Uitgangsvraag 3: Welke prognostische factoren moeten er beschreven worden in het pa-verslag van het resectiepreparaat van HCC patiënten?

Primaire studies

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<tr>
<th>Study ID</th>
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<th>Results multivariate analysis</th>
<th>Results other analyses</th>
<th>Critical appraisal of study quality</th>
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</table>
| Minagawa 2007 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing curative hepatic resection  
- N0M0  
- Patients without pathologic data, incomplete survival data and without data on operative curability, distant metastasis, or hepatic lymph node metastasis were excluded  
- A priori patient characteristics:  
  - Male: 79.5%  
  - 60+: 67%  
  - HBV: 19.8%; HCV: 66.5%  
  - Child-Pugh A: 62.4% | Number of HCC lesions (including intrahepatic metastasis)  
- Tumour diameter (largest dimension of tumour specimen)  
- Portal invasion (none, 3rd branch, 2nd branch, 1st branch or trunk)  
- Hepatic venous invasion (none, branch of HV, trunk of HV or IVC)  
- Bile duct invasion (none, intrahepatic bile duct, extrahepatic bile duct)  
- Grade of differentiation (well, moderately, poorly, undifferentiated)  
- Background liver (normal, hepatitis, cirrhosis)  
- Gross classification (type 1, 2 or 3, multinodular type, massive type of Eggel, diffuse type of Eggel)  
- Hepatic involvement (1 segment, 1 sector, 2 sectors, at least 3 sectors)  
- Fibrous capsule  
- Macroscopic intrahepatic metastasis (none, within 1 sector, within 2 sectors, 3 sectors or more) | Significant pathologic factors for OS (RR [95%CI]):  
- Vascular or bile duct invasion: RR 1.36 (1.29-1.43)  
- Liver cirrhosis: RR 1.26 (1.20-1.32)  
- Tumour diameter > 2cm: RR 1.21 (1.14-1.28)  
- Multiple HCC lesions: RR 1.18 (1.12-1.23)  
- Hepatic involvement > 1 segment: RR 1.14 (1.09-1.19)  
- Differentiation: RR 1.14 (1.08-1.20)  
- Gross classification: RR 1.13 (1.08-1.18) | Based on the results of the MVA, 3 factors were selected for the LCSGJ-T staging system: vascular or bile duct invasion, diameter, and single/multiple. Patients with 0 factors were T1, with 1 factor T2, 2 factors T3 and 3 factors T4 | Level of evidence: C  
- Population-based study  
- 5382 patients excluded based on exclusion criteria  
- Median follow-up: not reported |

Ikai 2004 | Retrospective single cohort study | Eligibility criteria:  
- Number of HCC lesions (including intrahepatic metastasis) | Significant pathologic factors | Level of evidence: C  
- Based on the results of the MVA, 3 factors were selected for the LCSGJ-T staging system: vascular or bile duct invasion, diameter, and single/multiple. Patients with 0 factors were T1, with 1 factor T2, 2 factors T3 and 3 factors T4  
- 5-year overall survival, LCSGJ-T vs. AJCC-T:  
  - T1: 70% vs. 61%  
  - T2: 58% vs. 46%  
  - T3: 41% vs. 30%  
  - T4: 24% vs. - |  


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<tr>
<td>Zhang 2000</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients with HCC undergoing curative or relatively curative hepatic resection o A priori patient characteristics: o Male: 87.5% o Mean age: 49.0 years o Preoperative TACE: 8.2%</td>
<td>Tumour diameter (maximal tumour dimension) Intrahepatic extent of tumour (H1: 1 segment; H2: 2 segments; H3: 3 segments; H4: &gt;3 segments) Extrahepatic metastasis Growth type (expansive or invasive growth) Septum formation Portal invasion Hepatic venous invasion Bile duct invasion Surgical curability Surgical free margin Background liver Fibrous capsule</td>
<td>Significant pathologic factors for OS (HR [95%CI]): Tumour diameter &gt; 10cm vs. ≤ 2cm: HR 2.53 (2.07-3.09) Multiple HCC lesions: HR 1.19 (1.05-1.35) Intrahepatic extent of tumour (H3/H4 vs. H1 or less): HR 1.03 (0.77-1.37) Extrahepatic metastasis: HR 2.19 (1.55-3.09) Portal vein invasion: HR 1.46 (1.31-1.62) Hepatic vein invasion: HR 1.17 (1.01-1.36) Surgical curability: HR 1.40 (1.18-1.65) Surgical free margin: HR 1.10 (1.01-1.20)</td>
<td>Level of evidence: C</td>
<td>Population-based study Follow-up results not obtained for 268/1725 cases: excluded from analysis Median follow-up: not reported No clear definitions of prognostic factors provided</td>
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<tr>
<td>Qiang 2006</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients with HCC undergoing curative hepatic resection o A priori patient characteristics:</td>
<td>Number of nodules Tumour capsule Tumour size of main nodule Tumour invasion (portal or hepatic vein)</td>
<td>Significant pathologic factors for DFS (RR [95%CI]): Daughter nodules: RR 9.259, p&lt;0.001 Vascular invasion: RR 2.662, p=0.007 Intraoperative thrombus: HR 0.247, p=0.005 Tumour size: HR 1.374, p=0.010 Tumour gross type: HR 0.202, p=0.003</td>
<td>Level of evidence: C</td>
<td>Lost-to-follow-up: 3.46% Median follow-up: not reported</td>
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| Fan 2009   | Retrospective single cohort study                                       | Male: 90.0%  
Age: 49.0 years  
HBV: 85.3%; HCV: 3.2%  
Cirrhosis: 90.4%  
Child-Pugh A: 47.0% | Cirrhosis  
Tumour differentiation (modified Edmondson)  
Total tumour size (sum of maximal diameter of each lesion)  
Number of nodules  
Tumour satellite  
Tumour site (left lobe, right lobe, bilobe)  
Tumour capsule  
Lymph node invasion  
Macrovascular invasion  
pTNM (UICC) | RR 1.46 (1.16–1.84)  
RR 1.46 (1.31–2.32)  
HR 1.74 (1.31–2.32)  
RR 1.71 (1.33–2.18)  
HR 1.50 (1.09–2.08)  
HR 1.56 (1.23–1.96) | HR 1.62 (1.33–1.98)  
HR 1.56 (1.23–1.96) | Level of evidence: C  
Lost-to-follow-up: N=81  
Mean follow-up: 35.3 months  
Consecutive patient inclusion |
| Wu 2011    | Retrospective single cohort study                                       | Patients with HCC  
Cirrhosis  
Tumour grade | Cirrhosis  
Tumour grade  
HCC size > 5 cm  
HCC size < 5 cm | HCC size > 5 cm  
HCC size < 5 cm | Level of evidence: C  
Lost-to-follow-up: N=81  
Mean follow-up: 35.3 months  
Consecutive patient inclusion |
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<td>Nathan 2009</td>
<td>Retrospective single cohort study</td>
<td>Funding/CoI: no CoI to declare; Setting: single university centre, Taiwan; Sample size: N=1048; Duration: 1/1999-6/2005</td>
<td>undergoing liver resection; A priori patient characteristics: o Male: 79.8% o Mean age: 56.3 years o HBV: 62.3%; HCV: 29.9%</td>
<td>Edmondson) Tumour size; Resection weight; Tumour satellite; Tumour rupture; Tumour capsule; Vascular invasion; Steatosis</td>
<td>Significant pathologic factors for OS (OR [95%CI]): Vascular invasion: OR 2.30 (1.69-3.12); Steatosis: OR 0.67 (0.47-0.95)</td>
<td>Significant pathologic factors for OS (OR [95%CI]): Vascular invasion: OR 1.64 (1.21-2.21); Cirrhosis: OR 1.70 (1.21-2.38)</td>
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<tr>
<td>Shimada 2005</td>
<td>Retrospective single cohort study</td>
<td>Funding/CoI: Support by grant 1KL2RR025906-01 from the National Center for Research Resources (NCRR); Setting: SEER database, US; Sample size: N=788; Duration: 1988-2005</td>
<td>Eligibility criteria: o Patients with HCC undergoing hepatic resection (not ablation or transplantation) o Patients with tumors &gt;5 cm in size or missing size data, extrahepatic tumor extension, or major vascular invasion were excluded o Patients with nodal disease (N1) or unknown N classification and patients with metastatic disease (M1) or unknown M classification were excluded o A priori patient characteristics: o Male: 70% o Median age: 63 years</td>
<td>Tumour grade (well, moderately, poorly, undifferentiated, unknown); Tumour size; Microvascular invasion; Number of nodules; Cirrhosis</td>
<td>Significant pathologic factors for OS (HR [95%CI]): Microvascular invasion: HR 1.44 (1.11-1.86); Tumour size &gt;2 cm: HR 1.51 (1.12–2.03); Multifocality: HR 1.44 (1.11–1.86); Cirrhosis: HR 1.67, p=0.003 (subset of 253 patients)</td>
<td>Level of evidence: C; Consecutive patients; Dropouts not reported; Median follow-up not reported</td>
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<td>Funding/CoI: Supported by a Grant-in-Aid for cancer research from the Ministry of Health,</td>
<td>Eligibility criteria: o Patients with HCC undergoing curative hepatic resection o Surviving at least 1 month after surgery</td>
<td>Tumour size; Resection margin; Number of nodules; Portal vein invasion; Intrahepatic metastases; Background liver</td>
<td>Significant pathologic factors for 10-year OS (OR [95%CI]): Intrahepatic metastases: OR 2.48 (1.31-4.68)</td>
<td>Dropouts: 8 patients who were lost to follow-up, and 14 patients who died of</td>
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- Funding/CoI: no CoI to declare
- Setting: single university centre, Taiwan
- Sample size: N=1048
- Duration: 1/1999-6/2005

- Setting: SEER database, US
- Sample size: N=788
- Duration: 1988-2005

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<td>Vauthey 2002</td>
<td>Retrospective single cohort study</td>
<td>• Eligibility criteria: &lt;ul&gt;&lt;li&gt;Patients with HCC undergoing curative hepatic resection&lt;/li&gt;&lt;li&gt;Surviving at least 1 month after surgery&lt;/li&gt;&lt;li&gt;Patients with incomplete survival data were excluded&lt;/li&gt;&lt;/ul&gt; • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 69%&lt;/li&gt;&lt;li&gt;Mean age: 59 years&lt;/li&gt;&lt;li&gt;HBV: 36%&lt;/li&gt;&lt;li&gt;Child-Pugh A: 83%&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Fibrosis stage  • Tumour size (largest dimension of tumour specimen)  • Number of nodules  • Tumour location (unilobar, bilobar)  • Microvascular invasion  • Macrovascular invasion  • Edmondson Steiner</td>
<td>Significant pathologic factors for OS (HR [95%CI]): &lt;ul&gt;&lt;li&gt;Major vascular invasion: HR 2.1 (1.4-3.3)&lt;/li&gt;&lt;li&gt;Microvascular invasion: HR 1.6 (1.2-2.1)&lt;/li&gt;&lt;li&gt;Tumour size &gt;5 cm: HR 1.4 (1.1–1.9)&lt;/li&gt;&lt;li&gt;Multifocality: HR 1.5 (1.1–1.9)&lt;/li&gt;&lt;li&gt;Severe fibrosis/cirrhosis: HR 1.6 (1.2-2.2)&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Portal vein invasion: OR 1.98 (1.05-3.74)  • Noncancerous liver parenchyma: OR 3.09 (1.69-5.64)  • Solitary nodule: OR 3.12 (1.62-6.02)</td>
<td>• Setting: single centre, Japan  • Sample size: N=481  • Duration: 1/1987-12/1993  • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 79.6%&lt;/li&gt;&lt;li&gt;Mean age: 60 years&lt;/li&gt;&lt;li&gt;Preoperative TACE: 68.4%&lt;/li&gt;&lt;/ul&gt;  • Labor, and Welfare of Japan  • Setting: single centre, Japan  • Sample size: N=481  • Duration: 1/1987-12/1993  • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 79.6%&lt;/li&gt;&lt;li&gt;Mean age: 60 years&lt;/li&gt;&lt;li&gt;Preoperative TACE: 68.4%&lt;/li&gt;&lt;/ul&gt;  • Critical appraisal of study quality: [Level of evidence: C]  • Dropouts not reported  • Median follow-up: 6 years</td>
</tr>
<tr>
<td>Regimbeau 2004</td>
<td>Retrospective single cohort study</td>
<td>• Eligibility criteria: &lt;ul&gt;&lt;li&gt;Patients with HCC undergoing curative partial hepatic resection&lt;/li&gt;&lt;li&gt;Exclusion of patients who died of unknown causes (N=28) or with follow-up &lt; 1 year (N=16)&lt;/li&gt;&lt;/ul&gt; • A priori patient characteristics: not presented for entire cohort</td>
<td>• Fibrosis grade  • Hepatitis grade  • Tumour size (largest dimension of tumour specimen)  • Number of nodules  • Tumour location (unilobar, bilobar)  • Histopathologic type (microtrabecular, macrotrabecular, acinar, diffuse)  • Tumour grade (Edmondson)  • Degree of necrosis  • Fibrous capsule  • Minor vascular invasion  • Major vascular invasion  • Nuclear polymorphism (mild, moderately, marked)  • Resection margin</td>
<td>Significant pathologic factors for early death due to recurrence (OR [SE]): &lt;ul&gt;&lt;li&gt;Nuclear polymorphism: OR 3.0 (0.52)&lt;/li&gt;&lt;li&gt;Tumour size &gt;5 cm: OR 3.0 (0.51)&lt;/li&gt;&lt;li&gt;Multifocality: OR 3.3 (0.50)&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Fibrosis stage  • Tumour size (largest dimension of tumour specimen)  • Number of nodules  • Tumour location (unilobar, bilobar)  • Histopathologic type (microtrabecular, macrotrabecular, acinar, diffuse)  • Tumour grade (Edmondson)  • Degree of necrosis  • Fibrous capsule  • Minor vascular invasion  • Major vascular invasion  • Nuclear polymorphism (mild, moderately, marked)  • Resection margin</td>
<td>• Setting: 4 centres, multinational  • Sample size: N=557  • Duration: 1980-1999  • Eligibility criteria: &lt;ul&gt;&lt;li&gt;Patients with HCC undergoing curative hepatic resection&lt;/li&gt;&lt;li&gt;Surviving at least 1 month after surgery&lt;/li&gt;&lt;li&gt;Patients with incomplete survival data were excluded&lt;/li&gt;&lt;/ul&gt; • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 69%&lt;/li&gt;&lt;li&gt;Mean age: 59 years&lt;/li&gt;&lt;li&gt;HBV: 36%&lt;/li&gt;&lt;li&gt;Child-Pugh A: 83%&lt;/li&gt;&lt;/ul&gt;  • Setting: 4 centres, multinational  • Sample size: N=557  • Duration: 1980-1999  • Eligibility criteria: &lt;ul&gt;&lt;li&gt;Patients with HCC undergoing curative partial hepatic resection&lt;/li&gt;&lt;li&gt;Surviving at least 1 month after surgery&lt;/li&gt;&lt;li&gt;Patients with incomplete survival data were excluded&lt;/li&gt;&lt;/ul&gt; • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 69%&lt;/li&gt;&lt;li&gt;Mean age: 59 years&lt;/li&gt;&lt;li&gt;HBV: 36%&lt;/li&gt;&lt;li&gt;Child-Pugh A: 83%&lt;/li&gt;&lt;/ul&gt;  • Level of evidence: C  • Dropouts not reported  • Median follow-up: 35 months</td>
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<td>Vauthey 2002</td>
<td>Retrospective single cohort study</td>
<td>• Eligibility criteria: &lt;ul&gt;&lt;li&gt;Patients with HCC undergoing curative hepatic resection&lt;/li&gt;&lt;li&gt;Surviving at least 1 month after surgery&lt;/li&gt;&lt;li&gt;Patients with incomplete survival data were excluded&lt;/li&gt;&lt;/ul&gt; • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 79.6%&lt;/li&gt;&lt;li&gt;Mean age: 60 years&lt;/li&gt;&lt;li&gt;Preoperative TACE: 68.4%&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Fibrosis stage  • Tumour size (largest dimension of tumour specimen)  • Number of nodules  • Tumour location (unilobar, bilobar)  • Microvascular invasion  • Macrovascular invasion  • Edmondson Steiner</td>
<td>Significant pathologic factors for early death due to recurrence (OR [SE]): &lt;ul&gt;&lt;li&gt;Nuclear polymorphism: OR 3.0 (0.52)&lt;/li&gt;&lt;li&gt;Tumour size &gt;5 cm: OR 3.0 (0.51)&lt;/li&gt;&lt;li&gt;Multifocality: OR 3.3 (0.50)&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Portal vein invasion: OR 1.98 (1.05-3.74)  • Noncancerous liver parenchyma: OR 3.09 (1.69-5.64)  • Solitary nodule: OR 3.12 (1.62-6.02)</td>
<td>• Setting: single centre, Japan  • Sample size: N=481  • Duration: 1/1987-12/1993  • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 79.6%&lt;/li&gt;&lt;li&gt;Mean age: 60 years&lt;/li&gt;&lt;li&gt;Preoperative TACE: 68.4%&lt;/li&gt;&lt;/ul&gt;  • Labor, and Welfare of Japan  • Setting: single centre, Japan  • Sample size: N=481  • Duration: 1/1987-12/1993  • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 79.6%&lt;/li&gt;&lt;li&gt;Mean age: 60 years&lt;/li&gt;&lt;li&gt;Preoperative TACE: 68.4%&lt;/li&gt;&lt;/ul&gt;  • Critical appraisal of study quality: [Level of evidence: C]  • Dropouts not reported  • Median follow-up: 6 years</td>
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<tr>
<td>Regimbeau 2004</td>
<td>Retrospective single cohort study</td>
<td>• Eligibility criteria: &lt;ul&gt;&lt;li&gt;Patients with HCC undergoing curative partial hepatic resection&lt;/li&gt;&lt;li&gt;Surviving at least 1 month after surgery&lt;/li&gt;&lt;li&gt;Patients with incomplete survival data were excluded&lt;/li&gt;&lt;/ul&gt; • A priori patient characteristics: &lt;ul&gt;&lt;li&gt;Male: 69%&lt;/li&gt;&lt;li&gt;Mean age: 59 years&lt;/li&gt;&lt;li&gt;HBV: 36%&lt;/li&gt;&lt;li&gt;Child-Pugh A: 83%&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Fibrosis stage  • Tumour size (largest dimension of tumour specimen)  • Number of nodules  • Tumour location (unilobar, bilobar)  • Histopathologic type (microtrabecular, macrotrabecular, acinar, diffuse)  • Tumour grade (Edmondson)  • Degree of necrosis  • Fibrous capsule  • Minor vascular invasion  • Major vascular invasion  • Nuclear polymorphism (mild, moderately, marked)  • Resection margin</td>
<td>Significant pathologic factors for early death due to recurrence (OR [SE]): &lt;ul&gt;&lt;li&gt;Nuclear polymorphism: OR 3.0 (0.52)&lt;/li&gt;&lt;li&gt;Tumour size &gt;5 cm: OR 3.0 (0.51)&lt;/li&gt;&lt;li&gt;Multifocality: OR 3.3 (0.50)&lt;/li&gt;&lt;/ul&gt;</td>
<td>• Portal vein invasion: OR 1.98 (1.05-3.74)  • Noncancerous liver parenchyma: OR 3.09 (1.69-5.64)  • Solitary nodule: OR 3.12 (1.62-6.02)</td>
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| Zhou 2010 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing curative hepatic resection  
- A priori patient characteristics:  
  - Male: 86.9%  
  - Median age: 65.8 years  
  - HBV: 36.3%; HCV: 46.4% | Tumour differentiation (Edmondson)  
- Vascular invasion  
- TNM stage  
- pAkt expression  
- PTEN expression  
- p27 expression  
- pS6 expression | Significant pathologic factors for OS (OR [95%CI]):  
- Tumour differentiation: OR 2.15 (1.32-1.51)  
- Vascular invasion: OR 4.98 (1.46-12.01)  
- TNM stage: OR 2.32 (1.11-3.09)  
- pAkt expression: 2.96 (1.18-10.79)  
- PTEN expression: 2.61 (1.69-3.98)  
- p27 expression: OR 1.69 (1.12-2.55)  
- pS6 expression: OR 3.86 (1.71-8.76) |  | Level of evidence: C  
- Consecutive patient inclusion  
- Median follow-up: 42 months  
- Vascular invasion not clearly defined |
| Yang 2009 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing hepatic resection  
- A priori patient characteristics:  
  - Male: 89.4%  
  - Age ≥ 50: 42.8%  
  - HBV: 92.5%  
  - Child-Pugh A: 81.1%  
  - Cirrhosis  
  - Tumour size  
  - Degree of necrosis  
  - Fibrous capsule  
  - Vein invasion  
  - Edmondson-Steiner Grade  
  - Tumour nodule number |  | Significant pathologic factors for OS [HR [95%CI]]:  
- Vein invasion: HR 48.74 (4.76-498.37) |  | Level of evidence: C  
- Consecutive patient inclusion  
- Median follow-up: 38 months  
- Dropouts not reported  
- No clear definition of prognostic factors |
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| Wang 2009 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing hepatic resection with curative intent  
- A priori patient characteristics:  
  - Male: 80.1%  
  - Mean age: 53.1 years  
  - HBV: 68.5%; HCV: 28.9%  
  - Child-Pugh A: 83.3% | Histopathology of non-tumour tissue  
- Adjacent tissue invasion  
- Tumour size (largest diameter of tumour)  
- Number of nodules (single vs. multiple)  
- Tumour location (unilateral, bilateral)  
- Micronodular invasion  
- Daughter nodule | Significant pathologic factors for DFS (RR [95%CI]):  
- Micronodular invasion: RR 1.85 (1.41-2.42)  
- Liver cirrhosis: RR 1.83 (1.40-2.40)  
- Tumour diameter >10cm: RR 2.07 (1.34-2.90)  
- Bilateral disease: RR 2.22 (1.16-4.26)  
- Daughter nodule: RR 2.18 (1.58-3.01) | Level of evidence: C  
- Consecutive patient inclusion  
- Mean follow-up: 3.6 years  
- Dropouts not reported |
| Duffy 2007 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing orthotopic liver transplantation  
- A priori patient characteristics:  
  - Male: 60%  
  - Mean age: 57 years  
  - HBV: 17%; HCV: 55% | Multifocal tumour  
- Lymphovascular invasion  
- Tumour differentiation (well, moderately, poorly)  
- Tumour size | Significant pathologic factors for OS:  
- Multifocal tumour: HR 0.22, p<0.001  
- Lymphovascular invasion: HR 2.44, p<0.001  
- Tumour differentiation: HR 4.53, p=0.002 | Level of evidence: C  
- Mean follow-up: 6.6 years  
- Dropouts not reported |
| Lim 2011 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing curative hepatic resection  
- No concomitant non-HCC cancers  
- A priori patient characteristics:  
  - Male: 61%  
  - Mean age: 61.3 years  
  - HBV: 66%  
  - Child-Pugh A: 93% | Cirrhosis  
- Adjacent tissue invasion  
- Tumour size (size of largest tumour)  
- Number of nodules  
- Tumour grade (Edmondson)  
- Microvascular invasion  
- Resection margin | Significant pathologic factors for OS (HR [95%CI]):  
- Microvascular invasion: HR 2.12 (1.52-2.97)  
- Invasion of contiguous organs: HR 2.74 (1.08-6.94)  
- Cirrhosis: HR 1.49 (1.07-2.07) | Level of evidence: C  
- Median follow-up: 27.7 months  
- Dropouts not reported |
| Pawlik 2004 | Retrospective single cohort study | Eligibility criteria:  
- Patients with HCC undergoing hepatic resection  
- Cirrhosis  
- Tumour size (largest) | Cirrhosis  
- Tumour size (largest) | Significant pathologic factors for OS (HR [95%CI]):  
- Cirrhosis: HR 2.12 (1.52-2.97)  
- Invasion of contiguous organs: HR 2.74 (1.08-6.94)  
- Cirrhosis: HR 1.49 (1.07-2.07) | Level of evidence: C  
- Median follow-up: 33 years  
- Dropouts not reported |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Method</th>
<th>Patient characteristics</th>
<th>Prognostic factors included in analysis</th>
<th>Results multivariate analysis</th>
<th>Results other analyses</th>
<th>Critical appraisal of study quality</th>
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</thead>
<tbody>
<tr>
<td>Lei 2006</td>
<td>Retrospective single cohort study</td>
<td>Funding/CoI: no CoI to declare Setting: single centre, Taiwan Sample size: N=440 Duration: 7/1991-1/1999</td>
<td>Eligibility criteria: • Patients with HCC undergoing hepatic resection • Patients dying in the hospital before discharge were excluded • A priori patient characteristics: not reported for entire group o Male: 86.8% • Mean age: 59.6 years o HBV: 65.7%; HCV: 22% Fibrosis score Adjacent tissue invasion Tumour size Number of nodules Tumour location Microvascular invasion Macrovascular invasion</td>
<td>Log-rank (95%CI, p value): Tumour size: 1.20-1.93, p=0.006 Number of nodules: 1.21-2.38, p=0.001 Tumour location (unilobar, bilobar): Tumour size: 1.21-2.38, p=0.001 Microvascular invasion: HR 1.88 (1.44-2.46) Macrovascular invasion: HR 2.36 (1.50-3.72) Fibrosis/cirrhosis: HR 2.16 (1.48-3.15)</td>
<td>Dropouts not reported</td>
<td>Level of evidence: C</td>
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<tr>
<td>Wang 2010</td>
<td>Retrospective single cohort study</td>
<td>Funding/CoI: supported by the Special Research Foundation of the National Nature Science Foundation of China (30872487); no CoI to declare Setting: single university centre, China Sample size: N=438 Duration: 1/1991-12/2004</td>
<td>Eligibility criteria: • Patients with HCC undergoing partial hepatic resection • Patients dying in the hospital before discharge were excluded • A priori patient characteristics: not reported for entire group o Male: 86.8% • Mean age: 50 years Tumour size (sum of largest diameter of each nodule) Number of nodules Tumour location (unilobar, bilobar) Capsular invasion Satellite nodules Resection margin</td>
<td>Significant pathologic factors for OS (95%CI, p value): Tumour size: 1.17-1.6, p&lt;0.001 Capsular invasion: 0.48-0.99, p=0.047 Resection margin: 0.5-0.91, p=0.011 Macrovascular invasion: 1.18-1.56, p=0.003</td>
<td>Median follow-up: 66 months</td>
<td>Level of evidence: C</td>
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<tr>
<td>Lauwers 2002</td>
<td>Retrospective single cohort study</td>
<td>Funding/CoI: not reported Setting: multicentre, multinational Sample size: N=425 Duration: 1980-1998</td>
<td>Eligibility criteria: • Patients with HCC undergoing complete resection and with complete histopathologic information • Patients who died within 30 days after Tumour size (largest dimension of each nodule) Nuclear grade (G1, G2, G3) Tumour stage (AJCC) Mitosis activity Tumour size (largest dimension of each nodule) Nuclear grade (G1, G2, G3) Tumour stage (AJCC)</td>
<td>Significant pathologic factors for OS: Microvascular invasion: p=0.001 Nuclear grade 3: p=0.008</td>
<td>Dropouts not reported Same patients as</td>
<td>Level of evidence: C</td>
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<td>Wu 2005</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients with cirrhosis and HCC undergoing elective curative hepatectomy o Patients with recurrent HCC whose first liver resection was carried out elsewhere and those who underwent emergency surgery for ruptured HCC were excluded</td>
<td>Tumour size Number of nodules Tumour capsule Satellite nodules Resection margin Vascular invasion Tumour grade (Edmondson) Tumour stage (UICC)</td>
<td>Significant pathologic factors for OS (RR [95%CI]): • TNM stage II: RR 0.26 (0.15-0.46) • TNM stage III: RR 0.48 (0.29-0.63)</td>
<td>Significant pathologic factors for DFS (RR [95%CI]): • TNM stage II: RR 0.73 (0.57-0.93) • TNM stage III: RR 0.88 (0.73-1.07)</td>
<td>Level of evidence: C • Median follow-up: 49.6 and 40.1 months • Dropouts not reported • No clear definition of vascular invasion</td>
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<tr>
<td>Zhang 2009</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients with liver cirrhosis and newly diagnosed HCC undergoing liver resection</td>
<td>Tumour size Number of nodules Tumour location (unilobar, bilobar) Tumour capsule Resection margin Vascular invasion (portal or hepatic vein invasion) TNM stage (UICC)</td>
<td>Significant pathologic factors for OS: • Tumour location (1 lobe/2 lobes): HR 4.93 • Vascular invasion: HR 2.82 • Tumour capsule: HR 2.51</td>
<td>Significant pathologic factors for DFS: • Tumour location (1 lobe/2 lobes): HR 48.81 • Vascular invasion: HR 3.97 • Tumour capsule: HR 2.39</td>
<td>Level of evidence: C • Median follow-up: 21 months • 10% (46/458) were lost in follow-up</td>
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<td>Vauthey 2007</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients who underwent liver transplantation for HCC o Patients with fibrolamellar variant of HCC and those who died postoperatively were excluded A priori patient characteristics: not reported for entire group o Male: 81.8% o Median age: 56 years o Child-Pugh A: 23.5% o HCV: 48.6%; HBV: 18.1%</td>
<td>The following staging systems were evaluated: AJCC/UICC, Japanese TNM and Pittsburgh - were OS and RFS longer for patients with low stage vs. more advanced stage</td>
<td>For OS and RFS, sequential stages were different only for AJCC/UICC: OS: o II vs. I: HR 1.58 (1.08-2.30) o IIIA vs. II: HR 1.995 (1.25-3.19) RFS: o II vs. I: HR 1.74 (1.21-2.49) o IIIA vs. II: HR 2.01 (1.29-3.14)</td>
<td>Level of evidence: C</td>
<td>Consecutive patient inclusion Median follow-up: 40 months Dropouts not reported</td>
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<tr>
<td>Eguchi 2011</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients with HCC who had undergone liver resection with curative intent o Patients who survived more than 10 years without recurrence of HCC (N=281) and those who died from recurrent HCC within 5 years of liver resection were identified (N=918) A priori patient characteristics: 10y RFS vs. died within 5 years o Male: 77.9% vs. 82.2% o Median age: 57.5 vs. 60.8 years o Child-Pugh A: 79.1% vs. 85.1% o HCV: 52.0% vs. 75.1%; HBV: 32.2% vs. 22.0%</td>
<td>Tumour size Number of nodules Intrahepatic metastases Non-cancerous liver (normal, chronic hepatitis, fibrosis, cirrhosis) Vascular invasion (microscopic portal vein invasion?) Tumour differentiation (well, moderate, poor, unknown) Macroscopic type: type 1 (simple nodular type), type 2 (simple nodular type with extranodular growth), type 3 (confluent multinodular type), type 4 (multinodular type), type 5 (others, including infiltrative, mass and diffuse types) or unknown</td>
<td>Significant pathologic factors for death from recurrence within 5 years (OR [95%CI]): Tumour size &gt;5 cm: OR 2.56 (1.16-5.65) Poor tumour differentiation: OR 3.33 (1.46-7.60) Intrahepatic metastasis: OR 2.34 (1.02-5.37)</td>
<td>Level of evidence: C</td>
<td>Median follow-up: 11.2 and 0.9 years respectively Dropouts not reported</td>
</tr>
<tr>
<td>Liu 2009</td>
<td>Retrospective single cohort study</td>
<td>Eligibility criteria: o Patients with HCC Tumour size Liver cirrhosis</td>
<td>Significant pathologic factors for RFS (HR)</td>
<td>Level of evidence: C</td>
<td>Median follow-up: 11.2 and 0.9 years respectively Dropouts not reported</td>
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<tr>
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<td>• Funding/CoI: supported by the Research Foundation from Shanghai Municipal Education Commission, PR China, No 06CZ016; no CoI to declare</td>
<td>who had undergone liver resection</td>
<td>• Intrahepatic metastases</td>
<td>[95%CI]):</td>
<td>• Median follow-up: not reported</td>
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<td>• Setting: single university centre, China</td>
<td>A priori patient characteristics:</td>
<td>• Tumour capsule</td>
<td>Intrahepatic metastasis: HR 2.32 (1.24-4.72)</td>
<td>• Lost to follow-up: 19.5%</td>
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<td>• Sample size: N=458</td>
<td>o Male: 71.4%</td>
<td>• Histological grade (well, moderately, poor)</td>
<td>P53: HR 2.67 (1.25-6.84)</td>
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<td>• Duration: 1/2002-6/2005</td>
<td>o Median age: not reported</td>
<td>• P53</td>
<td>BUBR1: HR 3.25 (1.42-7.9)</td>
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<td>o HBV: 76.2%</td>
<td>• Ki67</td>
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<td>• BUBR1 overexpression</td>
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