         |
| AFP at recurrence (ng/mL)                  | 166.85            | 26.4 [1.8, 3,864] | 34 [1.2, 365,210] | 0.332   |
| AFP ≥400 ng/mL                             | 5/14 (35.7)       | 6/26 (23.1)       | 11/40 (27.5)      | 0.469   |
| MDT modality                               |                   |                   |                   | 0.019   |
| Cryoablation                               | 0 (0.0)           | 2 (7.4)           | 2 (4.7)           |         |
| IMRT                                       | 0 (0.0)           | 2 (7.4)           | 2 (4.7)           |         |
| MWA  | 0 (0.0)           | 2 (7.4)           | 2 (4.7)           |         |
| MWA, SBRT                                  | 0 (0.0)           | 1 (3.7)           | 1 (2.3)           |         |
| SBRT                                       | 0 (0.0)           | 6 (22.2)          | 6 (14.0)          |         |
| SRS  | 0 (0.0)           | 1 (3.7)           | 1 (2.3)           |         |
| Surgery                                    | 0 (0.0)           | 2 (7.4)           | 2 (4.7)           |         |
| Surgery + palliative PORT                  | 0 (0.0)           | 1 (3.7)           | 1 (2.3)           |         |
| TACE                                       | 1 (6.3)           | 0 (0.0)           | 1 (2.3)           |         |
| Y90  | 1 (6.3)           | 0 (0.0)           | 1 (2.3)           |         |
| Sites of first failure <sup>†</sup>        |                   |                   |                   |         |
| Liver                                      | 9 (56.3)          | 5 (18.5)          | 14 (32.6)         | 0.018   |
| Lungs                                      | 8 (50.0)          | 3 (11.1)          | 11 (25.6)         | 0.01    |
| Abdominal nodes                            | 5 (31.3)          | 9 (33.3)          | 14 (32.6)         | >0.99   |

Table 1 (continued)

Table 1 (continued)

| Characteristics    | PolyM1 (n=16) | OligoM1 (n=27) | Overall (n=43) | P value |
|--------------------|---------------|----------------|----------------|---------|
| Bone               | 4 (25.0)      | 6 (22.2)       | 10 (23.3)      | 0.835   |
| Mediastinal nodes  | 2 (12.5)      | 2 (7.4)        | 4 (9.3)        | 0.621   |
| Adrenals           | 1 (6.3)       | 2 (7.4)        | 3 (7.0)        | >0.99   |
| Peritoneal cavity  | 1 (6.3)       | 0 (0.0)        | 1 (2.3)        | 0.372   |
| Brain              | 0 (0.0)       | 1 (3.7)        | 1 (2.3)        | >0.99   |
| Other <sup>‡</sup> | 1 (6.3)       | 2 (7.4)        | 3 (7.0)        | >0.99   |

Data are presented as median [range] or n (%). †, patients could have multiple sites of first recurrence; ‡, other sites include perirectal nodes, broad ligament of the uterus, kidney, and abdominal wall. PolyM1, polyrecurrent; oligoM1, oligorecurrent; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AFP, alpha-fetoprotein; MDT, metastasis-directed therapy; IMRT, intensity-modulated radiation therapy; MWA, microwave ablation; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; PORT, post-operative radiation therapy; TACE, transarterial chemoembolization; Y90, Yttrium-90 radioembolization.

sorafenib alone (n=11), lenvatinib or cabozantinib (n=6), and gemcitabine/cisplatin (n=2) as either first or second-line therapy.

Nineteen (44%) patients received MDT, including seven patients who received stereotactic ablative radiotherapy, and two who received conventionally-fractionated radiotherapy to a definitive dose. The majority of patients receiving MDT had oligoM1 disease at recurrence (18/20; 90%).

#### *Association of pre-transplant characteristics with extent of recurrence*

Among the pre-transplant clinical variables, age, sex, and baseline HCC status (i.e., within or not within Milan criteria) before transplant were similar between the oligoM1 and polyM1 groups (Table 2). The number of loco-regional treatments of HCC prior to transplant appeared to have no statistically significant impact on oligoM1 or polyM1 recurrence. Transplant waitlist duration for the polyM1 group (266 days) was longer than that of the oligoM1 group (199 days) but this difference was not statistically significant. Those with oligoM1 recurrence more frequently had low pre-transplant alpha-fetoprotein (AFP;  $\leq 100$  ng/mL) compared to those with polyM1 (P=0.043). Explant pathology showed that a greater proportion of patients with polyM1 than those with oligoM1 had microvascular invasion (94% vs. 41%, P=0.001) and poor cellular differentiation of their transplant specimen (50% vs. 12%, P=0.0081). There was no difference between the two groups when comparing necrosis status of the largest lesion, the number of lesions, or the area of the largest lesion (Table 2).

Regression analyses (Table 3) showed the following pre-treatment clinical variables to be independent predictors of polyM1 recurrence: AFP level before transplantation  $>100$  ng/mL (OR: 4.40; 95% CI: 1.11–17.48), poor cellular differentiation (OR: 7.33; 95% CI: 1.549–34.695) and presence of microvascular invasion in the explanted liver (OR: 21.82; 95% CI: 2.50–190.12). However, in multivariable analysis, only microvascular invasion predicted for polyM1 recurrence.

#### *OligoM1 vs. polyM1 disease at initial recurrence*

Patients with oligoM1 disease had superior OS compared to patients with polyM1 disease at the time of recurrence with a median survival of 16.2 (95% CI: 11.3, 21.1) vs. 4.0 (95% CI: 1.4, 6.6) months (log-rank P=0.001; Figure 1), and 3-year OS rates of 28.4% vs. 6.3%. Amongst patients with oligoM1 disease, an AFP level  $\geq 400$  ng/mL at recurrence was associated with a median OS of 9.5 (95% CI: 4.5, 14.6) compared to 17.7 (95% CI: 16.1, 19.4) months for patients with AFP  $<400$  ng/mL (log-rank P=0.015).

#### *Association of clinical characteristics with survival*

Among all patients with HCC recurrence (Table 4), AFP  $\geq 400$  ng/mL at recurrence was associated with inferior OS [hazard ratio (HR): 2.63; 95% CI: 1.17, 5.91; P=0.02] while oligoM1 disease (HR: 0.34; 95% CI: 0.17, 0.68; P=0.002) and receipt of MDT-All (HR: 0.37; 95% CI: 0.17, 0.81; P=0.012) were associated with improved OS. Age, sex, race, and Eastern Cooperative Oncology Group

**Table 2** Clinical characteristics of patients who had recurrence after liver transplantation (n=43)

| Characteristics                                 | OligoM1 (n=27)    | PolyM1 (n=16) | P value |
|---|-------------------|---------------|---------|
| Age (years)                                     | 61 [45–72]        | 58 [44–69]    | 0.5374  |
| Baseline HCC within Milan criteria <sup>†</sup> |                   |               | >0.99   |
| No  | 6 [22]            | 3 [19]        |         |
| Yes   | 21 [78]           | 13 [81]       |         |
| AFP before transplant (ng/mL)                   |                   |               | 0.043   |
| >100  | 5 [19]            | 8 [50]        |         |
| ≤100  | 22 [81]           | 8 [50]        |         |
| Listing to transplant (days)                    | 199 [1–936]       | 266 [6–1,929] | 0.3124  |
| Number of TACE before transplant                |                   |               | 0.719   |
| >2  | 7 [26]            | 3 [19]        |         |
| ≤2  | 20 [74]           | 13 [81]       |         |
| Explant pathological examination                |                   |               |         |
| Cellular differentiation                        | n=25 <sup>‡</sup> |               | 0.0081  |
| Poor  | 3 [12]            | 8 [50]        |         |
| Moderate/well                                   | 22 [88]           | 8 [50]        |         |
| Microvascular invasion                          |                   |               | 0.001   |
| Yes   | 11 [41]           | 15 [94]       |         |
| No  | 16 [59]           | 1 [6]         |         |
| Necrosis status of largest lesion               |                   |               | >0.99   |
| Partial   | 21 [78]           | 13 [81]       |         |
| Complete  | 6 [22]            | 3 [19]        |         |
| Number of lesions                               |                   |               | >0.99   |
| >3  | 10 [37]           | 6 [38]        |         |
| ≤3  | 17 [63]           | 10 [63]       |         |
| Area of largest tumor (cm <sup>2</sup> )        |                   |               | 0.186   |
| >5  | 16 [59]           | 13 [81]       |         |
| ≤5  | 11 [41]           | 3 [19]        |         |

Data are presented as median [range] or n [%]. <sup>†</sup>, patients outside of Milan criteria were downstaged prior to transplant; <sup>‡</sup>, two patients had no residual viable tumor in the liver specimen. OligoM1, oligorecurrent; polyM1, polyrecurrent; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization.

(ECOG) performance status at the time of recurrence were not associated with OS. Given the expected dependency between the receipt of MDT-All and oligoM1 disease, MDT-All was not included in the multivariable regression model, while elevated AFP and oligoM1 disease were included. Both elevated AFP ≥400 ng/mL (HR: 2.44; 95% CI: 1.08, 5.52; P=0.033) and oligoM1 disease (HR: 0.42;

95% CI: 0.21, 0.87; P=0.018) remained independently associated with OS in multivariable analysis.

#### *Effect of MDT on outcomes in patients with initial oligoM1 disease*

Amongst the 27 patients with oligoM1 disease at recurrence,



**Table 3** Performance of clinical variables in predicting polyM1 disease post-liver transplantation (n=41)

| Characteristics                                 | Univariable         |         | Multivariable       |         |
|---|---------------------|---------|---------------------|---------|
|   | OR (95% CI)         | P value | OR (95% CI)         | P value |
| Cellular differentiation                        |                     |         |                     |         |
| Poor  | 5.25 (1.23–22.39)   | 0.025   | 3.60 (0.64–20.14)   | 0.145   |
| Moderate/well                                   | 1 (reference)       |         |                     |         |
| Tumor necrosis status                           |                     |         |                     |         |
| Partial   | 1.24 (0.26–5.83)    | 0.787   |                     |         |
| Complete  | 1 (reference)       |         |                     |         |
| Microvascular invasion                          |                     |         |                     |         |
| Yes   | 21.82 (2.50–190.12) | 0.005   | 14.64 (1.48–144.77) | 0.022   |
| No  | 1 (reference)       |         |                     |         |
| Number of tumors                                |                     |         |                     |         |
| >3  | 1.02 (0.28–3.66)    | 0.976   |                     |         |
| ≤3  | 1 (reference)       |         |                     |         |
| Area of largest tumor (cm <sup>2</sup> )        |                     |         |                     |         |
| >5  | 2.98 (0.68–12.98)   | 0.146   |                     |         |
| ≤5  | 1 (reference)       |         |                     |         |
| Number of TACE before transplantation           |                     |         |                     |         |
| >2  | 0.66 (0.144–3.02)   | 0.592   |                     |         |
| ≤2  | 1 (reference)       |         |                     |         |
| AFP level before transplantation (ng/mL)        |                     |         |                     |         |
| >100  | 4.40 (1.11–17.48)   | 0.035   | 1.25 (0.23–6.82)    | 0.797   |
| ≤100  | 1 (reference)       |         |                     |         |
| Baseline HCC within Milan criteria <sup>†</sup> |                     |         |                     |         |
| No  | 0.81 (0.17–3.80)    | 0.787   |                     |         |
| Yes   | 1 (reference)       |         |                     |         |

<sup>†</sup>, patients outside of Milan criteria were downstaged prior to transplant. PolyM1, polyrecurrent; OR, odds ratio; CI, confidence interval; TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

15 (55.6%) received MDT-All, 3 (11.1%) received MDT to at least one metastasis, and 9 (33.3%) received no MDT. There was no significant difference in the receipt of systemic therapy, ECOG performance status or AFP at recurrence between MDT-All and MDT to limited or no sites (*Table 5*). Patients who received MDT-All more frequently had liver involvement (5/15, 33.3%) than those who did not receive MDT-All (0/12, 0.0%;  $P=0.047$ ), but otherwise there was no significant difference in the site of metastases between the two groups. Two patients underwent

surgery as part of MDT-All in our cohort. One patient underwent a Whipple resection in the setting of a mass causing extrinsic compression of the common bile duct, with negative margins; this patient subsequently developed polymetastatic recurrence however maintained local control at the resection site. The second patient had a humeral metastasis causing pathological fracture and underwent radical resection with placement of a humeral head prosthesis, followed by post-operative palliative radiation therapy at an outside facility. The patient maintained local





**Table 4** Univariable and multivariable Cox regression analysis of clinical or treatment characteristics predictive of OS from the time of initial recurrence in the overall cohort (n=43)

| Characteristics             | Univariable       |         | Multivariable     |         |
|-----------------------------|-------------------|---------|-------------------|---------|
|                             | HR (95% CI)       | P value | HR (95% CI)       | P value |
| Age                         | 0.99 (0.94, 1.03) | 0.512   |                   |         |
| Sex                         |                   |         |                   |         |
| Male                        | 1 (reference)     | –       |                   |         |
| Female                      | 0.49 (0.17, 1.39) | 0.179   |                   |         |
| Race                        |                   |         |                   |         |
| White                       | 1 (reference)     | 0.432   |                   |         |
| Black                       | 1.62 (0.75, 3.52) | 0.22    |                   |         |
| Asian                       | 0.83 (0.19, 3.56) | 0.803   |                   |         |
| ECOG PS at recurrence       |                   |         |                   |         |
| 0 to 1                      | 1 (reference)     | –       |                   |         |
| 2 and above                 | 1.43 (0.72, 2.85) | 0.306   |                   |         |
| AFP ≥400 ng/mL              |                   |         |                   |         |
| No                          | 1 (reference)     | –       | 1 (reference)     | –       |
| Yes                         | 2.63 (1.17, 5.91) | 0.02    | 2.44 (1.08, 5.52) | 0.033   |
| OligoM1                     |                   |         |                   |         |
| No                          | 1 (reference)     | –       | 1 (reference)     | –       |
| Yes                         | 0.34 (0.17, 0.68) | 0.002   | 0.42 (0.21, 0.87) | 0.018   |
| MDT to all sites            |                   |         |                   |         |
| No                          | 1 (reference)     | –       |                   |         |
| Yes                         | 0.37 (0.17, 0.81) | 0.012   |                   |         |
| Systemic therapy received   |                   |         |                   |         |
| No                          | 1 (reference)     | –       |                   |         |
| Yes                         | 1.07 (0.54, 2.1)  | 0.847   |                   |         |
| Time to recurrence (years)  | 0.98 (0.94, 1.01) | 0.22    |                   |         |
| Liver disease at recurrence |                   |         |                   |         |
| No                          | 1 (reference)     | –       |                   |         |
| Yes                         | 0.91 (0.42, 1.98) | 0.819   |                   |         |

OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AFP, alpha-fetoprotein; oligoM1, oligorecurrent; MDT, metastasis-directed therapy.

Taken together, our study suggests aggressive MDT at initial recurrence may delay disease progression and improve survival in patients presenting with limited recurrence. Moreover, the ongoing long-term survival (>4 years) of multiple patients with oligoM1 recurrence who received MDT-All suggests that MDT may be curative in select

patients.

Additionally, our findings suggest that pre-transplant characteristics, specifically the presence of microvascular invasion and poorly differentiated HCC, are associated with polymetastatic recurrence. A number of clinical factors have previously been identified as a risk factor for

**Table 5** Characteristics of patients with oligoM1 disease (n=27) stratified by receipt of MDT to all metastases

| Characteristics  | Received MDT-All  |                   | Overall (n=27)    | P value |
|--|-------------------|-------------------|-------------------|---------|
|  | No (n=12)         | Yes (n=15)        |                   |         |
| Age (years)  | 58.3 (44.3, 70.7) | 67.3 (44.3, 70.7) | 58.9 (44.3, 70.7) | 0.548   |
| Sex  |                   |                   |                   | 0.182   |
| Male   | 11 (91.7)         | 10 (66.7)         | 21 (77.8)         |         |
| Female   | 1 (8.3)           | 5 (33.3)          | 6 (22.2)          |         |
| Race   |                   |                   |                   | 0.107   |
| White  | 5 (41.7)          | 12 (80.0)         | 17 (63.0)         |         |
| Black  | 6 (50.0)          | 2 (13.3)          | 8 (29.6)          |         |
| Asian  | 1 (8.3)           | 1 (6.7)           | 2 (7.4)           |         |
| ECOG PS at recurrence  |                   |                   |                   | 0.398   |
| 0 to 1   | 7 (58.3)          | 12 (80.0)         | 19 (70.4)         |         |
| 2 and above  | 5 (41.7)          | 3 (20.0)          | 8 (29.6)          |         |
| Number of lesions at recurrence                                  | 2.0 (1.0, 3.0)    | 1.0 (1.0, 3.0)    | 1.0 (1.0, 3.0)    | 0.083   |
| Number of metastatic sites at first failure                      |                   |                   |                   | 0.612   |
| 1  | 10 (83.3)         | 12 (80.0)         | 22 (81.5)         |         |
| 2  | 2 (16.7)          | 3 (20.0)          | 5 (18.5)          |         |
| AFP at recurrence (ng/mL)  | 166.85            | 26.4 (1.8, 3,864) | 34 (1.2, 365,210) | 0.332   |
| AFP ≥400 ng/mL <sup>‡</sup>                                      | 3 (25.0)          | 3 (21.4)          | 6 (23.1)          | >0.99   |
| Site of first failure  |                   |                   |                   |         |
| Liver  | 0 (0.0)           | 5 (33.3)          | 5 (18.5)          | 0.047   |
| Abdominal nodes  | 5 (41.7)          | 4 (26.7)          | 9 (33.3)          | 0.448   |
| Lungs  | 2 (16.7)          | 1 (6.7)           | 3 (11.1)          | 0.569   |
| Mediastinal nodes  | 1 (8.3)           | 1 (6.7)           | 2 (7.4)           | >0.99   |
| Adrenals   | 1 (8.3)           | 1 (6.7)           | 2 (7.4)           | >0.99   |
| Bone   | 3 (25.0)          | 3 (20.0)          | 6 (22.2)          | >0.99   |
| Brain  | 0 (0.0)           | 1 (6.7)           | 1 (3.7)           | >0.99   |
| Other <sup>†</sup>   | 2 (16.7)          | 0 (0.0)           | 2 (7.4)           | >0.99   |
| Peritoneal cavity  | 0 (0.0)           | 0 (0.0)           | 0 (0.0)           | N/A     |
| Time to recurrence (months)                                      | 10.2 (2.7, 32.8)  | 13.8 (0.1, 41.3)  | 10.6 (0.1, 41.3)  | 0.719   |
| Year of recurrence   |                   |                   |                   |         |
| 2005–2016  | 7 (58.3)          | 7 (46.7)          | 14 (51.9)         | 0.704   |
| 2017–2022  | 5 (41.7)          | 8 (53.3)          | 13 (48.1)         |         |
| Initiated systemic therapy prior to polyprogression <sup>‡</sup> | 7 (58.3)          | 4 (28.6)          | 11 (42.3)         | 0.233   |

Data are presented as n (%) or median (range). <sup>†</sup>, other sites include kidney and abdominal wall; <sup>‡</sup>, n=26 for this analysis due to 1 patient in the MDT-All arm with missing data for this characteristic. OligoM1, oligorecurrent; MDT, metastasis-directed therapy; MDT-All, MDT to all sites of disease; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AFP, alpha-fetoprotein; N/A, not available.



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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Johns Hopkins Medicine (No. IRB00344985) and individual consent for this retrospective analysis was waived.

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