Published in final edited form as:
Liver Transpl. 2011 October ; 17(Suppl 2): S147–S158. doi:10.1002/lt.22367.

What Is the Role of Adjuvant Therapy After Liver Transplantation for Hepatocellular Carcinoma?

Christophe Duvoux[1], **Tetsuya Kiuchi**[2], **Bernhard Pestalozzi**[3], **Ronald Busuttil**[4], and **Rebecca Miksad**[5]

[1]Liver Transplant Unit, Henri Mondor Hospital AP-HP, Paris–Est Créteil University, Créteil, France [2]Division of Transplantation Surgery, Department of Surgery, Nagoya University Hospital, Nagoya University of Medicine, Nagoya, Japan [3]Clinic and Polyclinic for Oncology, University Hospital, Zurich, Switzerland [4]Division of Liver and Pancreas Transplantation, Department of Surgery, University of California Los Angeles, Los Angeles, CA [5]Division of Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

Liver transplantation (LT) is a potentially curative treatment for hepatocellular carcinoma (HCC) because it removes both the tumor and the underlying cirrhotic liver (which can give rise to new tumors). However, the early experience with LT for HCC in the 1980s was disappointing because of the relatively high recurrence rates (65% of all patients in 1 series[1]) and the discouraging overall survival results (5-year survival = 10%–35%).[1–4] In particular, the prognosis of patients with recurrent HCC after LT was dismal: in historical series, the median survival time after recurrence was 6 months, and there were virtually no survivors beyond 3 years (Fig. 1).

Because of these early results with LT and worldwide organ shortages, orthotopic LT is generally restricted to HCC patients with an expected 5-year post-LT survival rate > 50%. In addition, most LT programs require HCC patients to have an expected 5-year post-LT survival rate similar to that of patients with benign liver diseases (ie, 70%).[5] To achieve these post-LT survival goals, the Milan criteria[6] were adopted as a liver recipient prioritization tool more than 10 years ago by the United Network for Organ Sharing and by the majority of transplant programs worldwide. In multiple evaluations, the Milan criteria have consistently identified patients who will achieve 5-year post-LT survival rates ranging from 65% to 80% and experience 5-year tumor recurrence rates ranging from 8% to 15%.[7–9]

The continued rise in the number of patients diagnosed with HCC means that HCC has emerged as a major LT indication despite the restrictive Milan criteria: in most LT programs, HCC is now the LT indication for 25% to 35% of patients. Because of the number of organs directed to HCC patients, the persistence of post-LT recurrence is a vexing medical and ethical problem of increasing importance. Therefore, efforts to decrease the rates of post-LT tumor recurrence, to prevent recurrence-induced graft losses, and to further improve overall survival have included antitumor adjuvant therapy after LT. However, the data for this approach remain sparse and controversial; this is particularly true for the potential of adjuvant therapy to extend transplant eligibility criteria.

In this article, we discuss the following questions about adjuvant therapy after LT for HCC:

Address reprint requests to Christophe Duvoux, M.D., Liver Transplant Unit, Henri Mondor Hospital AP-HP, Paris–Est Créteil University, Créteil, France. christophe.duvoux@hmn.aphp.fr.

Potential conflict of interest: Nothing to report.

1. What are the results of the current experience with adjuvant therapy after LT for HCC?
2. What are the approaches that should be considered to improve the quality of trials for adjuvant therapy after LT for HCC?
    a. What are the best compounds to test in the adjuvant setting?
    b. What are the target populations for adjuvant therapy?
    c. What are the optimal endpoints for testing the efficacy of adjuvant therapy after LT for HCC?

MATERIALS AND METHODS

We searched MEDLINE (PubMed), the Cochrane Hepato-Biliary Group Controlled Trials Register, and the Cochrane Library (through 2010) to identify all trials (single-arm and controlled) that evaluated antitumor adjuvant therapy after LT for HCC. The key words were *hepatocellular carcinoma*, *liver transplantation*, and *adjuvant therapy*. Studies evaluating both neoadjuvant therapy and adjuvant therapy were included. Studies of immunosuppressive agents in adjuvant therapy were excluded if no other antitumor agent was evaluated. The identified trials were independently reviewed by 3 authors (C.D., T.K, and R.M.), and discrepancies were resolved by consensus.

Because of the importance of the post-LT HCC recurrence risk to decision making for adjuvant therapy, we also searched the same databases for prognostic models of post-LT HCC recurrence. The key words for this search were *prognostic model*, *hepatocellular carcinoma*, and *liver transplantation*.

The levels of evidence and the recommendations were independently graded according to the standards of the Centre for Evidence-Based Medicine (March 2009) by 3 authors (C.D., T.K, and R.M.), and discrepancies were resolved by consensus.

ANALYSIS

Question 1. What Are the Results of the Current Experience With Adjuvant Therapy After LT for HCC?

Principles of Adjuvant Therapy—The goal of antitumor adjuvant therapy after LT is the improvement of patient outcomes through the reduction of HCC recurrence and the improvement of overall survival. Adjuvant therapy may achieve this goal through the elimination of undetectable micrometastases present at the time of surgery. However, not all patients require adjuvant therapy to remain cancer-free, and some patients will survive for only a short time despite adjuvant therapy. Therefore, the potential benefits of adjuvant therapy must be weighed against the potential risks. The complex surgical and immunosuppression issues in the posttransplant setting and the potential for treatment toxicity make this balance particularly important for post-LT adjuvant therapy for HCC.

In contrast to adjuvant therapy after the surgical treatment of other cancers, post-LT antitumor adjuvant therapy for HCC must also be considered in the context of overall liver graft allocation. Because of the scarcity of organs and ethical issues, post-LT adjuvant therapy for HCC must be expected to provide sufficient net benefits to make LT appropriate according to accepted allocation principles. Although specific allocation rules may vary over time and by region, the current general acceptance of the Milan criteria suggests that post-LT adjuvant therapy must keep the average 5-year recurrence rate below 15% and provide an average 5-year survival rate of at least 60%.

Current Experience With Adjuvant Therapy After LT—In the early 1990s, researchers began to evaluate the impact of adjuvant therapy on the prevention of recurrence after LT. Eight nonrandomized studies were identified: 4 prospective studies (1 with historical controls) and 4 retrospective case series (251 patients in all).[10–17] Four randomized controlled studies were also identified (213 patients in all).[18–21] The study results and the assessed levels of evidence are summarized in Tables 1 (nonrandomized studies) and 2 (randomized studies).

Although several nonrandomized studies have suggested a modest benefit from adjuvant therapy, most randomized trials have not. In addition, the results from all adjuvant therapy studies must be interpreted with caution because of the heterogeneity of the treatment approaches, the adjuvant agents, the inclusion criteria, and the treatment regimens as well as the small sample sizes.

Treatment Approach: The evaluation of post-LT adjuvant therapy trials is complicated by the use of neoadjuvant and intraoperative therapies. Although neoadjuvant therapy is commonly considered to be systemic chemotherapy, some patients may undergo transplantation after exposure to chemotherapy from chemoembolization. Other neoadjuvant therapies may include tumor-directed treatments such as radiofrequency ablation. The control of neoadjuvant therapy for the direct evaluation of the effects of adjuvant therapy is limited in most studies. Intraoperative therapy may be systemic or liver/peritoneum-directed. Finally, the length of adjuvant therapy varies between studies.

Variable Agents: A diverse group of agents have been evaluated in the post-LT adjuvant setting. Doxorubicin, an anthracycline antibiotic used as a single agent or in combination with cisplatin and fluorouracil, has been studied most rigorously. Epirubicin, an agent in the same class of chemotherapeutics, has also been evaluated. Other agents include Licartin, mitoxantrone, gemcitabine in combination with cisplatin, and mitoxantrone. Finally, the use of immunosuppression agents (which may have an impact on tumor recurrence) has varied within and between studies.

Diverse Inclusion Criteria/Target Populations: The target populations fall into 2 main groups: (1) patients chosen for transplantation according to extended criteria and (2) patients with a high risk of recurrence according to the explant pathology (whether or not they met the Milan criteria before the operation).

Small Sample Sizes: Most studies of post-LT adjuvant therapy have been small, and only a minority of them have been designed as randomized controlled trials.[18–21] The 4 published randomized controlled trials of post-LT adjuvant therapy enrolled only 213 patients in all.

Study Endpoints: The study endpoints have varied greatly between trials (from recurrence to overall survival and disease-free recurrence), and this makes comparisons difficult.

Trial Results—Although multiple nonrandomized studies of doxorubicin given during LT (alone or in combination with other agents) have suggested a survival benefit (evidence level 4), 2 randomized studies of single-agent doxorubicin during LT did not demonstrate a statistically significant benefit (evidence level 2b).[18,19] Epirubicin, which is in the same class of chemotherapeutics, also did not show a survival benefit in a randomized trial of adjuvant therapy. These results are consistent with the results for doxorubicin in the setting of advanced HCC, for which it showed a modest response rate and small and variable survival benefits. Overall, the current data disfavor the pursuit of adjuvant doxorubicin studies (recommendation grade B−), and the use of adjuvant doxorubicin in clinical practice cannot be recommended (recommendation grade B−).

More recently, Licartin, an ^{131}I-radiolabeled murine monoclonal antibody that specifically binds to HCC cells expressing an HCC-specific molecule (HAb18G/CD147), was tested in a small placebo-controlled, randomized, double-blind study in China.[20]

At the 1-year follow-up, the HCC recurrence rate was significantly lower for the treatment group (26.7%) versus the control group (57.1%); the absolute difference was 30.4%. Likewise, the survival rate was 82.5% for the treatment group and 61.9% for the control arm (evidence level 2b; Fig. 2). However, the number of patients was limited, and the follow-up was short (1 year). These encouraging results, therefore, deserve confirmation (recommendation grade C by the extrapolation of a single level 2b study).

In summary, single-arm, retrospective studies suggest a role for adjuvant therapy, but their level of evidence (level 4) is not strong enough to make any definite conclusions, particularly with respect to specific agents. The results from controlled studies are mixed (ie, negative, inconclusive, or requiring confirmation).

Overall, although some level 4 studies and 1 level 2 study may be consistent with recommendation grade C for any type of adjuvant therapy for HCC, we favor recommendation grade D for the post-LT use of doxorubicin because of the inconsistency and inconclusiveness of the studies and the 2 level 2b studies that failed to demonstrate any efficacy of doxorubicin.

On the basis of the limited evidence to date, we believe that adjuvant therapy after LT for HCC cannot be recommended outside the setting of a clinical trial. Additional, well-designed trials are mandatory for further examining the role of adjuvant therapy.

Question 2. What Are the Approaches That Should Be Considered to Improve the Quality of Trials for Adjuvant Therapy After LT for HCC?

Applicability of Adjuvant Therapy to LT and Specific Requirements—In the setting of LT for HCC, the applicability of adjuvant therapy is intrinsically limited by several factors unique to the transplant patient.

Eligibility for transplantation is based on careful screening designed to select those patients with a low risk of recurrence. Therefore, the incremental benefit of adjuvant therapy is relatively small for the majority of transplant patients. In this setting, a demonstration of efficacy would require a large number of patients.

For patients at a high risk for tumor recurrence after LT, the tumor burden and the tumor behavior were generally underestimated before LT. The risk of recurrence in these patients may be as high as 30% to 40%. Therefore, in order to achieve goals based on the Milan criteria for optimal liver allocation, adjuvant therapy for these patients would need to achieve a 20% absolute reduction in the 5-year recurrence rate. However, these patients may differ from typical transplant patients with HCC, and generalizations may be limited.

Social, medical, legal, and political factors that affect the relative sizes of the donor liver pool and the potential recipient pool may also affect the threshold benefit required to demonstrate the efficacy of adjuvant therapy.

To date, post-LT adjuvant therapies based on conventional chemotherapy agents have failed to demonstrate efficacy. The evaluations of newer agents such as the multikinase inhibitor sorafenib (which has been approved for the treatment of patients with advanced renal cancer and unresectable HCC[22]) are still in the early phases. Therefore, the current data for guiding the development of large randomized controlled studies are limited.

Because of these limitations, it is important to define the optimal conditions under which the efficacy of new compounds may be tested. For this purpose, we address the following questions:

1. What are the best compounds or strategies for post-LT adjuvant therapy?
2. What is the best population to target with adjuvant therapy, and who are the best candidates to be enrolled in clinical trials of post-LT adjuvant therapy?
3. What are the best endpoints to choose?
4. How do we demonstrate the efficacy of adjuvant therapy?

What Are the Best Compounds or Strategies for Post-LT Adjuvant Therapy?— Because of the lack of significant survival benefits from traditional chemotherapies for advanced HCC and in the post-LT setting, it is unlikely that traditional chemotherapies will have a major impact in the adjuvant LT setting.

Therefore, we believe that novel agents should be developed in well-designed trials. In particular, the results of sorafenib and Licartin are discussed here for advanced HCC and in the post-LT setting, respectively. Rapalogs, which are primarily used as antirejection agents in organ transplantation but may also have antiproliferative properties, will be discussed by a separate conference working group.

Sorafenib: Sorafenib is a multitargeting tyrosine kinase inhibitor that inhibits tumor growth and angiogenesis. Because of the results of the Sorafenib HCC Assessment Randomized Protocol trial,[22] sorafenib has become the standard first-line treatment for advanced and unresectable HCC (evidence level 1b). Sorafenib is currently being tested in the adjuvant setting after the resection or radiofrequency ablation of HCC in a multicenter phase 3 study [Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM)].

Data about the use of sorafenib after LT are scarce. The experience with sorafenib after LT is based on a limited number of patients, and so far, its use has been reported mostly in patients with HCC recurrence.[23–26] Dose adjustments due to sorafenib-related side effects have been required in 40%[23] to 66%[24,27] of these patients. Additional information is, therefore, required before sorafenib is tested in the adjuvant setting, in which the risk-benefit ratio is different. A phase 1 study of sorafenib for 6 months after LT for high-risk HCC is being led by Columbia University (New York, NY) and is currently accruing patients; this study should help to define dose tolerability (the principal investigator is A. Siegel). For this study, high-risk patients are being defined as (1) patients outside the Milan criteria before or at the time of transplantation, (2) patients with microvascular or macrovascular invasion, and (3) patients with poorly differentiated tumors according to histological findings. The dosage starts at 200 mg of sorafenib per day and reaches 400 mg twice per day in the fourth and final cohort. Patients begin to take sorafenib 4 to 16 weeks after transplantation once the immunosuppressant doses are stabilized. A phase 1 study of sorafenib for 6 months after LT, which was led by the University of Washington (Seattle, WA), was recently closed because of slow accrual; this suggests that studies with complex eligibility requirements may be challenging. Proposals are currently being developed for a large multicenter study (a phase 2 randomized controlled trial) of high-risk patients (ie, patients on the borderline for the Milan criteria) being treated with sorafenib for 2 years after orthotopic LT. Because of the complexities of post-LT studies, it seems reasonable to wait for the results of the phase 1 trial and also to wait for signals from the STORM trial before a sorafenib study in the adjuvant setting is finalized and begun.

Licartin: As discussed previously, the results from a randomized controlled trial of Licartin[20] are attractive. However, these results should be interpreted with caution until the results from a longer follow-up period and confirmatory evidence are produced. In particular, Licartin should be tested in larger studies of more generalized populations.

Other Targeted Agents: New targeted agents at various stages of evaluation for advanced HCC may be useful for post-LT adjuvant therapy. However, any evaluation in the post-LT setting should be delayed until the results of current studies are known.

Rapalogs: As mentioned previously, a separate working group will focus on this class of agents, which have immunosuppressive and antitumor properties that merit further evaluation.

Immunotherapy: In the adjuvant setting, immunotherapy may be an attractive option because of its high specificity, low systemic toxicity, and limited drug interactions. However, this potential remains to be confirmed because we cannot exclude the possibility that some of the immune mechanisms by which HCC cells escape immunotherapy in the nontransplant setting (eg, the generation of suppressor cells[28]) may be amplified by immunosuppressive therapies.

What Is the Best Population to Target With Adjuvant Therapy, and Who Are the Best Candidates to Be Enrolled in Clinical Trials of Post-LT Adjuvant Therapy?—Virtually all patients who undergo transplantation for HCC are at risk for recurrence and may benefit from adjuvant therapy, which can prevent recurrence-induced graft loss and optimize the use of the liver graft pool (a scarce and collective resource).

Patients undergoing transplantation for HCC generally fall into 3 categories: patients with a low risk of recurrence (5-year rate = 8%–15%), who account for the majority of recipients; patients with an intermediate risk of recurrence (5-year rate = 20%–30%); and patients with a high risk of recurrence (5-year rate > 35%–40%). Generally, patients falling within the Milan criteria before the operation have a low or intermediate risk of recurrence.

As previously mentioned, demonstrating the efficacy of adjuvant therapy in low- and intermediate-risk patients would require a considerable number of patients and many participating study sites, which would greatly increase the logistical complexity of a randomized trial.

In contrast, a study of high-risk patients is more likely to produce a benefit signal in a reasonably sized study, as observed in the Licartin trial. However, patients known to have a high risk of recurrence before the operation are generally not eligible for LT, in large part because of allocation and ethical issues raised by the limited supply of organs. Even a substantial recurrence or survival benefit from adjuvant therapy for high-risk patients may not produce outcomes equivalent to those achieved for low-risk patients. Therefore, performing transplantation for high-risk patients with extended criteria before LT with the intention of enrolling them in an adjuvant therapy trial may be considered unethical because of allocation issues and distributive ethics. Furthermore, the use of expanded criteria for an adjuvant therapy trial raises ethical issues about the design of the control arm.

To take these limitations into account, we believe that the best approach is the study of adjuvant therapy in patients whose liver explants demonstrate that the tumor burden, behavior, or both were underestimated despite the standard and thorough preoperative evaluation. This approach also benefits from the gold standard: the pathological evaluation of tumor characteristics (including tumors that are difficult to assess with preoperative

imaging because of tumor differentiation and microvascular invasion). The primary limitations are (1) the need for a standardized, reproducible, and accurate definition of patients with a high risk of recurrence and (2) the issue of generalizability to low-risk patients. However, we believe that high-risk patients who are selected a posteriori are the optimal study population because an untreated control arm in a randomized controlled study of adjuvant therapy is ethically acceptable.

Prognostic Models: Pathological features that are predictive of recurrence have been extensively studied, and several pathological predictors have been identified: the tumor size and number,[29] tumor differentiation,[9,30–33] microvascular invasion,[30,31,34,35] satellite nodules,[36] and molecular signatures (eg, an allelic imbalance). A number of predictive models of recurrence have also been designed over the last decade.[29,34,37–42] For the conference, these prognostic models were reviewed. We identified 4 models that exclusively focus on the pathological predictors of recurrence[29,37,39,41] and that may be useful for selecting high-risk patients. These models and the assessed levels of evidence are summarized in Table 3.

The Metroticket model[29] has recently become popular for predicting the prognosis after LT for HCC (evidence level 2b/4). This model is based on an analysis of a cohort of 1556 explants and takes into account the tumor size and number and microvascular invasion. Although it is potentially useful for stratifying patients for adjuvant therapy trials, the Metroticket model has not been validated in an external cohort and was actually designed to predict overall survival rather than recurrence.

The predicting cancer recurrence score (PCRS)[41] was derived from a multivariate analysis of 94 patients who were accurately staged preoperatively; 12 experienced recurrence (evidence level 2b). The model is based on the tumor size (cutoff = 4.5 cm), macrovascular invasion, tumor differentiation, and a bilobar distribution. Although it was originally based on a very small number of events, this model has separated patients into groups with low (0%), intermediate (19.4%), and high risks of recurrence (60%) with excellent accuracy (area under the receiver operating characteristic curve = 0.91). This model has been validated in 2 small and independent cohorts (31 and 41 patients).

The pathological score to predict recurrence,[39] a Canadian scoring system, was derived from a study of 75 patients who underwent transplantation for HCC; 20 of the patients experienced recurrence (evidence level 2b/4). The independent negative pathological predictors were microvascular invasion (the strongest predictor), a tumor size ≥ 3 cm, the nuclear grade, microsatellitosis, and the presence of giant/bizarre cells. The score stratifies the risk of HCC recurrence into 3 tiers: low (<5%), high (40%–65%), and very high (>95%). This model has not been validated in an external population.

The Pittsburgh prognostic risk score,[37] an older model, was used to examine risk factors for tumor recurrence in the explants of 344 consecutive LT patients (evidence level 2b/4). Bilobarly distributed tumors, size of the greatest tumor (2 to 5 cm and > 5 cm) and vascular invasion (microscopic and macroscopic) were identified as three independent predictors. The prognostic risk score grouped patients into 5 categories of tumor recurrence risk. The proposed prognostic risk score system correlated extremely well with tumor-free survival after LT (100%, 61%, 40%, 5%, and 0% at 5 years for grades 1–5, respectively). However, this model has not been validated externally, and a bilobar distribution is not universally considered to be a predictor.[9]

The retrospective design of the cohort studies on which these models are based is consistent with evidence level 4, although the associated clinical decision rules (ie, scoring systems)

merit the consideration of evidence level 2. Overall, the recommendation grade for using these scoring systems for the identification of patients with a high risk of recurrence is C+.

The explant-based predictive models of recurrence consistently share the tumor size and number, vascular invasion (directly or through microsatellite nodules), and tumor differentiation (to a lesser extent) as independent predictors. Patients presenting with high-risk tumors because of pretransplant understaging could be considered candidates for an adjuvant therapy trial. The further refinement and prospective validation of prognostic models that are designed to improve the identification of high-risk patients are important for the efficient and ethical development of randomized controlled trials of post-LT adjuvant therapy.

What Are the Best Endpoints to Choose?—The identification of the optimal endpoint for trials of post-LT adjuvant therapy is complicated by the fact that patients are at risk of morbidity and mortality from multiple competing sources. Therefore, a careful consideration of possible endpoints is important[43] (Table 4). Overall survival is the gold standard for phase 3 oncology trials because it is the endpoint least subject to bias. However, the competing risks of morbidity and mortality from transplantation and the number of patients and the length of follow-up that are required for sufficient power to assess overall survival make alternatives attractive, particularly for phase 2 trials.

The expected competing risks of morbidity and mortality for post-LT patients differ from those for other HCC patients. Although LT immunosuppression may lead to unique drug-drug interactions and complications, many LT patients recover relatively normal liver function and avoid the comorbidities of hepatitis and cirrhosis. However, post LT morbidity and mortality is potentially significant, particularly in the initial post-surgery period when adjuvant therapy may be initiated. Therefore, time-to-recurrence is an acceptable primary/secondary endpoint for Phase II and III studies, as proposed by a prior consensus panel for adjuvant HCC therapy.[44] Specific postoperative morbidities following LT, such as delayed graft function, renal function impairment, coagulopathy, and bleeding, also raise the issue of the best time for starting adjuvant therapy. For this reason, adjuvant therapy could be difficult to start until 4 weeks after LT (unlike therapy for other solid tumors).

Particularly for a centralized review of imaging performed at standard intervals for treatment and control arms, the time to recurrence is a cleaner endpoint than a composite endpoint such as disease-free survival,[44] and it may be less influenced by confounders. A competing risk model of the time to recurrence can estimate HCC-related deaths in the setting of LT.

The time to recurrence may be associated with overall survival for targeted post-LT adjuvant therapies because they are relatively well tolerated. However, surrogacy has not been formally proven. In addition, the pathway through which adjuvant therapies affect overall survival (presumably through HCC recurrence) requires validation. For example, some animal data suggest that sorafenib has a beneficial effect with respect to portal hypertension,[45] which may be independent of its effect on HCC, and sorafenib may have an independent survival effect. In all cases, safety data should be collected.

How Do We Demonstrate the Efficacy of Adjuvant Therapy?—According to the aforementioned concepts and considerations, the best strategy for testing potential post-LT adjuvant agents requires a 2-step process. First, dose studies should identify agents and doses that are safe in the post-LT setting and compatible with standard immunosuppressive agents.

The early detection of efficacy signals should be demonstrated first in a clearly defined patient population with a high risk of recurrence according to explant pathology evaluations. However, for ethical reasons and because of resource allocation issues, patients should meet standard transplant criteria according to their preoperative evaluation. These trials of post-LT adjuvant therapy should be powered to demonstrate a reduction of recurrence to the level of intermediate risk-patients: a 20% absolute reduction in the risk of recurrence or a 20% absolute increase in recurrence-free survival.

For phase 2 proof-of-concept trials, historical controls may not be adequate because of the significant changes in LT survival rates over time. Therefore, randomized phase 2 studies should be considered.[44] For such trials, a reasonably limited number of patients may be enrolled if a population with a high risk of recurrence is again targeted. A follow-up period of at least 3 years is important for capturing early and late recurrences.

The stratification of variables that may significantly affect recurrence should be considered: the preoperative treatment of tumors as a bridge to LT, down-staging approaches, and postoperative immunosuppression based on mammalian target of rapamycin inhibitors and rapalogs.

As a second step, a phase 3 study of intermediate-and low-risk patients may be possible instead of a randomized phase 2 study of this population for adjuvant therapies with substantial efficacy signals for high-risk patients. The design of such a trial should be carefully evaluated because its feasibility (like that of stage II colon cancer trials) could be intrinsically limited by the need to enroll a huge number of patients to show an absolute benefit of 2% to 3%.

SUMMARY AND RECOMMENDATIONS

HCC has emerged as a leading indication for LT in many programs worldwide. A reduction in the risk of recurrence after LT for HCC with adjuvant therapy may maximize the benefits of LT.

Adjuvant therapy has been tested for almost 2 decades in the post-LT setting, but the data are inconclusive. The level of evidence is not high enough to recommend its use on a routine basis.

Now that advances are being made in systemic therapy for advanced HCC, new and well-designed trials are desperately needed to determine whether similar gains can be made in the post-LT adjuvant setting. Key considerations for post-LT adjuvant therapy trials are as follows: the homogeneous and ethical selection of patients with a high risk of recurrence, stratification by confounding factors such as pretransplant therapies and posttransplant immunosuppression, relevant endpoints focusing on recurrence, and appropriate follow-up. Sorafenib, which is currently approved for the treatment of advanced HCC, and Licartin, which may affect post-LT recurrence, are 2 compounds that deserve further evaluations in the adjuvant setting.

Abbreviations

HCC	hepatocellular carcinoma
LT	liver transplantation
NA	not available
NS	not significant

PCRS	predicting cancer recurrence score
pTNM	pathological tumor-node-metastasis
STORM	Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma
TACE	transarterial chemoembolization

References

1. O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. Ann Surg. 1988; 207:373–379. [PubMed: 2451484]
2. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg. 1991; 15:270–285. [PubMed: 1851588]
3. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg. 1993; 218:145–151. [PubMed: 8393649]
4. Iwatsuki S, Gordon RD, Shaw BW Jr, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg. 1985; 202:401–407. [PubMed: 2996449]
5. Ioannou GN, Perkins JD, Carithers RL Jr. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology. 2008; 134:1342–1351. [PubMed: 18471511]
6. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–699. [PubMed: 8594428]
7. Figueras J, Ibañez L, Ramos E, Jaurrieta E, Ortiz-de-Urbina J, Pardo F, et al. Selection criteria for liver transplantation in early-stage hepatocellular carcinoma with cirrhosis: results of a multicenter study. Liver Transpl. 2001; 7:877–883. [PubMed: 11679986]
8. Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 1999; 19:311–322. [PubMed: 10518310]
9. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, et al. Role of immunosuppression and tumor differentiation in predicting recurrence after liver transplantation for hepatocellular carcinoma: a multicenter study of 412 patients. World J Gastroenterol. 2006; 12:7319–7325. [PubMed: 17143948]
10. Stone MJ, Klintmalm GB, Polter D, Husberg BS, Mennel RG, Ramsay MA, et al. Neoadjuvant chemotherapy and liver transplantation for hepatocellular carcinoma: a pilot study in 20 patients. Gastroenterology. 1993; 104:196–202. [PubMed: 8380393]
11. Cherqui D, Piedbois P, Pierga JY, Duvoux C, Vavasseur D, Tran Van-Nhieu J, et al. Multimodal adjuvant treatment and liver transplantation for advanced hepatocellular carcinoma. A pilot study Cancer. 1994; 73:2721–2726.
12. Roayaie S, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. Ann Surg. 2002; 235:533–539. [PubMed: 11923610]
13. Hsieh CB, Chou SJ, Shih ML, Chu HC, Chu CH, Yu JC, Yao NS. Preliminary experience with gemcitabine and cisplatin adjuvant chemotherapy after liver transplantation for hepatocellular carcinoma. Eur J Surg Oncol. 2008; 34:906–910. [PubMed: 18166289]
14. Olthoff KM, Rosove MH, Shackleton CR, Imagawa DK, Farmer DG, Northcross P, et al. Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. Ann Surg. 1995; 221:734–741. [PubMed: 7794077]
15. Zhang ZH, Ma LW, Song SB, Xiu DR, Wang JJ, Yang XX, Jia YM. Adjuvant chemotherapy after orthotopic liver transplantation for advanced hepatocellular carcinoma [in Chinese]. Zhonghua Zhong Liu Za Zhi. 2005; 27:45–47. [PubMed: 15771799]

16. Chen GH, Lu MQ, Cai CJ, Yang Y, He XS, Zhu XF. Clinical study of adjuvant individualized chemotherapy for hepatocellular carcinoma after liver transplantation [in Chinese]. Zhonghua Wai Ke Za Zhi. 2004; 42:1040–1043. [PubMed: 15498315]

17. Sun J, Hou BH, Jian ZX, Ou YL, Ou JR. Value of perioperative adjuvant therapy in liver transplantation for advanced hepatocellular carcinoma. Nan Fang Yi Ke Da Xue Xue Bao. 2007; 27:471–473. [PubMed: 17545034]

18. Söderdahl G, Bäckman L, Isoniemi H, Cahlin C, Höckerstedt K, Broomé U, et al. A prospective, randomized, multi-centre trial of systemic adjuvant chemotherapy versus no additional treatment in liver transplantation for hepatocellular carcinoma. Transpl Int. 2006; 19:288–294. [PubMed: 16573544]

19. Pokorny H, Gnant M, Rasoul-Rockenschaub S, Gollackner B, Steiner B, Steger G, et al. Does additional doxorubicin chemotherapy improve outcome in patients with hepatocellular carcinoma treated by liver transplantation? Am J Transplant. 2005; 5(pt 1):788–794. [PubMed: 15760403]

20. Xu J, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, et al. A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation. Hepatology. 2007; 45:269–276. [PubMed: 17256759]

21. Li N, Zhou J, Weng D, Zhang C, Li L, Wang B, et al. Adjuvant adenovirus-mediated delivery of herpes simplex virus thymidine kinase administration improves outcome of liver transplantation in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2007; 13:5847–5854. [PubMed: 17908978]

22. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. for SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378–390. [PubMed: 18650514]

23. Yoon DH, Ryoo BY, Ryu MH, Lee SG, Hwang S, Suh DJ, et al. Sorafenib for recurrent hepatocellular carcinoma after liver transplantation. Jpn J Clin Oncol. 2010; 40:768–773. [PubMed: 20494947]

24. Kim R, El-Gazzaz G, Tan A, Elson P, Byrne M, Chang YD, Aucejo F. Safety and feasibility of using sorafenib in recurrent hepatocellular carcinoma after orthotopic liver transplantation. Oncology. 2010; 79:62–66. [PubMed: 21071991]

25. Yeganeh M, Finn RS, Saab S. Apparent remission of a solitary metastatic pulmonary lesion in a liver transplant recipient treated with sorafenib. Am J Transplant. 2009; 9:2851–2854. [PubMed: 20021481]

26. Bhoori S, Toffanin S, Sposito C, Germini A, Pellegrinelli A, Lampis A, Mazzaferro V. Personalized molecular targeted therapy in advanced, recurrent hepatocellular carcinoma after liver transplantation: a proof of principle. J Hepatol. 2010; 52:771–775. [PubMed: 20347502]

27. Dharancy S, Romano O, Lohro R, Pageaux GP, De Ledinghen V, Hurtova M, et al. Tolerability of sorafenib in recurrent hepatocellular carcinoma after liver transplantation: a case-control study. Liver Transpl. 2008; 14(suppl 1):S216.

28. Korangy F, Höchst B, Manns MP, Greten TF. Immunotherapy of hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol. 2010; 4:345–353. [PubMed: 20528121]

29. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. for Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009; 10:35–43. [PubMed: 19058754]

30. Jonas S, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology. 2001; 33:1080–1086. [PubMed: 11343235]

31. Klintmalm GB. Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. Ann Surg. 1998; 228:479–490. [PubMed: 9790338]

32. Roayaie S, Schwartz JD, Sung MW, Emre SH, Miller CM, Gondolesi GE, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl. 2004; 10:534–540. [PubMed: 15048797]

33. Tamura S, Kato T, Berho M, Misiakos EP, O'Brien C, Reddy KR, et al. Impact of histological grade of hepatocellular carcinoma on the outcome of liver transplantation. Arch Surg. 2001; 136:25–30. [PubMed: 11146770]
34. Marsh JW, Dvorchik I, Subotin M, Balan V, Rakela J, Popechitelev EP, et al. The prediction of risk of recurrence and time to recurrence of hepatocellular carcinoma after orthotopic liver transplantation: a pilot study. Hepatology. 1997; 26:444–450. [PubMed: 9252157]
35. Molmenti EP, Klintmalm GB. Liver transplantation in association with hepatocellular carcinoma: an update of the International Tumor Registry. Liver Transpl. 2002; 8:736–748. [PubMed: 12200772]
36. Plessier A, Codes L, Consigny Y, Sommacale D, Dondero F, Cortes A, et al. Underestimation of the influence of satellite nodules as a risk factor for post-transplantation recurrence in patients with small hepatocellular carcinoma. Liver Transpl. 2004; 10(suppl 1):S86–S90. [PubMed: 14762846]
37. Iwatsuki S, Dvorchik I, Marsh JW, Madariaga JR, Carr B, Fung JJ, Starzl TE. Liver transplantation for hepatocellular carcinoma: a proposal of a prognostic scoring system. J Am Coll Surg. 2000; 191:389–394. [PubMed: 11030244]
38. Ito T, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transpl. 2007; 13:1637–1644. [PubMed: 18044766]
39. Parfitt JR, Marotta P, Alghamdi M, Wall W, Khakhar A, Suskin NG, et al. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. Liver Transpl. 2007; 13:543–551. [PubMed: 17394152]
40. Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation. 2008; 85:1726–1732. [PubMed: 18580463]
41. Chan EY, Larson AM, Fix OK, Yeh MM, Levy AE, Bakthavatsalam R, et al. Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: implications for surveillance studies and new adjuvant therapies. Liver Transpl. 2008; 14:956–965. [PubMed: 18581511]
42. Toso C, Asthana S, Bigam DL, Shapiro AM, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology. 2009; 49:832–838. [PubMed: 19152426]
43. Punt CJ, Buyse M, Köhne CH, Hohenberger P, Labianca R, Schmoll HJ, et al. Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. J Natl Cancer Inst. 2007; 99:998–1003. [PubMed: 17596575]
44. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. for Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008; 100:698–711. [PubMed: 18477802]
45. Hennenberg M, Trebicka J, Stark C, Kohistani AZ, Heller J, Sauerbruch T. Sorafenib targets dysregulated Rho kinase expression and portal hypertension in rats with secondary biliary cirrhosis. Br J Pharmacol. 2009; 157:258–270. [PubMed: 19338580]

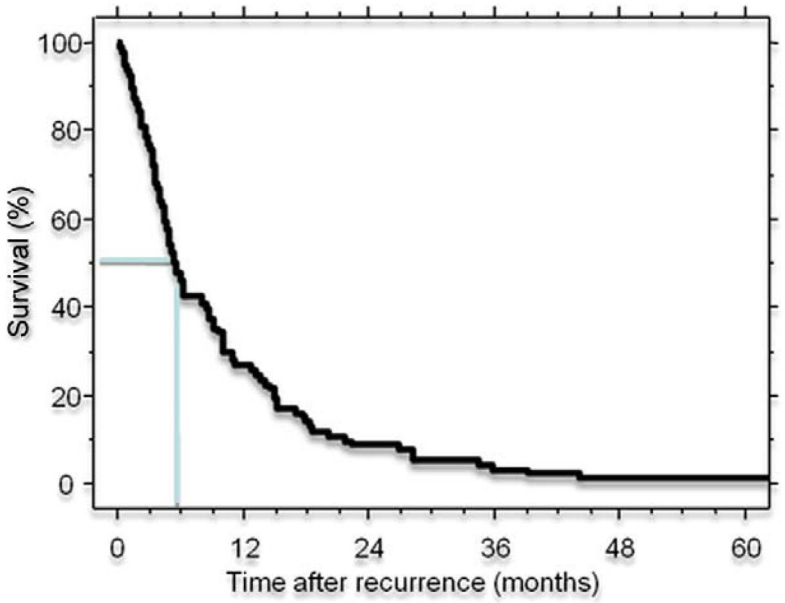

Figure 1.
Natural history of HCC recurrence after LT (94 recurrences in 497 French patients transplanted between 1988 and 1998).

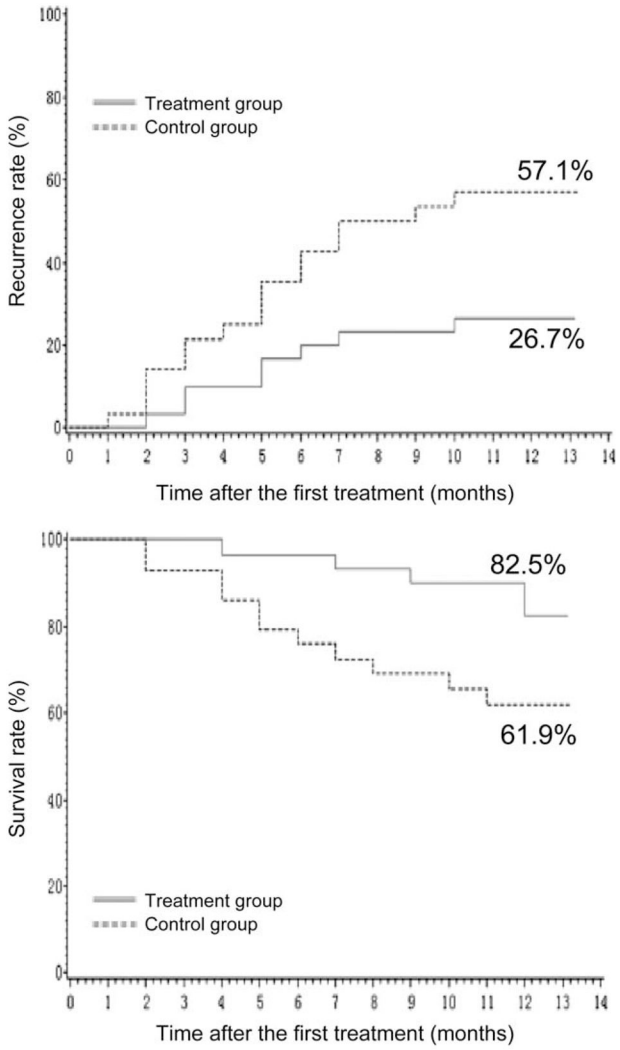

Figure 2.
Impact of Licartin on the recurrence and survival rates after LT for HCC.

TABLE 1

Adjuvant Therapies After LT for HCC: Nonrandomized Studies

Study	Treatment	Patients Outside the Milan Criteria/ Total Patients (n/ N)	Study Design	Disease-Free Survival (%)*	Overall Survival (%)*	Results of Proposed Adjuvant Therapy	Level of Evidence
Stone et al.[10] (1993)	Doxorubicin before, during, and after LT	17/20 (HCC diameter > 5 cm)	Single arm prospective study with no control group	54 (3 years)	59 (3 years); 39 (5-year update)	The treatment may provide a benefit.	4
Olthoff et al.[14] (1995)	Doxorubicin, fluorouracil, and cisplatin	15/25	Prospective with historical controls	46 (3 years)	46 versus 5.8 (3 years)†	The treatment may provide a benefit.	4
Cherqui et al.[11] (1994)	TACE and radiotherapy before LT and mitoxantrone after LT	14/14	Single arm and prospective with no control group	47 (5 years)	54 (5 years)	The treatment may provide a benefit.	4
Roayaie et al.[12] (2002)	TACE before LT and doxorubicin during and after LT	43/43	Prospective with no control group	48 (5 years)	44 (5 years)	The treatment may provide a benefit.	4
Zhang et al.[15] (2005)	Doxorubicin, fluorouracil, and cisplatin after LT	10/10	Retrospective case series	__‡	NA	The treatment may provide a benefit.	4
Chen et al.[16] (2004)	Individualized chemotherapy based on the adenosine triphosphate tumor chemosensitivity assay	Unknown/21 cases and 52 controls	Retrospective case series with controls	60.0 versus 37.8 (2 years)§	74 versus 70 (2 years)//	The treatment may provide a benefit.	4
Sun et al.[17] (2007)	TACE before LT and doxorubicin, fluorouracil, and cisplatin after LT	Unknown/20 cases (pTNM stages III and IVa) and 16 controls	Retrospective case series with controls	40.5 versus 15.6 (2 years)	47.1 versus 20.5 (2 years)	The treatment may provide a benefit.	4
Hsieh et al.[13] (2008)	Gemcitabine and cisplatin	15/30	Retrospective case series	56 (2 years)	72 (3 years)	Efficacy is suggested in patients beyond the Milan criteria	4

*The follow-up period is shown in parentheses.

†Statistically significant ($P < 0.001$).

‡Three of 10 patients experienced recurrence.

§Statistically significant ($P < 0.05$).

// Not statistically significant.

TABLE 2

Adjuvant Therapies After LT for HCC: Prospective Randomized Controlled Trials

Study	Treatment	Treated Patients/ Controls (n/ n)	Follow-Up (Years)	Disease-Free Survival: Treated Patients/ Controls (%/%)	Overall Survival: Treated Patients/ Controls (%/%)	Results	Level of Evidence
Söderdahl et al.[18] (2006)	Doxorubicin: 10 mg/m^2 weekly before and after LT and 15 mg/m^2 during LT for a maximum cumulative dose of 400 mg/m^2	19/27	3	63/50 (P = NS)	63/70 (P = NS)	No statistical improvement *	2b
Pokorny et al.[19] (2005)	Doxorubicin: 15 mg/m^2 biweekly before, during, and after LT for a cumulative LT dose of 300 mg/m^2	34/28	5	43/53 (P = NS)	38/40 (P = NS)	No impact of adjuvant therapy on disease-free or overall survival	2b
Xu et al.[20] (2007)	Licartin: 15.4 MBq/kg monthly for 3 months	30/30	1	57.1/26.7 (P = 0.017)	82.5/61.9 (P = 0.028)	Reduced recurrence and increased survival with Licartin	2b
Li et al.[21] (2007)	Epirubicin after LT with or without thymidine kinase to the peritoneum during LT	23/22	3	43.5/9.1 (P = 0.001)	69.6/19.6 (P = 0.001)	Reduced recurrence	2b

* The study was stopped early because of a lack of demonstrated benefits.

TABLE 3

Selection of 4 Explant-Based Prognostic Models for LT for HCC

Study	Design	Patients Within the Milan Criteria/ Total Patients (n/ N)	Follow-Up	Model Components	Proposed Model	Main Results	Level of Evidence*
Mazzaferro et al.[29] (2009)	Multicenter, retrospective cohort	1112/1556	53 months (median)	Largest size, number, and microvascular invasion	Up-to-7 criteria (largest size plus number)	5-year overall survival: 71.2% (47.4% with microvascular invasion)	2b/4
Chan et al.[41] (2008)	Retrospective cohort with validation	Test cohort: —/116 Validation cohorts: 31 and 41	Test: 27 months Validation: 104 and 28 months (mean)	Largest size (1 point), bilobar distribution (2 points), macrovascular invasion (3 points), and not well differentiated (−3 points)	PCRS	5-year overall survival: 90% with PCRS ≤ 0, 65% with PCRS = 1 or 2, and 20% with PCRS ≥ 3	2b
Parfitt et al.[39] (2007)	Retrospective cohort	50/75	8 years (mean)	Microvascular invasion, microsatellitosis, giant/ bizarre cells, and largest size ≥ 3 cm	3.5–4 points for each variable	Incidence of recurrence: <5% with 0–4 points, 40%–65% with 7–7.5 points, and >95% with 10.5–14.5 points	2b/4
Iwatsuki et al.[37] (2000)	Retrospective cohort	—/344	91 months (mean)	Bilobar distribution, largest size (>2 or 5 cm), and microvascular/ macrovascular invasion	Prognostic risk score (3.1–15.0 points for each variable)	5-year disease-free survival: 100% with <7.5 points, 61% with ≤11.0 points, 40% with <15.0 points, and 5% with ≥15.0 points	2b/4

*Evidence level 2b is based on clinical decision rules (scoring systems), and evidence level 4 is based on a retrospective study of populations.

TABLE 4

Comparison of Endpoints for Adjuvant Treatments

	Endpoints		
Events	**Disease-Free Survival**	**Recurrence-Free Survival**	**Overall Survival**
Locoregional recurrence	Event	Event	Ignore
Distant metastases	Event	Event	Ignore
Second primary (same cancer)	Event	Ignore	Ignore
Second primary (another cancer)	Event	Ignore	Ignore
Death from the same cancer	Event	Event	Event
Death from another cancer	Event	Ignore	Event
Non–cancer-related death	Event	Ignore	Event
Treatment-related death	Event	Ignore	Event
Lost to follow-up	Censor	Censor	Censor

NOTE: Adapted with permission from *Journal of the National Cancer Institute*.[43] Copyright 2007, Oxford University Press.