**Supplementary
materials**

*Methods: Molecular analysis*

The majority of patients were genomically characterized using biopsy tissue at initial diagnosis prior to the start of therapy. [13] Mutations were characterized using either solid tumor tissue or circulating cell-free DNA (cfDNA). Patients were screened for single nucleotide variants, insertions, deletions, copy number gains, and gene fusions. Tissue-based testing assessed up to 324 genes and associated biomarkers; FoundationOne CDx (Foundation Medicine, Cambridge, MA, USA) was the most recently used assay. Liquid biopsies using peripheral blood were performed using the FoundationACT, FoundationOne Liquid, or FoundationOne Liquid CDx (Foundation Medicine) assays. Immunohistochemistry was used for DNA mismatch repair enzymes. Further molecular testing was ordered at the discretion of the treatment team. For this series, 151 of 220 (69%) of chemotherapy-treated patients and 50 of 61 (82%) RT-treated patients had molecular characterization. Frequencies of the most commonly mutated genes were compared between treatment cohorts. An exploratory analysis of associations between mutation status and cause of death was also performed.

*Results: Mutational profiling*

Commonly mutated genes are shown in Supplemental Table 11. *TP53*, *IDH1*, *CDK2A*, and *KRAS* were most commonly mutated in both cohorts. Mutation frequency did not differ significantly between treatment cohorts aside from *CDKN2A* (25% vs. 10%; *P*=0.028) and *CKDN2B* (15% vs. 4%; *P*=0.047), which were more commonly mutated in the chemotherapy alone cohort. Commonly co-occurring mutations are shown in Supplemental Figure 5. *TP53* mutations were commonly seen in conjunction with *IDH1*, *CDKN2A*, and *KRAS* mutations.

*Results: Mutational correlates with causes of death*

An exploratory pairwise univariate logistic regression (Supplemental Table 12) revealed few significant associations of genetic mutations with cause of death in the study cohort. *FGFR2*, *BAP1*, and *PIK3CA* mutations were associated were a higher risk of death due to progressive lung disease. No associations with mutational status and death due to TRLF were identified.



**Supplemental Figure 1**. National Cancer Data Base cohort selection for patients with M1 ICC treated with chemotherapy alone.

|  |  |  |
| --- | --- | --- |
|  | **Univariate logistic regression** | **Multivariable logistic regression** |
| **Attribute** | **Odds ratio** | **95% CI** | ***P*-value** | **Odds ratio** | **95% CI** | ***P*-value** |
| Age at diagnosis, years | 1.02 | 1.00-1.05 | 0.072 |  |  |  |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 1.11 | 0.63-1.96 | 0.724 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  |  |  |  |
|  2-3 | 0.69 | 0.29-1.63 | 0.392 |  |  |  |
| CA 19-9, U/mL | 1.00 | 1.00-1.00 | 0.333 |  |  |  |
| Maximal tumor size, cm | 1.0 | 0.93-1.07 | 0.962 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.14 | 0.59-2.21 | 0.703 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 0.87 | 0.40-1.88 | 0.720 |  |  |  |
| Non-regional nodal mets at diagnosis | 0.55 | 0.31-0.97 | 0.040\* | 0.24 | 0.12-0.50 | <0.001\* |
| Peritoneal mets at diagnosis | 0.49 | 0.26-0.95 | 0.034\* | 0.20 | 0.09-0.46 | <0.001\* |
| Osseous mets at diagnosis | 0.24 | 0.10-0.55 | 0.001\* | 0.12 | 0.05-0.31 | <0.001\* |
| Lung mets at diagnosis | 1.17 | 0.66-2.07 | 0.587 |  |  |  |
| Portal vein thrombus | 2.21 | 1.05-1.69 | 0.037\* | 2.12 | 0.92-4.90 | 0.080 |
| Satellitosis | 1.10 | 0.60-2.02 | 0.748 |  |  |  |
| Chemotherapy duration, months | 1.08 | 1.01-1.16 | 0.019\* | 1.07 | 1.00-1.15 | 0.059 |

**Supplemental Table 1**. Univariate and multivariable logistic regression for factors associated with receipt of liver RT. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model. \* Significant at 5% level.

****

***P*<0.001**

***P*<0.001**

**A**

**B**

****

**C**

***P*<0.001**

**Supplemental Figure 2**. Kaplan-Meier curves for (A) local control, (B) intrahepatic disease progression-free survival, and (C) extrahepatic disease progression-free survival, stratified by treatment cohort.

|  |  |  |
| --- | --- | --- |
| **Site of first progression following treatment initiation** | **Chemotherapy alone (n=220)** | **Liver RT (n=61)** |
| No radiographically confirmed progression | 33 (15%) | 6 (10%) |
| Liver | 58 (26%) | 17 (28%) |
| Distant | 60 (27%) | 20 (33%) |
| Concurrent liver + distant | 69 (31%) | 18 (30%) |

**Supplemental Table 2**. Radiographically-confirmed sites of first progression following treatment initiation.



**Supplemental Figure 3**. Overall survival stratified by sites of radiographically-confirmed first progression following treatment initiation.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | ***P*-value** | **Hazard ratio** | **95% CI** | ***P*-value** |
| Age at diagnosis, years | 1.01 | 1.00-1.02 | 0.022\* | 1.02 | 1.00-1.03 | 0.019\* |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 0.92 | 0.69-1.22 | 0.556 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  | (Reference) |  |  |
|  2-3 | 2.46 | 1.60-3.75 | <0.001\* | 2.05 | 1.31-3.22 | 0.002\* |
| CA 19-9, U/mL | 1.000005 | 0.9999943-1.000016 | 0.351 |  |  |  |
| Maximal tumor size, cm | 1.02 | 0.98-1.05 | 0.343 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.26 | 0.90-1.77 | 0.184 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 1.17 | 0.80-1.71 | 0.430 |  |  |  |
| Non-regional nodal mets at diagnosis | 1.18 | 0.89-1.56 | 0.261 |  |  |  |
| Peritoneal mets at diagnosis | 1.22 | 0.91-1.64 | 0.186 |  |  |  |
| Osseous mets at diagnosis | 1.19 | 0.87-1.61 | 0.275 |  |  |  |
| Lung mets at diagnosis | 1.11 | 0.83-1.48 | 0.469 |  |  |  |
| Portal vein thrombus | 0.83 | 0.54-1.29 | 0.405 |  |  |  |
| Satellitosis | 1.03 | 0.77-1.40 | 0.826 |  |  |  |
| Chemotherapy duration, months | 0.91 | 0.87-0.95 | <0.001\* | 0.91 | 0.87-0.95 | <0.001\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.57 | 0.41-0.78 | <0.001\* | 0.47 | 0.34-0.66 | <0.001\* |
| RT pts only: RT BED10 | 1.01 | 0.99-1.02 | 0.314 |  |  |  |
| RT pts only: Ablative BED10 | 0.84 | 0.45-1.56 | 0.576 |  |  |  |

**Supplemental Table 3**. Univariate and multivariable Cox analyses for factors associated with overall survival following diagnosis with 6-month landmark. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model. \* Significant at 5% level.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | ***P*-value** | **Hazard ratio** | **95% CI** | ***P*-value** |
| Age at diagnosis, years | 1.00 | 0.98-1.01 | 0.624 |  |  |  |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 0.99 | 0.73-1.34 | 0.934 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  | (Reference) |  |  |
|  2-3 | 1.80 | 1.15-2.82 | 0.010\* | 1.70 | 1.06-2.73 | 0.028\* |
| CA 19-9, U/mL | 1.00001 | 1.000003-1.000018 | 0.008\* | 1.000006 | 0.999998-1.000001 | 0.169 |
| Maximal tumor size, cm | 0.99 | 0.96-1.03 | 0.693 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.11 | 0.77-1.59 | 0.583 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 1.41 | 0.89-2.22 | 0.145 |  |  |  |
| Non-regional nodal mets at diagnosis | 1.24 | 0.91-1.69 | 0.183 |  |  |  |
| Peritoneal mets at diagnosis | 1.02 | 0.74-1.41 | 0.906 |  |  |  |
| Osseous mets at diagnosis | 1.33 | 0.96-1.84 | 0.085 |  |  |  |
| Lung mets at diagnosis | 1.11 | 0.82-1.51 | 0.500 |  |  |  |
| Portal vein thrombus | 0.58 | 0.34-0.97 | 0.037\* | 0.82 | 0.48-1.39 | 0.466 |
| Satellitosis | 1.17 | 0.84-1.62 | 0.354 |  |  |  |
| Chemotherapy duration, months | 0.90 | 0.85-1.94 | <0.001\* | 0.89 | 0.84-0.93 | <0.001\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.22 | 0.14-0.35 | <0.001\* | 0.22 | 0.14-0.35 | <0.001\* |
| RT pts only: RT BED10 | 0.98 | 0.96-1.00 | 0.069 |  |  |  |
| RT pts only: Ablative BED10 | 0.59 | 0.25-1.41 | 0.236 |  |  |  |

**Supplemental Table 4**. Univariate and multivariable Cox analyses for factors associated with local control following treatment initiation. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model.
\* Significant at 5% level.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | ***P*-value** | **Hazard ratio** | **95% CI** | ***P*-value** |
| Age at diagnosis, years | 1.01 | 1.00-1.02 | 0.098 |  |  |  |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 0.94 | 0.73-1.20 | 0.601 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  | (Reference) |  |  |
|  2-3 | 1.70 | 1.20-2.40 | 0.003\* | 1.58 | 1.11-2.25 | 0.011\* |
| CA 19-9, U/mL | 1.000008 | 1.000002-1.000015 | 0.016\* | 1.000006 | 0.999999-1.000012 | 0.097 |
| Maximal tumor size, cm | 1.02 | 0.99-1.05 | 0.220 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.16 | 0.87-1.54 | 0.327 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 1.20 | 0.86-1.68 | 0.293 |  |  |  |
| Non-regional nodal mets at diagnosis | 1.19 | 0.93-1.53 | 0.169 |  |  |  |
| Peritoneal mets at diagnosis | 1.20 | 0.93-1.55 | 0.166 |  |  |  |
| Osseous mets at diagnosis | 1.12 | 0.86-1.46 | 0.407 |  |  |  |
| Lung mets at diagnosis | 1.05 | 0.82-1.34 | 0.704 |  |  |  |
| Portal vein thrombus | 1.17 | 0.83-1.66 | 0.370 |  |  |  |
| Satellitosis | 1.18 | 0.92-1.53 | 0.197 |  |  |  |
| Chemotherapy duration, months | 0.85 | 0.82-0.89 | <0.001\* | 0.85 | 0.81-0.89 | <0.001\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.57 | 0.35-0.63 | <0.001\* | 0.43 | 0.32-0.59 | <0.001\* |
| RT pts only: RT BED10 | 1.00 | 0.99-1.01 | 0.887 |  |  |  |
| RT pts only: Ablative BED10 | 0.88 | 0.49-1.60 | 0.682 |  |  |  |

**Supplemental Table 5**. Univariate and multivariable Cox analyses for factors associated with intrahepatic distant progression-free survival following treatment initiation. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model.
\* Significant at 5% level.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | ***P*-value** | **Hazard ratio** | **95% CI** | ***P*-value** |
| Age at diagnosis, years | 1.00 | 1.00-1.01 | 0.471 |  |  |  |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 0.88 | 0.69-1.12 | 0.305 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  | (Reference) |  |  |
|  2-3 | 1.71 | 1.22-2.42 | 0.002\* | 1.55 | 1.07-2.23 | 0.019\* |
| CA 19-9, U/mL | 1.000008 | 1.000001-1.000015 | 0.023\* | 1.000004 | 0.999997-1.000011 | 0.274 |
| Maximal tumor size, cm | 1.02 | 0.99-1.05 | 0.197 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.22 | 0.91-1.63 | 0.182 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 1.01 | 0.72-1.41 | 0.958 |  |  |  |
| Non-regional nodal mets at diagnosis | 1.02 | 0.80-1.31 | 0.845 |  |  |  |
| Peritoneal mets at diagnosis | 1.30 | 1.00-1.68 | 0.048\* | 1.12 | 0.86-1.46 | 0.415 |
| Osseous mets at diagnosis | 1.27 | 0.97-1.66 | 0.086 |  |  |  |
| Lung mets at diagnosis | 1.13 | 0.88-1.45 | 0.328 |  |  |  |
| Portal vein thrombus | 1.06 | 0.75-1.50 | 0.760 |  |  |  |
| Satellitosis | 1.08 | 0.83-1.39 | 0.574 |  |  |  |
| Chemotherapy duration, months | 0.86 | 0.82-0.89 | <0.001\* | 0.85 | 0.82-0.89 | <0.001\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.44 | 0.33-0.60 | <0.001\* | 0.42 | 0.31-0.57 | <0.001\* |
| RT pts only: RT BED10 | 1.00 | 1.00-1.02 | 0.448 |  |  |  |
| RT pts only: Ablative BED10 | 0.89 | 0.49-1.62 | 0.711 |  |  |  |

**Supplemental Table 6.** Univariate and multivariable Cox analyses for factors associated with extrahepatic distant progression-free survival following treatment initiation. A threshold of P<0.05 on univariate analysis was used for variable selection into the multivariable model.
\* Significant at 5% level

|  |  |  |  |
| --- | --- | --- | --- |
| **Attribute** | **Chemotherapy only****(n=112)** | **Chemotherapy + Liver RT (n=56)** | ***P*-value** |
| Median age at diagnosis (IQR), years  | 66 (56-71) | 63 (56-69) | 0.235 |
| Sex |  |  | 0.625 |
|  Male | 57 (51%) | 31 (55%) |
|  Female | 55 (49%) | 25 (45%) |
| ECOG performance status |  |  | 0.234 |
|  0-1 | 75 (55%) | 13 (42%) |
|  2-3 | 62 (45%) | 18 (58%) |
| Median baseline CA 19-9 (IQR), U/mL | 129 (49-1167) | 66 (19-1049) | 0.190 |
| Median tumor size in greatest dimension (IQR), cm | 9.0 (5.8-12.2) | 8.7 (6.1-12.0) | 0.892 |
| T stage |  |  | 0.694 |
|  1-2 | 89 (79%) | 43 (77%) |
|  3-4 | 23 (21%) | 13 (23%) |
| N stage |  |  | 0.646 |
|  0 | 15 (13%) | 9 (16%) |
|  1 | 97 (87%) | 47 (84%) |
| Sites of metastasis at diagnosis |  |  |  |
|  Non-regional nodes | 70 (63%) | 28 (50%) | 0.137 |
|  Peritoneal | 41 (37%) | 13 (23%) | 0.084 |
|  Lung | 47 (42%) | 26 (46%) | 0.622 |
|  Bone | 43 (38%) | 7 (13%) | <0.001\* |
| Portal vein thrombus at diagnosis | 16 (14%) | 10 (18%) | 0.651 |
| Satellite lesions at diagnosis | 77 (69%) | 38 (68%) | 1.000 |
| Child-Pugh score prior to treatment initiation\* (n=99 for chemo only, n=46 for L-RT) |  |  | 0.979 |
|  5A | 45 (45%) | 22 (48%) |
|  6A | 34 (34%) | 14 (30%) |
|  7B | 10 (10%) | 6 (13%) |
|  8B | 7 (7%) | 3 (7%) |
|  9B | 2 (2%) | 1 (2%) |
|  10C | 1 (1%) | 0 (0%) |
| Mutations present (n=71 for chemo only, n=46 for L-RT) |  |  |  |
|  *TP53* | 20 (28%) | 12 (26%) | 0.835 |
|  *IDH1* | 17 (24%) | 13 (28%) | 0.667 |
|  *CDKN2A* | 13 (18%) | 5 (11%) | 0.308 |
|  *KRAS* | 12 (17%) | 7 (15%) | 1.000 |
|  *ARID1A* | 14 (20%) | 8 (17%) | 0.813 |
|  *BAP1* | 14 (20%) | 4 (9%) | 0.123 |
|  *FGFR2* | 10 (14%) | 2 (4%) | 0.122 |
| Type of 1st line chemotherapy used  |  |  | 0.014\* |
|  Gemcitabine/cisplatin  ± nab-paclitaxel | 84 (75%) | 51 (91%) |
|  Other | 28 (25%) | 5 (9%) |
| Median duration of 1st line chemotherapy (IQR), months | 3.4 (1.9-6.3) | 4.1 (2.2-7.0) | 0.127 |
| Radiotherapy details |  |  |  |
|  Time from diagnosis to RT, months |  | 10.7 (6.1-16.7) |  |
|  Median dose, Gy (IQR) |  | 62.3 (54.5-67.5) |  |
|  Median number of fractions (IQR) |  | 15 (15-15) |  |
|  Median BED10, Gy |  | 96.8 (76.6-97.9) |  |
|  Received ablative RT  (≥80.5 Gy BED10) |  | 41 (73%) |  |

**Supplemental Table 7**. Baseline characteristics and treatment details for M1 ICC patients for propensity score-matched cohorts, stratified by treatment group. Categorical variables were compared using Fisher’s exact tests and continuous variables were compared using the Wilcoxon rank-sum test. Sums of individual percentages may not equal 100% due to rounding. \* Significant at 5% level.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | **P-value** | **Hazard ratio** | **95% CI** | **P-value** |
| Age at diagnosis, years | 1.03 | 1.01-1.06 | 0.017\* | 0.99 | 0.95-1.02 | 0.475 |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 0.95 | 0.56-1.61 | 0.859 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  | (Reference) |  |  |
|  2-3 | 2.47 | 1.31-4.66 | 0.005 | 1.73 | 0.80-3.76 | 0.164 |
| CA 19-9, U/mL | 1.000011 | 1.9999744-1.000047 | 0.559 |  |  |  |
| Maximal tumor size, cm | 0.99 | 0.94-1.05 | 0.810 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.37 | 0.77-2.42 | 0.285 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 1.26 | 0.67-2.35 | 0.469 |  |  |  |
| Non-regional nodal mets at diagnosis | 1.49 | 0.90-2.46 | 0.124 |  |  |  |
| Peritoneal mets at diagnosis | 1.04 | 0.64-1.71 | 0.866 |  |  |  |
| Osseous mets at diagnosis | 1.14 | 0.66-1.95 | 0.644 |  |  |  |
| Lung mets at diagnosis | 1.10 | 0.67-1.80 | 0.705 |  |  |  |
| Portal vein thrombus | 1.49 | 0.71-3.12 | 0.286 |  |  |  |
| Satellitosis | 1.19 | 0.69-2.05 | 0.522 |  |  |  |
| Chemotherapy duration, months | 0.75 | 0.67-0.85 | <0.001\* | 0.73 | 0.64-0.84 | <0.001\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.36 | 0.23-0.59 | <0.001\* | 0.29 | 0.16-0.51 | <0.001\* |

**Supplemental Table 8**. Stratified univariate and multivariable Cox analyses for propensity score-matched cohorts for factors associated with overall survival following diagnosis. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model.
\* Significant at 5% level.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | ***P*-value** | **Hazard ratio** | **95% CI** | ***P*-value** |
| Age at diagnosis, years | 1.04 | 1.01-1.07 | 0.021\* | 1.00 | 0.96-1.04 | 0.835 |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 1.16 | 0.63-2.15 | 0.638 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  | (Reference) |  |  |
|  2-3 | 2.87 | 1.27-6.47 | 0.011\* | 2.06 | 0.82-5.15 | 0.122 |
| CA 19-9, U/mL | 1.00001 | 0.9999346-1.000085 | 0.797 |  |  |  |
| Maximal tumor size, cm | 0.96 | 0.90-1.03 | 0.252 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.41 | 0.71-2.79 | 0.326 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 1.30 | 0.63-2.67 | 0.476 |  |  |  |
| Non-regional nodal mets at diagnosis | 1.29 | 0.70-2.36 | 0.415 |  |  |  |
| Peritoneal mets at diagnosis | 1.21 | 0.66-2.20 | 0.540 |  |  |  |
| Osseous mets at diagnosis | 0.92 | 0.48-1.73 | 0.786 |  |  |  |
| Lung mets at diagnosis | 1.15 | 0.63-2.08 | 0.649 |  |  |  |
| Portal vein thrombus | 0.84 | 0.34-2.08 | 0.703 |  |  |  |
| Satellitosis | 1.45 | 0.72-2.91 | 0.298 |  |  |  |
| Chemotherapy duration, months | 0.83 | 0.74-0.93 | 0.001\* | 0.82 | 0.71-0.94 | 0.005\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.50 | 0.30-0.83 | 0.007\* | 0.40 | 0.22-0.72 | 0.002\* |

**Supplemental Table 9**. Stratified univariate and multivariable Cox analyses for propensity score-matched cohorts for factors associated with overall survival following diagnosis with 6-month landmark. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model. \* Significant at 5% level.

***P*<0.001**

**A**

**B**

***P*=0.006**

**Supplemental Figure 4**. Survival curves for propensity score-matched cohorts comparing chemotherapy alone vs. L-RT (A) without landmark, and (B) with landmark at 6 months. Stratified log-rank analysis revealed significantly longer survival for L-RT for comparisons without landmark and with 6-month landmark. \* Significant at 5% level.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Endpoint (95% CI, unless otherwise noted)** | **Chemotherapy alone (n=112)** | **Liver RT (n=56)** |
| Following diagnosis | Follow-up time (IQR), months | 9 (5-18) | 19 (14-27) |
| Median overall survival, months | 9 (8-12) | 20 (16-24) |
| Overall survival at 12 months | 38% (30-48%) | 84% (71-91%) |
| Overall survival at 24 months | 16% (10-23%) | 36% (24-49%) |
| Following chemotherapy initiation | Median local control, months | 8 (6-11) | 36 (16-*undefined*) |
| Local control at 12 months | 38% (27-49%) | 79% (65-88%) |
| Local control at 24 months | 12% (5-21%) | 54% (37-69%) |
| Median intrahepatic progression-free survival, months | 5 (4-6) | 13 (11-14) |
| Intrahepatic progression-free survival at 12 months | 16% (10-23%) | 53% (39-35%) |
| Intrahepatic progression-free survival at 24 months | 6% (2-11%) | 15% (7-25%) |
| Median extrahepatic progression-free survival, months | 4 (3-5) | 11 (7-14) |
| Extrahepatic progression-free survival at 12 months | 13% (8-20%) | 43% (30-55%) |
| Extrahepatic progression-free survival at 24 months | 3% (1-7%) | 14% (7-25%) |
| Following radiotherapy initiation | Median local control, months |  | 6 (4-9) |
| Local control at 12 months |  | 72% (53-84%) |
| Local control at 24 months |  | 53% (29-72%) |
| Median intrahepatic progression-free survival, months |  | 6 (4-9) |
| Intrahepatic progression-free survival at 12 months |  | 31% (18-45%) |
| Intrahepatic progression-free survival at 24 months |  | 17% (7-30%) |
| Median extrahepatic progression-free survival, months |  | 4 (3-6) |
| Extrahepatic progression-free survival at 12 months |  | 26% (15-39%) |
| Extrahepatic progression-free survival at 24 months |  | 16% (7-28%) |

**Supplemental Table 10**. Summary of disease-related outcomes for propensity score-matched cohorts stratified by treatment cohort.

|  |  |  |  |
| --- | --- | --- | --- |
| **Attribute** | **Chemotherapy only****(n=51)** | **Chemotherapy + Liver RT (n=51)** | ***P*-value** |
| Median age at diagnosis (IQR), years  | 63 (56-69) | 63 (53-71) | 0.880 |
| Sex |  |  | 0.314 |
|  Male | 33 (65%) | 27 (53%) |
|  Female | 18 (35%) | 24 (47%) |
| ECOG performance status |  |  | 1.000 |
|  0-1 | 45 (88%) | 44 (86%) |
|  2-3 | 6 (12%) | 7 (14%) |
| Median baseline CA 19-9 (IQR), U/mL | 126 (32-1162) | 92 (18-1700) | 0.331 |
| Median tumor size in greatest dimension (IQR), cm | 9.0 (5.4-12.0) | 9.0 (6.4-12.0) | 0.773 |
| T stage |  |  | 0.828 |
|  1-2 | 35 (69%) | 37 (73%) |
|  3-4 | 16 (31%) | 14 (27%) |
| N stage |  |  | 0.577 |
|  0 | 6 (12%) | 9 (18%) |
|  1 | 45 (88%) | 42 (82%) |
| Sites of metastasis at diagnosis |  |  |  |
|  Non-regional nodes | 29 (57%) | 28 (55%) | 1.000 |
|  Peritoneal | 11 (22%) | 14 (27%) | 0.646 |
|  Lung | 29 (57%) | 19 (37%) | 0.074 |
|  Bone | 8 (16%) | 7 (14%) | 1.000 |
| Portal vein thrombus at diagnosis | 5 (10%) | 10 (20%) | 0.263 |
| Satellite lesions at diagnosis | 37 (73%) | 34 (67%) | 0.667 |
| Child-Pugh score prior to treatment initiation\* (n=46 for chemo only, n=41 for L-RT) |  |  | 0.733 |
|  5A | 28 (61%) | 19 (46%) |
|  6A | 10 (22%) | 13 (32%) |
|  7B | 4 (9%) | 5 (12%) |
|  8B | 3 (7%) | 3 (7%) |
|  9B | 1 (2%) | 1 (2%) |
|  10C | 0 (0%) | 0 (0%) |
| Mutations present(n=33 for chemo only, n=43 for L-RT) |  |  |  |
|  *TP53* | 7 (21%) | 14 (33%) | 0.311 |
|  *IDH1* | 7 (21%) | 13 (30%) | 0.438 |
|  *CDKN2A* | 6 (18%) | 4 (9%) | 0.315 |
|  *KRAS* | 10 (30%) | 6 (14%) | 0.097 |
|  *ARID1A* | 5 (15%) | 9 (21%) | 0.566 |
|  *BAP1* | 7 (21%) | 2 (5%) | 0.035\* |
|  *FGFR2* | 6 (18%) | 2 (5%) | 0.071 |
| Type of 1st line chemotherapy used  |  |  | 0.741 |
|  Gemcitabine/cisplatin  ± nab-paclitaxel | 45 (88%) | 47 (92%) |
|  Other | 6 (12%) | 4 (8%) |
| Median duration of 1st line chemotherapy (IQR), months | 2.7 (1.6-6.2) | 4.1(2.1-7.0) | 0.862 |
| Radiotherapy details |  |  |  |
|  Time from diagnosis to RT, months |  | 8.1 (5.6-11.1) |  |
|  Median dose, Gy (IQR) |  | 62.5 (50.4-67.5) |  |
|  Median number of fractions (IQR) |  | 15 (15-15) |  |
|  Median BED10, Gy |  | 96.0 (75.0-97.9) |  |
|  Received ablative RT  (≥80.5 Gy BED10) |  | 37 (73%) |  |

**Supplemental Table 11**. Baseline characteristics and treatment details for M1 ICC patients for sensitivity analysis propensity score-matched cohorts, stratified by treatment group. Categorical variables were compared using Fisher’s exact tests and continuous variables were compared using the Wilcoxon rank-sum test.
\* Significant at 5% level.
\*Sums of individual percentages may not equal 100% due to rounding.

|  |  |  |
| --- | --- | --- |
|  | **Univariate Cox regression** | **Multivariable Cox regression** |
| **Attribute** | **Hazard ratio** | **95% CI** | **P-value** | **Hazard ratio** | **95% CI** | **P-value** |
| Age at diagnosis, years | 1.05 | 1.01-1.10 | 0.014\* | 1.06 | 1.01-1.12 | 0.029\* |
| Sex |  |  |  |  |  |  |
|  Male | (Reference) |  |  |  |  |  |
|  Female | 0.77 | 0.34-1.75 | 0.533 |  |  |  |
| ECOG performance status |  |  |  |  |  |  |
|  0-1 | (Reference) |  |  |  |  |  |
|  2-3 | 1.75 | 0.51-5.98 | 0.372 |  |  |  |
| CA 19-9, U/mL | 1.00010 | 0.99994-1.0003 | 0.229 |  |  |  |
| Maximal tumor size, cm | 1.03 | 0.92-1.14 | 0.648 |  |  |  |
| T stage |  |  |  |  |  |  |
|  1-2 | (Reference) |  |  |  |  |  |
|  3-4 | 1.78 | 0.79-4.02 | 0.167 |  |  |  |
| N stage |  |  |  |  |  |  |
|  0 | (Reference) |  |  |  |  |  |
|  1 | 2.50 | 0.78-7.97 | 0.121 |  |  |  |
| Non-regional nodal mets at diagnosis | 0.87 | 0.41-1.82 | 0.706 |  |  |  |
| Peritoneal mets at diagnosis | 1.67 | 0.61-4.59 | 0.323 |  |  |  |
| Osseous mets at diagnosis | 1.75 | 0.51-5.98 | 0.372 |  |  |  |
| Lung mets at diagnosis | 1.50 | 0.67-3.34 | 0.321 |  |  |  |
| Portal vein thrombus | 0.71 | 0.23-2.25 | 0.566 |  |  |  |
| Satellitosis | 1.14 | 0.41-3.15 | 0.796 |  |  |  |
| Chemotherapy duration, months | 0.79 | 0.67-0.93 | 0.004\* | 0.78 | 0.66-0.93 | 0.007\* |
| Treatment stratum |  |  |  |  |  |  |
|  Chemo alone | (Reference) |  |  | (Reference) |  |  |
|  Chemo + L-RT | 0.36 | 0.19-0.68 | 0.002\* | 0.20 | 0.07-0.54 | 0.002\* |

**Supplemental Table 12**. Stratified univariate and multivariable Cox analyses for sensitivity analysis propensity score-matched cohorts for factors associated with overall survival following diagnosis. A threshold of *P*<0.05 on univariate analysis was used for variable selection into the multivariable model.
\* Significant at 5% level.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Mutated gene | **All patients(n=212)** | **Chemotherapy only(n=151)** | **Chemotherapy + Liver RT (n=50)** | ***P*-value** |
| *TP53* | 62 (31%) | 47 (31%) | 15 (30%) | 1.000 |
| *IDH1* | 43 (21%) | 28 (19%) | 15 (30%) | 0.111 |
| *CDKN2A* | 43 (21%) | 38 (25%) | 5 (10%) | 0.028\* |
| *KRAS* | 41 (20%) | 33 (22%) | 8 (16%) | 0.424 |
| *ARID1A* | 34 (17%) | 24 (16%) | 10 (20%) | 0.518 |
| *FGFR2* | 30 (15%) | 26 (17%) | 4 (8%) | 0.168 |
| *BAP1* | 29 (14%) | 24 (16%) | 5 (10%) | 0.361 |
| *CDKN2B* | 24 (12%) | 22 (15%) | 2 (4%) | 0.047\* |
| *PIK3CA* | 18 (9%) | 15 (10%) | 3 (6%) | 0.570 |
| *BRAF* | 18 (9%) | 17 (11%) | 1 (2%) | 0.048 |
| *ATM* | 15 (7%) | 10 (6%) | 5 (10%) | 0.534 |
| *PBRM1* | 15 (7%) | 6 (7%) | 5 (10%) | 0.534 |
| *LRP1B* | 13 (6%) | 10 (7%) | 3 (6%) | 1.000 |
| *MLL2* | 12 (6%) | 8 (5%) | 4 (8%) | 0.498 |
| *IDH2* | 13 (6%) | 8 (5%) | 5 (10%) | 0.317 |
| *BRCA2* | 13 (6%) | 10 (7%) | 3 (6%) | 1.000 |
| *PRKDC* | 13 (6%) | 11 (7%) | 2 (4%) | 0.525 |
| *NRAS* | 13 (6%) | 8 (5%) | 5 (10%) | 0.317 |
| *SMAD4* | 13 (6%) | 9 (6%) | 4 (8%) | 0.740 |
| *IRS2* | 9 (4%) | 8 (5%) | 1 (2%) | 0.456 |

**Supplemental Table 13**. List of twenty most commonly observed mutations.



**Supplemental Figure 5**. Co-occurrence of twenty most commonly observed mutations.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cause of death: Liver** | **Cause of death: Biliary** | **Cause of death: Peritoneum** | **Cause of death: Lung** |
| Mutated gene | **Odds ratio** | ***P*-value** | **Odds ratio** | ***P*-value** | **Odds ratio** | ***P*-value** | **Odds ratio** | ***P*-value** |
| *TP53* | 1.95 | 0.08 | 1.18 | 0.714 | 1.42 | 0.359 | 0.69 | 0.347 |
| *IDH1* | 1.03 | 0.935 | 0.298 | 0.111 | 1.13 | 0.785 | 0.73 | 0.492 |
| *CDKN2A* | 1.03 | 0.931 | 1.36 | 0.517 | 0.50 | 0.174 | 1.10 | 0.823 |
| *KRAS* | 1.41 | 0.427 | 0.98 | 0.970 | 0.76 | 0.577 | 0.93 | 0.867 |
| *ARID1A* | 1.58 | 0.312 | 0.78 | 0.662 | 0.82 | 0.692 | 0.51 | 0.197 |
| *FGFR2* | 0.90 | 0.798 | 0.63 | 0.468 | 0.24 | 0.061 | 2.51 | 0.026\* |
| *BAP1* | 0.51 | 0.085 | 0.58 | 0.396 | 0.89 | 0.820 | 2.66 | 0.015\* |
| *CDKN2B* | 0.76 | 0.565 | 0.61 | 0.518 | 1.66 | 0.323 | 1.34 | 0.570 |
| *PIK3CA* | 0.95 | 0.932 | 0.35 | 0.313 | *Undefined* | *Undefined* | 3.03 | 0.027\* |
| *BRAF* | 5.60 | 0.100 | 1.62 | 0.479 | 0.27 | 0.217 | 0.83 | 0.780 |

**Supplemental Table 14**. Univariate logistic regressions of causes of death associated with the ten most commonly observed mutations.