**Supplement material.**

**Table S1. Summary of included studies for the treatment of HCC recurrence in LT patients.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First Author and Year** | **Country** | **Type of Study** | **Time Frame** | **Patients with HCC recurrence** | **Treatment for HCC recurrence**  (Number of patients, if available) | **Main Findings** | **Overall Survival** |
| **Ringe et al. 1995[1]** | Germany | CR |  | 1 | Re-transplantation | Liver re-transplantation is effective to treat late HCC recurrence + HBV liver disease | Alive at 2 yr |
| **Regalia et al. 1998[2]** | Italy | RCS | 1987-1996 | 21 | Surgery ± CT, ± RT (7)  BSC ± CT, ± RT, ± PEI (14) | The prognosis differed significantly in the 7 patients with resectable recurrence (57% 4-yr survival) vs. the 14 patients with unresectable disease (14% 4-yr survival). | 62% at 1 yr  43% at 2 yr  29% at 3 yr  23% at 5 yr |
| **Castroagudin et al. 2002[3]** | Spain | CR |  | 1 | Bilateral adrenal metastasectomy | Surgical resection of metastases may be indicated in patients with good performance status and absence of additional metastasic disease. | Disease-free at 35 months |
| **Catalano et al. 2004[4]** | Italy | RCS | 1996-2002 | 2 | Hepatic surgery | Hepatic graft resection is a graft-saving option, but early diagnosis and correct timing are crucial. | 18 and 20 months |
| **Roayaie et al. 2004[5]** | USA | RCS | 1988-2002 | 57 | Hepatic surgery (5), lung resection (7), hepatic RFA (3), adrenalectomy (2), chest wall resection (1), doxorubicin (15), TACE (3), external beam radiation (4), BSC (17) | The absence of bone metastases, recurrence more than 12 months from transplant, and surgical treatment of the recurrence were independently associated with significantly longer survival. | 8,7 months  22% at 5 yr |
| **Stippel et al.**  **2005[6]** | Germany | CR |  | 1 | Ovarectomy + sirolimus (montherapy) | Radical surgical treatment and immunosuppression may achieve tumor-free survival in selected patients. | Disease-free at 19 months |
| **Rivera et al.**  **2006[7]** | USA | CR |  | 1 | Surgery, CT, SIRT (Yttrium-90) | Efficacious treatment for multifocal HCC recurrence. | Disease-free at 4 months |
| **Escartin et al.**  **2007[8]** | Spain | RCS | 1988-2005 | 28 | Multimodality | HCC recurrence was difficult to treat curatively. | 7 months |
| **Ho et al. 2007[9]** | USA | CR |  | 1 | RFA | Efficacious treatment for intra-hepatic HCC recurrence | Disease-free at 24 months |
| **Ko et al. 2007[10]** | Korea | RCS | 1992-2005 | 28 | TACE | TACE produces an effective tumor response for targeted HCC recurrence. | 47.9% at 1 yr  6% at 3 yr  0% at 5 yr |
| **Bates et al. 2008[11]** | USA | RCS | 2000-2006 | 5 | Pulmonary resection | Resection of pulmonary HCC recurrence is a reasonable and safe treatment and should result in survival similar to the nontransplant population. | 22.5 months |
| **Kwon et al. 2008[12]** | Korea | RCS | 1999-2006 | 7 | Pulmonary resection | Pulmonary metastasectomy is safe and associated a good outcome in LT patients. | NR |
| **Lee et al. 2008[13]** | Korea | RCS | 2000-2006 | 24 | Systemic chemotherapy | Palliative chemotherapy has tolerable toxicity but unsatisfactory efficacy. | 4.1 months |
| **Marangoni et al. 2008[14]** | Uk | RCS | 1988-2006 | 4 | Hepatic resection | Recipients with recurrent HCC in graft may benefit from resection, but cure is uncommon. | 20 months  75% at 1 yr |
| **Alamo et al. 2009[15]** | Spain | RCS |  | 7 | mTOR | mTOR long-term effectiveness to control neoplastic recurrence is yet to be seen | NR |
| **Yeganeh et al. 2009[16]** | USA | CR |  | 1 | Lung metastasectomy (wedge resection) + Sorafenib | Complete response of metastatic HCC | Alive at 18 months |
| **Zhang et al. 2009[17]** | China | RCS | 2004-2008 | 10 | Computed tomography guided brachytherapy | Safe and effective therapy on intra-hepatic recurrent HCC | 13.6 months |
| **Bhoori et al. 2010[18]** | Italy | CR |  | 1 | Surgical resection, Sorafenib, Everolimus | A personalized approach aimed to treat recurrent HCC is possible through analysis of tumoral molecular pathways. | Alive at 8 months |
| **Han et al. 2010[19]** | Korea | RCS | 1998-2008 | 12 | Pulmonary resection | Pulmonary metastasectomy is safe. | NR |
| **Herden et al. 2010[20]** | Germany | CR |  | 1 | Sorafenib | Severe adverse events (Sorafenib-induced hepatitis) required treatment interruption | NR |
| **Kim et al. 2010[21]** | USA | RCS | 2007-2010 | 9 | Sorafenib | Sorafenib has tolerable toxicity but dose adjustment may be required | 84% at 4 months |
| **Kornberg et al. 2010[22]** | Germany | RCS | 1994-2007 | 16 | Surgery (7), TACE (10), RT (3), Sorafenib (1), BSC (5) | Multivariate analysis identified late (>24 months) post transplant tumor relapse and surgical therapy as independent predictors of long-term survival after HCC recurrence. | 10.5 months  41.7% at 5 yr |
| **Shin et al. 2010[23]** | Korea | RCS | 1999-2005 | 28 | Multimodality | Multi-organ HCC recurrence has a very poor prognosis. For local recurrence, surgical resection should be considered. | 11.7 months  52.8% at 1yr  15.8% at 3 yr |
| **Taketomi et al. 2010[24]** | Japan | RCS | 1996-2007 | 17 | Surgery (9)  RT ± CT ± RFA (8) | Overall survival rates of the surgical group (87.5% at 5 yr) were significantly better than those of the nonsurgical group (0% at 5 yr) | 76.5% at 1 yr  51.3% at 3 yr  34.2% at 5 yr |
| **Tan et al. 2010[25]** | China | RCC | 2004-2009 | 20 | TACE (10) vs.  TACE + Sorafenib (10) | TACE + Sorafenib group (14 months) showed a significantly better survival than single TACE treatment group (6 months). | 10 months |
| **Valdivieso et al. 2010[26]** | Spain | RCS | 1996-2008 | 23 | Surgery (11),  Sorafenib + mTOR (5),  Systemic CT (2)  BSC (8) | Survival was significantly higher among patients with R-0 surgery (33.2 months) compared to other patients (11.9 months) | 22.5 months |
| **Wang et al. 2010[27]** | USA | CR |  | 1 | Sorafenib + Sirolimus | mTOR inhibitor + Sorafenib may have anti-tumor activity in HCC recurrence. | Alive at 18 months |
| **Yoon et al. 2010[28]** | Korea | RCS | 2003-2008 | 13 | Sorafenib | Sorafenib may be a feasible treatment option regarding its efficacy and safety | 5.4 months |
| **Zhou et al. 2010[29]** | China | RCS |  | 28 | TACE (14) vs.  BSC (14) | Patients treated with TACE had significantly longer survival compared to those who did not. | NR |
| **Chok et al. 2011[30]** | China | RCS | 1994-2007 | 24 | Multimodality | The early recurrence group (17) when had significantly poorer overall survival compared with  the late recurrence group (7). | Early HCC recurrence:  100% at 1 yr  13.3% at 3 yr  6.7% at 5 yr  Late HCC recurrence:  100% at 1 yr  100% at 3 yr  71.4% at 5 yr |
| **Gomez-Martin et al. 2011[31]** | Spain | RCS | 2008-2010 | 31 | Sorafenib + mTOR | Co-administration of Sorafenib + mTOR could be effective despite notable toxicity | 19.3 months |
| **Kim et al. 2011[32]** | USA | CR |  | 1 | Sorafenib + mTOR | Complete radiologic response | Disease-free at 5 months |
| **Kim et al. 2011[33]** | Korea | RCS | 1995-2008 | 39 | TACE (11), systemic CT (11), RT (8), surgery (3), BSC (6) | Various clinical approaches have been used in absence of clinical guidelines. The time of HCC recurrence (late vs. early) was not a predictor of poor prognosis. | 6.9 months  34.3% at 1 yr  21.7% at 2 yr |
| **Pfiffer et al. 2011[34]** | Germany | RCS | 2002-2009 | 24 | Multimodality | Even in the Sorafenib era, surgical treatment of HCC recurrence still is the best option to prolong survival. | 23.1 months |
| **Takahara et al. 2011[35]** | Japan | CR |  | 2 | Sorafenib | Sorafenib is one option to treat recurrent HCC. | Alive at 16 months  Alive at 4 yr |
| **Waidmann et al. 2011[36]** | Germany | RCS |  | 3 | Sorafenib + mTOR | Close monitoring and careful dose titration is required since major toxicity may occur. | 8 months |
| **Carr 2012[37]** | Italy | RCS |  | 6 | TACE | TACE is a safe treatment, with 50% response rate | 23.6 months |
| **Chen et al. 2012[38]** | Taiwan | RCC | 2003-2011 | 15 | Surgery (5), TACE (4), RFA (1), CT (6), RT (8). | Surgery had significant benefit on survival after HCC solitary or localized resectable recurrence. Multiple metastases were usually unresponsive. | 19.2 months  100% at 1 yr for surgery  37.5% at 1 yr for TACE  0% at 1 yr for palliative CT/RT |
| **Hwang et al. 2012[39]** | Korea | RCC | 1997-2008 | 43 | Pulmonary resection (23), multimodality non-surgical treatments (20) | Survival rate was significantly greater in patients with resectable pulmonary metastases undergone metastasectomy than patients who received other treatments | For surgery group:  77.4% at 1 yr  30.6% at 2 yr  For non-surgical treatment group:  55.1% at 1 yr  0% at 2 yr |
| **Kitano et al. 2012[40]** | Japan | RCS | 1990-2010 | 3 | Pulmonary resection | Pulmonary metastasectomy in safe and feasible in selected patients. | NR |
| **Sotiropoulos et al. 2012[41]** | Germany | RCS | 2006-2011 | 14 | Sorafenib + mTOR | Sorafenib may be a feasible treatment option regarding efficacy and safety for recurrent HCC. | 12 months |
| **Staufer et al. 2012[42]** | Germany | RCS | 2000-2009 | 13 | Sorafenib ± mTOR | Side effects prevented full dosing of Sorafenib and necessitated dose reduction/discontinuation in the majority of patients. | 19.4 months  69% at 1 yr |
| **Vitale et al. 2012[43]** | Italy | RCS | 2005-2011 | 10 | Sorafenib ± mTOR | Sorafenib is a safe effective therapy. | 14.2 months |
| **Weinmann et al. 2012[44]** | Germany | RCS | 1998-2009 | 11 | Sorafenib + mTOR | Acceptable toxicity without deterioration of liver graft function. | 20.1 months |
| **Pfeiffenberger et al. 2013[45]** | Germany | RCC | 2002-2010 | 18 | Sorafenib ± mTOR (8) vs.  Multimodality (no Sorafenib)(10) | Sorafenib may represent a therapeutic option for recurrent HCC after LT with manageable side effects. | 9 months for Sorafenib group  2.3 months for Non-Sorafenib group |
| **Sommacale et al. 2013[46]** | France | RCS | 1997-2011 | 3 | Hepatic surgery (3) | Liver resection in LT patients is safe but associated with high morbidity rate. | 100% at 1 year |
| **Sposito et al. 2013[47]** | Italy | RCC | 1994-2011 | 39 | Sorafenib ± mTOR (15) vs.  BSC (24) | Sorafenib seems to be associated with an acceptable safety profile and benefit in survival. | 10.6 months for Sorafenib group  2.2 months for BSC group |
| **Toso et al. 2013[48]** | Canada / Swiss | RCS | 1996-2011 | 30 | Surgery (6), loco-regional therapy (3), BSC (21) | Patients with early HCC recurrence have worse survival. | 33 months |
| **Waghray et al. 2013[49]** | USA | RCC | 2001-2011 | 34 | Sorafenib (17) vs.  Multimodality (no Sorafenib)(17) | Sorafenib can be well tolerated and may be associated with a modest survival benefit. | 63% at 1 yr for Sorafenib group  23% at 1 yr for non-Sorafenib group |
| **Yoon et al. 2013[50]** | Korea | RCC | 1997-2009 | 25 | Curative-intent treatments (8), palliative treatments (17) | Multiple recurrence and palliative treatment for recurrent HCC were related to poor survival. | For curative treatment:  62.5% at 1 yr  25% at 3 yr  25% at 5 yr  For palliative treatments:  47.1% at 1 yr  0% at 3 yr |
| **Zavaglia et al. 2013[51]** | Italy | RCS | 2008-2010 | 11 | Sorafenib + Cyclosporine (4) or + mTOR (7) | Sorafenib, with or without mTOR, is poorly tolerated and rarely effective | 5 months  18% at 1 yr |
| **Alsina et al. 2014[52]** | USA | RCS | 2002-2013 | 22 | Sorafenib (9), multimodality + Sorafenib (9), BSC (4) | Sorafenib may improve survival | 30 months for Sorafenib group  20 months for non-Sorafenib group |
| **Cheng et al. 2014[53]** | Taiwan | RCS | 2002-2012 | 11 | TACE | TACE is beneficial for treating intra-hepatic multiple recurrence of HCC and it is associated with significantly better survival. | 6.6 months  12.5% at 1 yr |
| **De Simone et al. 2014[54]** | Italy | RCS |  | 7 | Sorafenib + mTOR | Treatment with Sorafenib + mTOR is challenging because treatment related complications. | 71.4% at 6 months |
| **Gringeri et al. 2014[55]** | Italy | CR |  | 1 | Laparoscopic microwave thermal ablation | Effective loco-regional treatment for solitary HCC recurrence | Alive at 24 months |
| **Gunay et al. 2014[56]** | Turkey | RCS | 2004-2012 | 16 | Surgery + Sorafenib + mTOR (7), Systemic CT + Sorafenib + mTOR (7), BSC (2) | The most effective treatment for isolated HCC recurrence is surgery. | 54.3% at 1 yr  9% at 3 yr  9% at 5 yr  21.4 months for surgical group  6.7 months for non surgical treatment group |
| **Mazloom et al. 2014[57]** | USA | CR |  | 1 | Stereotactic body radiation therapy | Safe and effective treatment modality | Alive at 1 yr |
| **Perricone et al. 2014[58]** | Italy | RCS | 2010-2013 | 4 | Sorafenib + mTOR | Combination regimen Sorafenib + Everolimus is poorly tolerated and can be associated with relevant treatment-related mortality. | 10.7 months |
| **Roh et al. 2014[59]** | Korea | RCS | 1996-2011 | 63 | Local treatments (24), systemic treatments (10), combined treatments (21), BSC (8) | The combined treatment with local and systemic therapies resulted in increased survival even in patients with multifocal HCC recurrences | 12 months  For local treatment group:  38% at 1 yr  9% at 2 yr  0% at 3 yr  For systemic treatment group:  60% at 1 yr  20% at 2 yr  0% at 3 yr  For the combined treatment group:  73% at 1 yr  65% at 2 yr  25% at 3 yr  For BSC group:  17% at 1 yr  0% at 2 yr |
| **Yamagami et al. 2014[60]** | Japan | RCS | 2007-2012 | 8 | TACE | TACE with an interventional-CT system is effective in the treatment of recurrent HCC. | 12.9 months  42.9% at 1 yr |
| **Sapisochin et al. 2014[61]** | Canada / Spain | RCS | 2000-2012 | 121 | Surgery (31), ablation (8), CT (10), RT (25), Sorafenib (14), TACE (1), BSC (32) | LT patients with HCC recurrence amenable to curative-intent treatments can experience long-term survival | 12.2 months  50% at 5 yr |

*CR: case report; RCS: retrospective case series; RCC: retrospective case-control/comparative study; CT: chemotherapy; RT: radiotherapy; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; BSC: best supportive care; SIRT: selective internal radiotherapy treatment; mTOR: mammalian target of rapamycin; HCC: hepatocellular carcinoma; LT: liver transplantation.*

**Table S2. Risk of bias for non-randomized clinical trials based on the *Newcastle-Ottawa Scale*. The study quality was assessed on nine items categorized into three main criteria. A maximum of 9 stars can be assigned to the highest quality. Studies awarded with 7 stars or more were considered at low risk of bias.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Criteria**  **Study** | **Selection** | **Comparability** | **Exposure** | **Overall**  **Score** |
| **Regalia et al. 1998[2]** | ★★★ | - | ★★★ | **6/9** |
| **Tan et al. 2010[25]** | ★★★ | ★ | ★★★ | **7/9** |
| **Chen et al. 2012[38]** | ★★★ | *-* | ★★ | **5/9** |
| **Hwang et al. 2012[39]** | ★★★ | *-* | ★★ | **5/9** |
| **Staufer et al. 2012[42]** | ★★★ | *-* | ★★ | **5/9** |
| **Pfeiffeenberger et al. 2013[45]** | ★★★★ | *-* | ★★ | **6/9** |
| **Sposito et al. 2013[47]** | ★★★★ | ★ | ★★★ | **8/9** |
| **Yoon et al. 2013[50]** | ★★★ | *-* | ★★ | **5/9** |
| **Waghray et al. 2013[49]** | ★★★★ | - | ★★ | **6/9** |
| **Gunay et al. 2014[56]** | ★★ | *-* | ★★ | **4/9** |
| **Roh et al. 2014[59]** | ★★★ | ★★ | ★★ | **7/9** |
| **Sapisochin et al. 2014[61]** | ★★★ | ★ | ★★ | **6/7** |

**Figure S1. Increasing number of publication on the management of recurrent HCC in LT patients.**

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