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Liver Transplantation Following Yttrium-90 Radioembolization: 15-year Experience in 207-Patient Cohort

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Abbreviations: HCC: hepatocellular carcinoma; **LT:** Liver transplantation **Y90:** Yttrium-90 radioembolization; **MELD**: Model of endstage liver disease; **BCLC:** Barcelona Clinic Liver Cancer; **cTACE:** conventional chemoembolization; **LRT**: locoregional therapy; **OS**: Overall survival; **RFS**: Recurrence-free survival; **TTP:** time-to-progression. **TTR:** Time-to-recurrence; **DSM:** Disease-specific-mortality; **MRI:** gadolinium-enhanced magnetic resonance imaging; **CT:** triphasic contrast-enhanced computerized tomography; **CP:** Child-Pugh; **IQR:** Interquartile range; **KM:** Kaplan-Meier analysis **CI:** 95% Confidence Interval; **ECOG:** Eastern Cooperative Oncology Group; **UNOS:** United Network for Organ Sharing; **AFP:** Alpha fetoprotein; **CTCAE:** Common terminology criteria for adverse events; **DCD:** Donor after cardiac death; **LLD:** Living Liver Donor; **DBD:** Donation after brain death. **ETOH:** Alcoholic cirrhosis; **NASH:** Non-alcoholic steatohepatitis; **PBC:** Primary biliary cirrhosis; **PSC:** Primary sclerosing cholangitis; **HCV:** Hepatitis C virus infection; **HBV:** Hepatitis B virus infection

ABSTRACT

Radioembolization (Y90) is used in hepatocellular carcinoma (HCC) as a bridging as well as downstaging liver directed therapy to curative liver transplantation. In this study we report long-term outcomes of liver transplantation (LT) for HCC patients bridged/downstaged by

Y90. Patients undergoing LT following Y90 between 2004-2018 were included, with staging by United Network of Organ Sharing (UNOS) TNM at baseline pre-Y90 and pre-LT. Post-Y90 toxicities were recorded. Histopathological data of HCC at explant were recorded. Long-term outcomes including overall survival (OS), recurrence-free survival (RFS), disease-specific mortality (DSM) and time-to-recurrence (TTR) were reported. Time-to-endpoint analyses were estimated using Kaplan-Meier. Uni/multivariate analyses were performed using log-rank test and Cox proportional hazards model, respectively. During the 15-year period, 207 patients underwent LT after Y90. OS from LT was 12.5 years, with median time to LT of 7.5 months (IQR: 4.4-10.3). 169 patients were bridged while 38 were downstaged to LT. 94 (45%), 60 (29%) and 53 (26%) patients showed complete, extensive and partial tumor necrosis on histopathology. Three, five and ten-year OS rates were 84%, 77%, and 60% respectively. Twenty-four patients developed recurrence, with median RFS of 120 (95%CI: 69-150) months. DSM at 3, 5 and 10 years was 6%, 11% and 16% respectively. There were no differences in OS/RFS for bridged or downstaged patients. RFS was higher in patients with complete/extensive versus partial tumor necrosis ($p<0.0001$). For UNOS T2 patients treated during the study period, 5.2% dropped out due disease progression. **Conclusion:** Y90 is an effective treatment for HCC in the setting of bridging/downstaging to LT. Patients who achieved extensive or complete necrosis had better RFS, supporting the practice of neoadjuvant treatment prior to LT.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, 5th most common malignancy in males, and the 2nd most common cause of cancer-related mortality.(1) Liver transplantation (LT) is the most effective treatment for HCC and is curative.(2) Mazzaferro has demonstrated 75% 4-year survival following LT and established the Milan criteria(3),(4).

Given the risk of dropout in case of progression beyond T2 stage, many centers have adopted locoregional therapy (LRT) to control HCC and prolong time-to-progression (TTP). Yttrium-90 radioembolization (Y90) has emerged over the past decade as a locoregional therapy with favorable efficacy, safety profile, and quality-of-life outcomes.(5-7) While conventional transarterial chemoembolization (cTACE) is the most commonly used treatment in this setting, there is little data on LT following Y90. A recent phase 2 randomized controlled trial demonstrated significantly longer TTP (>26 months) with Y90 compared to cTACE (6.8 months) (P=0.0012). This was the first level I evidence establishing improved TTP with Y90 over cTACE, and this has led to adoption of Y90 as standard arterial therapy for HCC.(8, 9)

In this study, we report the 15-year follow-up of efficacy and long-term survival of 207 HCC patients undergoing LT after Y90, the largest reported to date.

METHODS

This study was approved by the Northwestern University institutional review board and Health Insurance Portability and Accountability Act compliant. Between 2004 and 2018, 207 patients with unresectable HCC underwent LT after being treated with Y90 radioembolization as part of a bridging or downstaging care pathway. A comprehensive analysis of baseline characteristics at Y90 and LT were performed. Imaging and survival outcomes were also assessed.

Evaluation/Staging

A multidisciplinary team comprised of hepatology, oncology, transplant surgery, and interventional radiology reviewed all patients considered for LT and triaged to Y90 as was the deliberate practice and expertise of the institution. Routine contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) were performed, with HCC diagnosis by guidelines.(10) Liver function was assessed by Child-Pugh (CP) and tumor staging was performed by UNOS and Barcelona Clinic Liver Cancer classification (BCLC).

Y90 Radioembolization

Pretreatment mesenteric angiography and macroaggregated albumin scans were performed to assess vascularity, gastrointestinal flow, and lung shunting fraction. The device used was glass-based (Boston Scientific, Minneapolis, MN); this brachytherapy device approved by the Food and Drug Administration for HCC with or without PVT.(11) Planned administered dose was 120-150 Gy for lobar infusions and >190 Gy for segmental injections.(12, 13)

Follow-up

All patients were followed for any Y90 related toxicities following the National Cancer Institute Common Terminology Criteria v4.0 for 6 months or until LT, and subsequently by transplant hepatology following transplantation.[14] High-risk patients (ex: >T2) were followed with MRI every 6 months for 5 years and non-contrast chest CT every year.

Imaging Analysis

Baseline imaging reads were initially performed by diagnostic radiology. Confirmatory imaging review and tumor staging at Y90 and LT was assessed by interventional radiology (blinded). UNOS staging was based solely on size regardless of enhancement. RECIST 1.1 response status (index lesion) at transplant was included in uni/multivariate analyses to assess its prognostic value in post-transplant outcomes.

Bridging/Downstaging

Bridging was defined as the use of Y90 for tumor control and limiting progression of T1/T2 disease until an organ became available. Downstaging was defined as treatment of >T2 patients (outside the Milan criteria) with the intent of reducing tumor burden to ≤T2 (Milan criteria) at LT.

Liver Transplantation

Given the dearth of published data on transplantation in livers exposed to Y90, surgical parameters encountered intra-operatively were documented, including intra-operative blood loss, organ cold ischemia, and transfusions. Patients underwent post-transplant imaging follow-up per our institutional guidelines, which included ultrasonography and doppler scanning within the first 24 hours post-transplant, then at 14 days, 3, 6, 9, 12 months, followed by yearly scans thereafter. If deemed necessary, CT chest was performed concurrently with other abdominal imaging. Date and site (intra/extrahepatic) of HCC recurrence, when present, were documented.

Liver Explant Analysis

Explant pathology analysis was performed following LT prior to sequestering the liver per our institutional radiation safety expert's policies. Hepatic parenchymal architecture was examined for the presence fibrosis and/or cirrhosis, with all nodules encountered reported as grades 1, 2 and 3 for well, moderately and poorly differentiated HCC, respectively. Necrosis was reported as complete (no viable HCC), extensive (50-99% necrosis) and partial necrosis (<50%).

Overall/Recurrence-free Survival

Overall survival (OS) was calculated from LT until death or last date of follow-up using Kaplan-Meier (KM). Recurrence-free survival (RFS) was calculated from date of LT until date of tumor recurrence, metastases or death. Disease-specific mortality rate (DSMR: defined as death post-LT due to HCC recurrence) was calculated from the day of LT until death from recurrent HCC or metastases or until last follow-up. Time-to-recurrence (TTR) was also estimated using KM. Median follow-up time was calculated using reverse KM.(15, 16)

Uni/Multivariate Analyses

KM univariate analysis was conducted for OS, RFS, DSMR, and TTR with Log-rank test to compare factors including age, sex, Milan Criteria, bridging vs downstaging, and tumor necrosis at transplant. Multivariate analysis (Cox proportional hazards) was conducted for OS and RFS. All statistical analyses were conducted using MedCalc Statistical Software Versions 19.2.1 (Ostend, Belgium), with significance set at $p<0.05$.

RESULTS

Baseline Characteristics at Y90

Table 1 lists the baseline characteristics at the time of Y90. Median age was 60 years (IQR: 56-65). 99 (48%), 91 (44%) and 17 (8%) patients were CP Class A, B and C, respectively. 192 (93%) patients showed imaging signs of cirrhosis, while 15 (7%) were confirmed by biopsy. 9 (4%), 160 (77%), 22 (11%), 12 (6%) and 4 (2%) patients were stage T1, T2, T3, T4a and T4b stages, respectively. 164 (79.5%) patients were treatment-naïve.

Outcomes/Toxicities Following Y90

117 (57%) patients were listed for LT at Y90; while 90 (43%) were listed following Y90 treatment. The majority [167 (81%)] received one Y90 treatment before LT; 40 (19%) received ≥2 sessions. 37 (18%) patients received lobar treatment with a median dose of 124 Gy (IQR: 132-146), while 170 (82%) received radiation segmentectomy at a median dose of 260 Gy (IQR: 235-350). In patients with elevated AFP >13 ng/dl (n=93), the median percent AFP reduction following Y90 was 77% (IQR 51-95). In the 45-patient subset with baseline AFP >100, the median AFP reduction following Y90 was 93% (IQR 77-97) (**Supplementary Table 1**). 7 patients exhibited grade 3 albumin toxicities; all but 1 was pre-existing prior to Y90. 27 exhibited grade 3 bilirubin toxicities; all but 9 were pre-existing prior to Y90. At the time of transplant, 132 (64%) had normal AFP (≤13), while 62 (30%) exhibited AFP >13-100, and 13 (6%) had AFP (>100).

Baseline Characteristics at Transplantation

Table 2 shows baseline characteristics at LT, with a median age of 62 years (IQR: 57-66) for recipients and 48 for donors (IQR: 27-63). Eighty-seven (42%) patients were blood group A, 24 (11%), 90 (43%) and 6 (4%) were blood groups B, O and AB, respectively. The majority 102 (49%) had chronic hepatitis C virus infection as the main predisposing factor; 22 (10%) had chronic hepatitis B virus infection, while 30 (14%) and 13 (6%) had alcohol cirrhosis and

non-alcoholic steatohepatitis (NASH), respectively. Seventeen (8%) patients received live donor, 155 (75%) received liver donation after brain death (DBD) while 35 (17%) patients received donation after circulatory death (DCD). On pathological examination of liver explants, 94 (45%), 60 (29%) and 53 (26%) demonstrated complete, extensive and partial necrosis, respectively.

Tumor Stage at Y90 and at LT

Supplementary Table 2 summarizes UNOS stage at Y90 and at LT:

a) **Bridging within Milan:** 169 (82%) patients were within Milan (≤T2) at Y90. 166 (98%) patients were still within Milan criteria at LT, while 3 (2%) progressed to T3.

b) **Downstaging to T2:** 38 (19%) patients were beyond Milan before Y90, 18 (47%) were downstaged to T2, while 20 (53%) were transplanted with >T2 stage. Fourteen T3 were downstaged to T2 (64%). Two patients with T4a showed nodule resolution and downstaged to T2. Two T4b patients displayed complete resolution of their tumor thrombus and downstaged to T2.

c) Downgrading: One and four T1 and T2 patients, respectively, displayed resolution of treated hepatomas on cross sectional imaging to T0. 47 (23%) patients were downgraded from T2 to T1. 4 (2%) patients were downgraded from T4a to T3.

Intention-to-Treat Bridging UNOS T2 to Transplant Analysis

During the study time period, 362 HCC T2 patients underwent Y90. 150 patients were not listed due to: advanced age (N=50), cardiovascular and pulmonary comorbidities (N=23), concurrent malignancies (N=12), obesity (N=2), lack of psycho-social support (N=4), alcohol and/or drug abuse (N=12), non-compliance with transplant evaluation protocol (N=8), lack of follow-up (N=9), Bombay blood group (N=1), declined LT (N=15) and opted for resection (N=14). Of 212 listed T2 patients, at the time of data closure, 160 successfully underwent LT, 12 were still on the wait list, and 40 were delisted. Reasons for delisting included progressive disease (N=11), death from variceal bleed (N=1), development of systemic illness (N=8: cardiovascular disease, pulmonary hypertension, renal failure, septicemia), development of other malignancies (N=3), relocating to another state (N=2), and drug abuse (N=2). 13 patients refused transplant and were delisted after initially agreeing to being listed. This translates to 19% (40 of 212) dropping off the transplant list. Specifically, due to progressive disease, 5.2% (11 of 212) dropped off.

Median intention to treat OS of all T2 patients (N=362) was 94.4 months (CI: 79.2-120.0) from date of Y90 (**Figure 1**). Median OS of the 160 transplanted T2 patients was not reached, with 5- and 10-year survival rates of 82% and 56%, respectively. Median OS of the 202 non-transplanted T2 patients was 34.5 months (CI: 29.0-47.3), with better survival when stratified by CP class [67.5 months (CI: 40.0-80.2), 21.3 months (CI: 16.3-29.0), 6.0 months (CI: 4.0-11.3) for CP A (N=121), B (N=70) and C (N=11), respectively] (**Figure 2**).

Long-term Outcomes Following Transplantation

1-Overall Survival (OS): From date of Y90, the median OS of the 207 transplanted patients was 13 years (95%CI: 120-157) from Y90. From LT, median OS was 12.5 years (95%CI: 120-150), with survival rates at 3-, 5- and 10-years of 84%, 77% and 60%, respectively (**Figure 3**). Stratifying patients by age (<65 vs ≥65), patients <65 had significantly longer survival rates (P=0.003); median was not reached at 150 months with 3-, 5-, and 10-year

survival of 88%, 85% and 71% respectively. Liver-recipients ≥65 exhibited median OS of 12.5 years, with 3-, 5-, and 10-year survival rates of 73%, 58% and 43% respectively (**Table 3**). Of note, the 17 BCLC D (CP C) patients that received segmental Y90 and subsequently transplanted exhibited a 5-year survival of 91.5% (one death).

2-Tumor Recurrence: 24 (11.5%) patients developed tumor recurrence. **Supplementary Table 3** provides granular detail on the 24 recurrence cases. 10 (42%) patients were beyond Milan criteria at Y90, while 6 (25%) were beyond Milan criteria at LT. 17 (70%) of the 24 recurrences died at a median 29 (range: 5-83) months after LT, while 7 (30%) patients are alive at their last follow up at 8, 16, 72, 110, 111, 114 and 154 months. Recurrence-free probability was 76% at 10-years post LT (**Supplementary Figure 1**).

3-Mortality Rate: At time of data closure, 44 (21%) had died, with causes of death including cardiac decompensation (n=12, 6%) renal failure (n=2, 1%), infection (n=8, 4%), recurrent HCC (n=17, 8%), cerebrovascular disease (n=1, 0.5%) and other malignancies (n=4, 2%).

4-DSMR: No median was reached at 13 years for mortality rate from HCC recurrence. At 3-, 5- and 10 years post-LT, DSMR were 6%, 11% and 16%, respectively (**Supplementary Figure 2**).

5-RFS: Median RFS was 120 (95%CI: 69-150) months, with 3-, 5- and 10-year RFS rates of 77%, 65% and 43%, respectively (**Supplementary Figure 3**).

Univariate Analyses (Table 4)

1-OS: Univariate analyses for OS, showed only age to be a significant prognostic factor of survival. Median hazard ratio (HR) for patients ≥65 was 2.8 when compared to patients <65 (p=0.003). Different tumor stage at either Y90 or LT did not prove any significant effect on survival after LT. There was a trend towards better OS in patients achieving complete or

extensive tumor necrosis compared to <50% necrosis (p=0.056). A trend was noticed in patients achieving response by RECIST 1.1 (P=0.06).

2-RFS: Univariate analyses for RFS showed similar results to those of OS, supporting that age remains a significant prognosticator. Complete/extensive tumor necrosis demonstrated better RFS (p=0.0056).

3-DSMR: Patients within Milan at Y90 showed lower risk for DSMR compared those >T2 (HR: 0.21, *P* = 0.01). Similarly, patients who were within Milan criteria at LT had better DSMR (HR: 0.19, p = 0.02). Tumor necrosis showed strong significance on DSMR (P=0.0009). Patients with normal AFP (≤ 13 ng/dL) exhibited lower DSMR (HR: 0.23, P=0.0036).

4-TTR: Univariate analyses showed tumor characteristics to be strong predictors of recurrence. Patients within Milan at Y90 and LT had lower rates of recurrence (P=0.003 and 0.01, respectively). Tumor necrosis proved strongly associated with lower recurrence (P<0.0001), as was normal AFP (≤13 ng/dL) (P=0.0009). It should be noted that for the aforementioned analysis, we used largest lesional diameter (RECIST 1.1), not enhancement (mRECIST), thereby providing the most conservative imaging assessment. As an example, a completely necrotic 2 cm lesion that did not change in size was categorized as a persistent 2 cm tumor.

Multivariate Analysis

Multivariate analyses using Cox proportional-hazards regression was conducted for OS and RFS. Multivariate analysis was not conducted for DSMR and TTR endpoints due to insufficient endpoints. Age, tumor necrosis (>50%) and treatment response showed better OS outcomes (P=0.0048, 0.03 and 0.015, respectively). Similarly, RFS was significantly impacted by age (P=0.05), extensive tumor necrosis (>50%) (p=0.005), complete (100%) tumor necrosis (P=0.007), and normal AFP at transplant and (P=0.016) (**Table 5**).

Analysis of Tumor Recurrence by Necrosis

HCC recurrence was more commonly observed in patients with less necrosis on explant histo-pathology. Of 94 and 60 patients with complete and extensive necrosis, 2 (2%) and 4 (6.7%) developed recurrence after LT, respectively. In contradistinction, 18 out of 53 (34%) patients who had partial pathological response to Y90 developed recurrence (Chi-squared=35.5, $p<0.0001$). **Supplementary Figure 4** demonstrates an example of complete pathologic necrosis in an explant specimen.

DISCUSSION

LT is considered the most effective treatment for BCLC A cirrhotic, nonresectable HCC patients(17), providing 5-year OS approaching 75%.(4) Over the last decade, there has been a rise in the use of LRT prior to LT, with TACE remaining the most commonly used bridging/downstaging modality(18). Despite this, Y90 experience continues to grow, with our group first reporting long-term outcomes in 291 patient cohort, followed subsequently by a 1000-patient analysis.(7),(19) Also, while early retrospective comparative analyses found longer TTP for Y90 than TACE, these findings were subsequently confirmed in a prospective randomized trial(20). In totality, these results favor Y90 over TACE for early HCC awaiting LT.(8) Our center initiated the Y90 program in 2003, with the first case of LT post Y90 in 2004. The promising response, TTP, and downstaging prompted the shift in practice towards Y90 being the first-line arterial modality for HCC patients.(21) Since then, 207 patients underwent LT after Y90. We herein present the long-term outcomes and largest series published on the topic.

Overall Survival: OS was comparable to what is observed in non-HCC and non-Y90 LT patients.(22) While the majority were bridged, some downstaged patients also proceeded to LT after local board approval. While limiting recurrence could be attributed to disease control by LRT, there are conflicting data supporting this mechanism. In a recent study by Oligane, OS after LT was significantly longer in patients who underwent bridging LRT vs those that did not (75.9 vs 53.1 months, respectively; $P<0.001$).(23) In our cohort, 3, 5 and 10-year OS rates of 86%, 80% and 60% represent excellent outcomes, similar to LT for non-malignant liver disease.

At LT date, 184 patients were within Milan criteria ($\leq$T2), while 23 patients were beyond (>T2). The net OS for 207 patients was higher than currently reported results of long-term

outcomes of LT after HCC. (24) OS was not affected by tumor stage at Y90 or tumor stage at LT, with age of the recipient proving to have significant impact on survival.

Current evidence suggests that Milan criteria is a significant prognosticator for OS after LT.(25) There are many questions which have emerged, including whether imaging assessment and subsequent staging of patients after LRTs should include size of the entire lesion, or solely the enhancing portion? Evolving data support the notion that necrosis (decreased enhancement) following LRT correlates with complete pathologic necrosis following Y90.(26) Furthermore, certain studies suggest tumor response predicts better survival outcomes.(27, 28) This is consistent with a recent transplant multicenter consortium analysis of 3601 patients.(29) Similarly, our data show that tumor necrosis and RECIST response translated to better OS.

Recurrence-Free Survival: With a median recurrence-free survival of 10 years, LT after Y90 proves to be a definitive curative therapy for HCC. It should be also noted that neither HCC stage (≤T2 vs >T2) at Y90 nor at LT was of significant prognostic value for RFS [HR=0.9 at Y90 (p=0.69); HR=1.2 at LT (p=0.57)]. RFS has always been an ambiguous endpoint in HCC due to the confounding factor of underlying liver function on survival. While in liver transplantation RFS overcomes the confounding factor of cirrhosis on OS, it does not overcome other confounders such as age, comorbidities and other issues unique to transplantation. Since OS and RFS were more significantly affected by age than tumor stage, we focused on DSMR and time-to-recurrence as endpoints reflective of the effect of LRTs prior to LT.

HCC Recurrence: With 24 (12%) cases of post-LT HCC recurrence over a 13-year period,(30) LT proves to be an effective treatment for HCC. This low rate of recurrence is hypothesized to be attributed to Y90 providing tumor control and downstaging.(31) In our 207-patient cohort, there were 58 LT patients with tumors ≤T1. Of those, 51 initially presented as T2, and they were subsequently downstaged to T1 (n=47) or T0 (n=4). This highlights the importance of treating solitary 2-3 cm tumors, since those are likely to be

downstaged to T1, translating to a lowered recurrence rate post-LT. Explant tumor necrosis associated lower risk of recurrence (P<0.0001).

Disease-Specific Mortality: DSMR analysis was undertaken in order to assess the impact of Y90 and LT on survival. Of the 44 patients who reached their death endpoint, only 17 patients died of tumor recurrence, while the other 27 died from cardiac or infectious etiologies. DSMR was also significantly impacted by tumor stage prior to Y90 and LT, as well as degree of tumor necrosis at explant.

Alpha-fetoprotein: Treatment with Y90 was associated with significant reductions in AFP and in several cases, complete normalization. Normal AFP at transplant was associated lower recurrence and DSMR compared to those with elevated AFP. This is potentially attributable to better tumor biology (normal AFP) and/or achieving complete response to treatment with normalization of AFP.(32) However, this did not translate to improvement in survival.

Impact of Y90: While studying the impact of bridging LRT by intention-to-treat has been challenging, several studies show that bridging LRT is associated with favorable post-LT outcomes.(33) Oligane et al. reported that bridging LRT resulted in lower recurrence and longer OS when compared to patients who underwent LT without prior LRT. (23) Agopian et al. showed that patients with complete pathological response had better RFS. However, patients who received ≥3 LRT before transplant exhibited worse RFS.(29) Hence, the authors considered the increasing need for LRT as potential surrogate for aggressive tumor biology. Most recently, an Intention-to-treat analysis by Lai et al. suggested that LRT served as a protective factor, providing better outcomes post-LT, while tumor progression and ≥4 LRTs were strong prognostic factors of poor outcomes (aggressive tumor biology).(34) In our study, we conducted an independent intention-to-treat analysis of 362 T2 HCC patients treated over a 15-year period. Despite being within Milan criteria, only 212 were eligible for listing, of whom 160 underwent successful LT. The drop-out due to disease progression or

death occurred in few patients (5.2%). Therefore, Y90 appears to provide a high degree of disease stability/response, usually achieved by one treatment, resulting in few progressors. This finding was observed in a recent prospective randomized trial.(8) Despite this, patients who did not undergo LT for any reason still exhibited favorable OS, particularly those with CP A disease (67.5 months).

Also, the impact of pathologic necrosis was evident for all endpoints (OS, RFS, DSMR, TTR), with complete/extensive necrosis demonstrating significant OS benefit when compared to partial necrosis, leading to two different hypotheses. First, Y90 use prior to LT has its own significant impact on tumor recurrence, DSMR and OS after LT. Second, patients with partial necrosis + stable RECIST findings are at higher risk of developing recurrence, necessitating repeat treatment and conversion to extensive/complete necrosis + RECIST response prior to LT. Indeed, failure to achieve at least extensive necrosis may represent a de facto marker of aggressive tumor biology.(29)

Strengths and Limitations: This study is subject to strengths and limitations. It represents the largest cohort of transplanted patients treated with Y90 to date, with median time from Y90 to LT of 7.5 months. UNOS stages at Y90 and LT not being confined to Milan criteria reveal the effect of Y90 prior to LT at the pathology level. In order to provide more insight into the variable multifactorial nature of listing/unlisting with ultimate organ transplantation and the role of Y90, we generated an intention-to-treat analysis of UNOS T2 patients. RECIST 1.1 was used, demonstrating the continued importance of size criteria in assessing response in HCC. Limitations include the retrospective nature and well-known selection bias inherent to the transplantation process. Given the recent modifications to wait times prior to being transplanted, findings demonstrating longer TTP in the bridging setting are now more relevant.(8) Downstaging is only dealt with on a case-by-case basis in our region, preventing us from performing an ITT analysis without influence of the regional board.

CONCLUSION

Y90 is an effective treatment for early stage HCC in cirrhotic patients being bridged or downstaged to LT. Long-term OS outcomes are comparable to previously reported outcomes for non-malignant conditions. RFS is not different between patients bridged versus downstaged, or within versus beyond Milan criteria. Tumor recurrence and disease specific mortality are significantly affected by tumor stage and degree of necrosis. LRT with Y90 should be considered one of the standard treatment options prior to LT.

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FIGURE LEGEND

Figure 1: Post-Y90 Intention-to-Treat OS analysis of 362 T2 patients.

Figure 2: Post-Y90 OS of 202 T2 patients who did not undergo subsequent liver transplant.

Figure 3: Post-LT OS survival of 207 HCC patients treated with Y90.

Table 1: Baseline Characteristics at Y90

		Median [IQR] N (%)
Age (years)	60 [56-65]	
Sex	Male	156 (75%)
	Female	51 (25%)
ECOG	0	145 (70%)
	1	61 (29.5%)
	2	1 (0.5%)
Child-Pugh	A	99 (48%)
	B	91 (44%)
	C	17 (8%)
BCLC	A	106 (51%)
	B	20 (10%)
	C	64 (31%)
	D	17 (8%)
UNOS TNM	T1	9 (4%)
	T2	160 (77%)
	T3	22 (11%)
	T4a	12 (6%)
	T4b	4 (2%)
Imaging Cirrhosis	Present	192 (91%)
	Absent	15 (9%)
AFP (ng/dL)	<13 (normal)	114 (55%)
	13-100	48 (23%)
	>100	45 (22%)
	Range	0.8-15735
Prior Liver therapy	Surgical Resection	8 (3.5%)
	Prior HCC LRT	35 (17%)
	Treatment Naïve	164 (79.5%)
Listing	Prior to Y90	117 (57%)
	After Y90	90 (43%)
Y90 treatments prior to LT	1	167 (81%)
	2	33 (16%)

	3	6 (3%)
	4	1 (0.5%)
Y90 Administration	Lobar	37 (18%)
	Segmental	170 (82%)
Y90 Dose (Gy)	Lobar	124 [132-146]
	Segmental	260 [235-350]

Table 2: Baseline Characteristics at LT

		Median [IQR] *N(%)*	
Recipient	Age (years)	62 [57-66]	
	MELD-Na Score	13 [10-17]	
	Wait-list time (months)	7 [4-10]	
	Time from Y90 (months)	7.5 [4.4-10.3]	
	Etiology of HCC	Autoimmune hepatitis	3 (1.5%)
		Alpha 1 antitrypsin	1 (0.5%)
		Biliary Atresia	1 (0.5%)
		Cryptogenic	13 (6%)
		ETOH	30 (14%)
		HCV + ETOH	11 (5%)
		HCV	102 (49%)
		HBV	22 (10%)
		NASH	13 (6%)
		PBC	7 (3%)
		Wilson's	1 (0.5%)
		PSC	1 (0.5%)
		Hemochromatosis	2 (1%)
	AFP (ng/dL)	<13 (normal)	132 (64%)
		13-100	62 (30%)
		>100	13 (6%)
		Range	0.8-13774
	Blood Group	A	87 (42%)
		B	24 (11%)
		O	90 (43%)
		AB	6 (4%)
	Organs Transplanted	Liver Only	197 (95%)

		Liver & Kidney	10 (5%)
Donor	Age	48 [27-63]	
	Donor State	Living donor	17 (8%)
		DBD	155 (75%)
		DCD	35 (17%)
Surgical Parameters	Cold Ischemic Time (Hours)	7 [6-8]	
	RBCs (units)	7 [4-14]	
	Fresh Frozen Plasma (units)	8 [5-14]	
	Platelets (units)	2 [2-4]	
Explant	Liver Parenchyma	Cirrhosis	202 (97.5%)
		Bridging Fibrosis	5 (2.5%)
	Tumor Grade	Grade 1	37 (18%)
		Grade 2	69 (33%)
		Grade 3	6 (3%)
		Fibrolamellar	1 (0.5%)
		Mixed HCC-cholangiocarcinoma	4 (2%)
		Unable to identify due to extensive necrosis	90 (43.5%)
	Tumor Necrosis	Complete (100%)	94 (45%)
		Extensive (51-99%)	60 (29%)
		Partial (<50%)	53 (26%)

MELD-Na: New Model of end-stage liver disease-Sodium; HCV: Hepatitis C virus infection; HBV: Hepatitis B virus infection; ETOH: Alcoholic cirrhosis; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; DCD: Donor after cardiac death

Table 3: Survival and Recurrence Outcomes

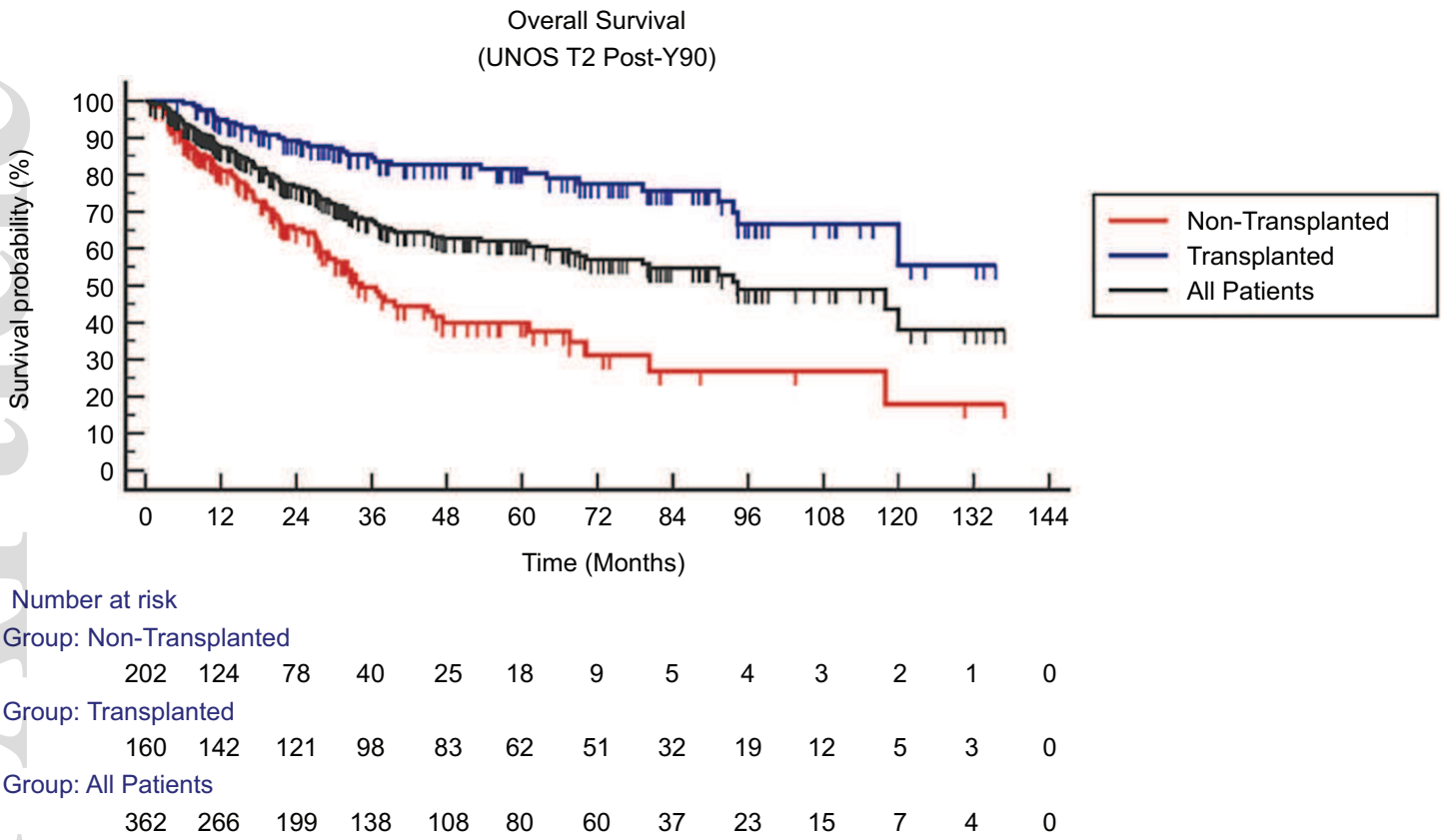
	Median	3-year	5-year	10-year
Overall Survival from Y90	157 mo. (13.1 years) [CI: 120-157]	87%	80%	62%
Overall Survival from LT	150 mo (12.5 years) [CI: 120-150]	84%	77%	60%
Recurrence-Free Survival from LT	120 mo (10.0 years) [CI:69-150]	77%	65%	43%
Disease-Specific Mortality Rate	Not Reached	6%	11%	16%
Time-to-Recurrence (Recurrence-Free Probability)	Not Reached	88%	79%	76%

Table 4: Univariate Analyses

Factor		N	Overall Survival		Recurrence-free Survival		Disease-Specific Mortality		Time-to-Recurrence	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	<65	145	1	**0.003**	1	**0.04**	1	0.11	1	0.5
	>65	62	2.8 (1.4-5.6)		1.78 (0.96 - 3.3)		2.47 (0.82-7.49)		0.75 (0.3-1.8)	
Sex	M	155	1.54 (0.8-3)	0.2	1.8 (1-3.4)	0.08	1.65 (0.57-4.78)	0.36	2.1 (0.88-5)	0.16
	F	52	1		1		1		1	
Milan at Y90	≤T2	169	1.1 (0.5-2.3)	0.87	0.9 (0.5-1.73)	0.71	0.21 (0.06-0.73)	**0.01**	0.2 (0.07-0.58)	**0.003**
	>T2	38	1		1		1		1	
Milan @ LT	≤T2	184	1.01 (0.42-2.46)	0.98	0.8 (0.36-1.82)	0.57	0.19 (0.04-0.82)	**0.02**	0.2 (0.06-0.69)	**0.01**
	>T2	23	1		1		1		1	
Bridging vs Downstaging vs Neither	Bridged	166	1	0.99	1	0.85	1	0.055	1	**0.02**
	Downstaged	18	1 (0.4-2.8)		0.98 (0.4-2.4)		2 (0.35-13)		2.3 (0.5-10.7)	
	Neither	23	0.99 (0.4-2.3)		1.2 (0.5-2.8)		3.4 (0.8-14.7)		3.3 (0.9-11)	
Donor	DBD	155	1	0.34	1	0.18	1	0.23	1	0.56
	DCD	35	1.7 (0.7-3.87)		1.78 (0.8-4)		2 (0.5-8.4)		1.7 (0.5-5.4)	
	LLD	17	1.05 (0.4-2.9)		0.79 (0.3-1.9)		2.4 (0.47-12.7)		1.4 (0.4-5.2)	
Tumor Necrosis	Complete	94	0.53 (0.26-1.1)	0.056	0.46 (0.2-0.8)	**0.0056**	0.1 (0.03-0.3)	**0.0009**	0.07 (0.03-0.19)	**<0.0001**
	Extensive	60	0.43 (0.2-0.9)		0.36 (0.17-0.76)		0.3 (0.09-1.1)		0.2 (0.07-0.61)	
	Partial	53	1		1		1		1	
RECIST 1.1 Response @ LT	Response	92	0.35 (0.11-1.11)	0.06	0.53 (0.19-1.5)	0.34	0.8 (0.12-5.5)	0.42	1.7 (0.35-8.2)	0.75
	Stable	97	0.52 (0.16-1.64)		0.59 (0.21-1.65)		1.59 (0.23-11.8)		2.03 (0.42-9.7)	
	Progression	18	1		1		1		1	
AFP	≤13	132	0.69 (0.37-1.28)	0.24	0.6 (0.34-1.1)	0.07	0.23 (0.09-0.61)	0.0036	0.25 (0.11-0.57)	0.0009
	>13	75	1		1		1		1	

Table 5: Multivariate Analyses

Parameter			OS		RFS	
		N	HR (CI)	P	HR (CI)	P
Age	≤65	145	1		1	
	>65	62	2.41 (1.31-4.44)	**0.0048**	1.79 (1-3.2)	**0.05**
Sex	M	155	1		1	
	F	52	0.62 (0.28-1.37)	0.24	0.49 (0.23-1.04)	0.063
RECIST 1.1	Response	92	0.31 (0.12-0.8)	**0.015**	0.44 (0.17-1.07)	0.07
	Stable	97	0.44 (0.18-1.1)	0.07	0.45 (0.18-1)	0.08
	Progression	18	1		1	
AFP	≤13	132	1		1	
	>13	75	1.67 (0.89-3.13)	0.11	2.03 (1.14-3.62)	**0.016**
Tumor Necrosis	Complete	94	0.5 (0.2-1.1)	0.07	0.41 (0.21-0.79)	**0.007**
	Extensive	60	0.4 (0.18-0.9)	**0.03**	0.33 (0.15-0.71)	**0.005**
	Partial	56	1		1	



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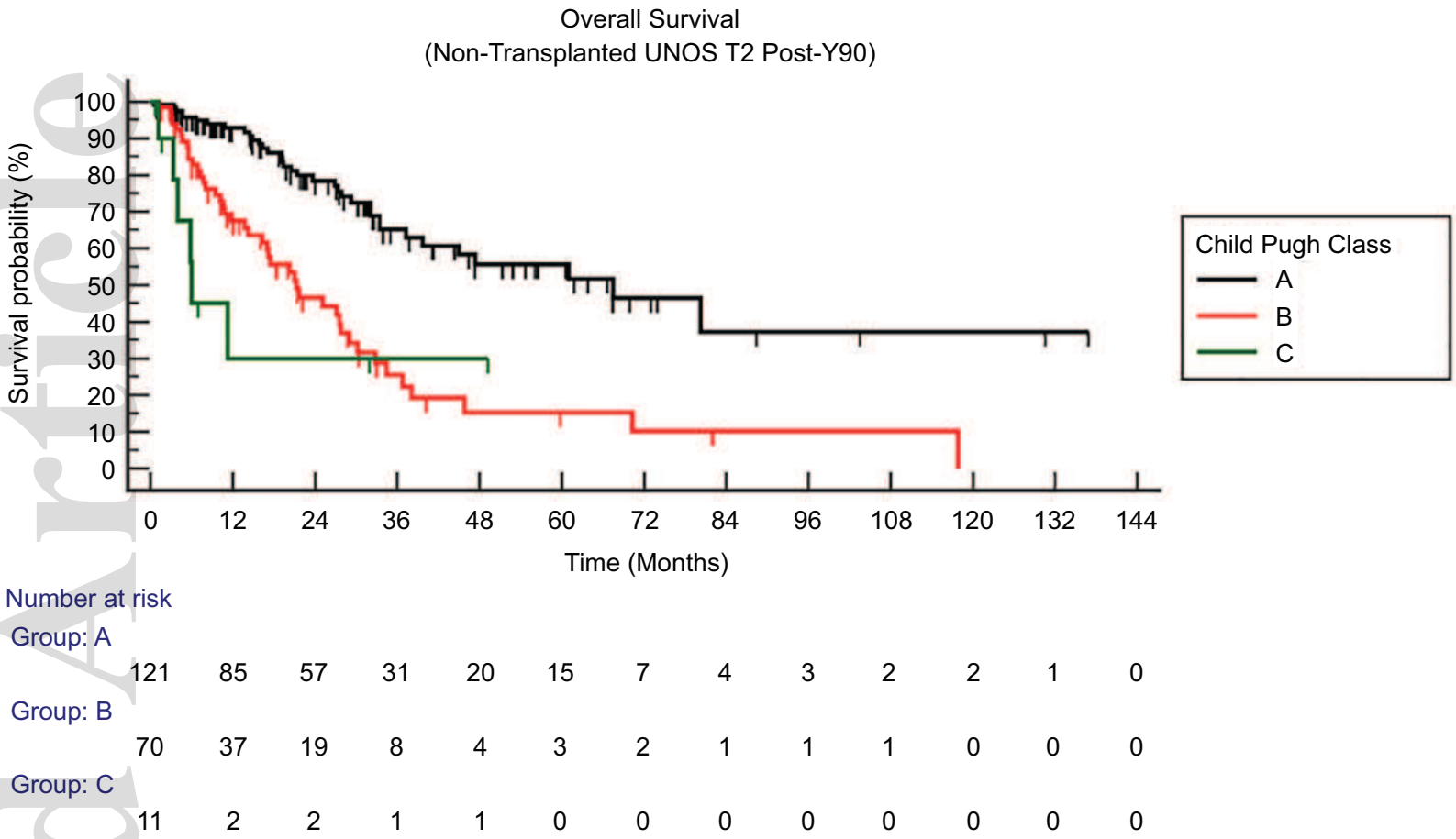

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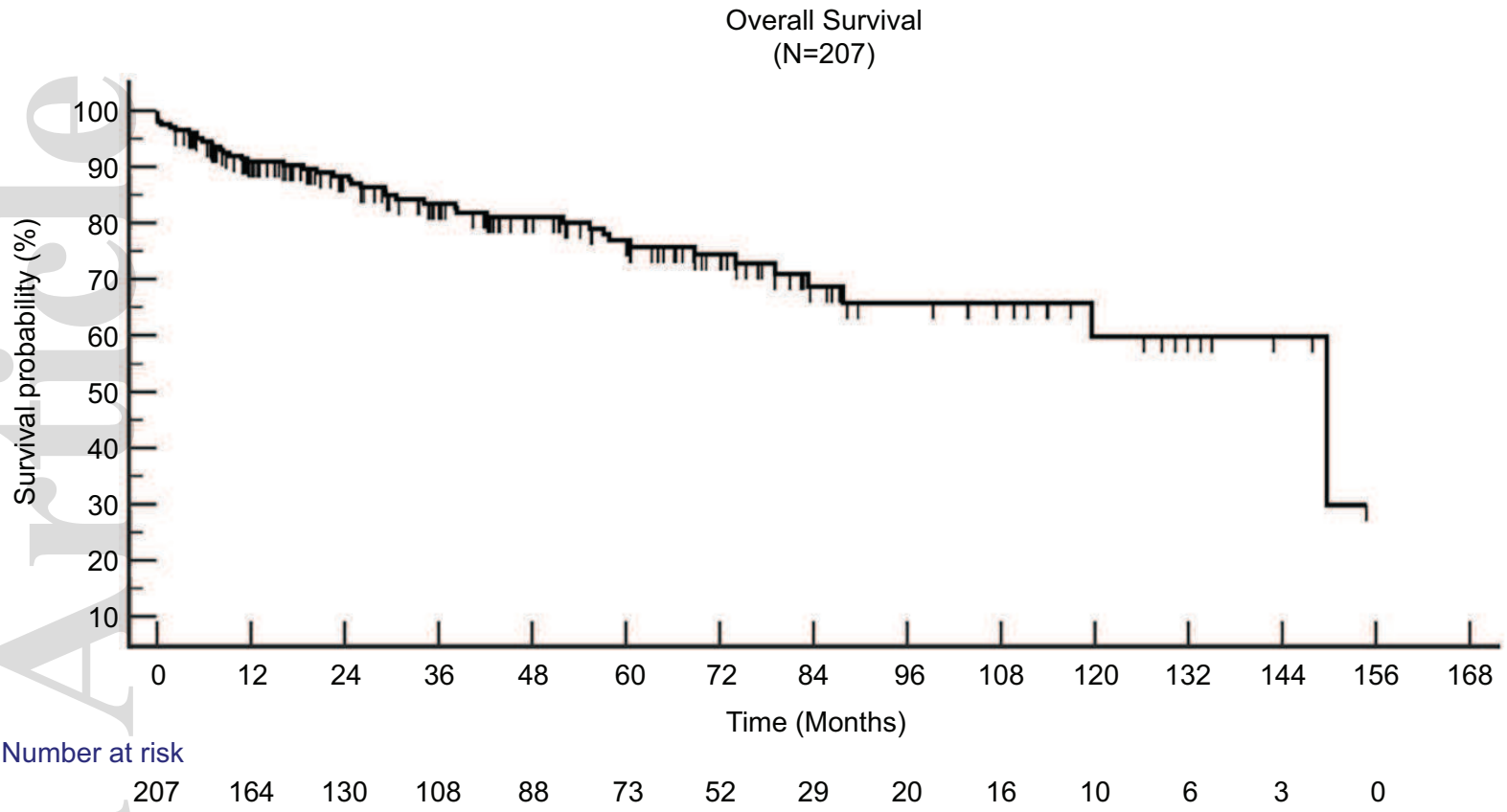

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