Polycystic Liver Disease: A Critical Appraisal of Hepatic Resection, Cyst Fenestration, and Liver Transplantation

To the Editor:

W e read the article by Schnelldorfer et al with great interest. They describe a single center cohort of polycystic liver patients, who underwent partial hepatectomy with cyst fenestration of the liver remnant (n = 124), cyst fenestration alone (n = 10), or liver transplantation (n = 7). As such this is an update from their earlier series on 31 patients resected between 1985 and 1993. The authors point out that surgery in polycystic liver is associated with significant morbidity but conclude that the degree of symptomatic relief and consequential improvement in performance status and overall health warrants its use. Consequently, they advocate hepatic resection as a valid treatment option in selected polycystic liver patients. We are grateful for the efforts of the authors to bring their collective experience to the table, but for several reasons we would like to share our concern about their conclusions.

The authors rightly point out that their series is the largest reported so far in the literature, but this is an immediate area for concern as it limits the generalization of the concept. We performed a thorough search in the literature to reveal all reported cases of patients with polycystic liver who underwent resection. We used the PubMed interface (http://www.ncbi.nlm.nih.gov/entrez) and our search strategy was performed with the following terms: polycystic liver; resection, for the period 1981–2009. Articles written in English were considered for inclusion. The references of the traced articles were scrutinized for additional papers. The search resulted in 26 publications reporting on 116 patients and only 10 series are larger than 4 patients (see supplement Figure 1 and Appendix 1: supplementary reference list at http://links.lww.com/SLA/A111). We found only 3 larger series on hepatic resection published in this century. These findings illustrate an important drawback of this technique nowadays: most centers do not have caseload to build expertise. Indeed, experience is one of the most critical factors that predict success. It took these authors of a renowned tertiary referral center 22 years to perform 124 procedures, which comes down to 5.6 patients per year. So, even at a high volume center this procedure is performed infrequently.

One of the reasons that physicians are reluctant to advise this procedure may be that complication risk is high. Indeed, the authors cite a procedure-related morbidity of 63%, whereas approximately 50% of these complications are major (Clavien grade: III to V). This is probably related to the fact that the normal anatomy of polycystic livers is extremely distorted, as the liver is not only larger, but it is rigid with limited mobility and there is difficult access to vascular supply. These elements count toward the long-operation times (average 324 minutes). The authors accept the high-complication rates because once the complications are resolved, the clinical performance status improves. We have little hope that the frequency of complications for hepatic resection will diminish significantly in the future. This is supported by the finding the average hospital stay in their first series (1985–1993) was 11 days, whereas the current series cites an average of 13 days. Thus, despite clear improvements in supportive clinical care over the last years, hospital stay for this indication increased.

An important drawback for hepatic resection is the high rate of adhesions. This is an unfavorable factor for future liver transplantation as explantation of the adhered liver becomes difficult. The authors favor partial hepatectomy above liver transplantation. Indeed, organ allocation is difficult in patients with a polycystic liver and preserved liver function. Despite these considerations, the authors report on 7 patients who underwent orthotopic liver transplantation and cite a 5-year patient survival of 60%. This compares unfavorably with other series. For example, we found that in a large cohort of 58 patients with isolated polycystic liver disease the 5-year patient survival was 92% and in the cohort with 121 patients with polycystic kidney and liver disease this survival rate was 89%. The collective experience on 218 patients from the European Liver Transplant Registry indicated a 5-year survival of 80%.

On balance we think the morbidity and mortality rate is too high for this group who had ECOG PS 0 or 1. We think that other options with lower complication rates such as laparoscopic fenestration and aspiration-sclerotherapy and even liver transplantation should be fully explored before hepatic resection is considered.

We believe that future efforts should be directed toward medical management of polycystic livers. Indeed, treatment with somatostatin analogues seems to be feasible in these patients, and the first report of randomized clinical trial are published.

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Reply:

We appreciate the comments of Drs. van Keimpema and Drenth based on their literature search regarding our article on the surgical management of patients with highly symptomatic polycystic liver disease.1 We agree with several of their comments regarding management issues relevant to the low frequency of this clinical entity, the consequent limited clinical experience even in high-volume centers, and the significant morbidity associated with our reported combined hepatic resection and fenestration operation. They suggest that patients with highly symptomatic patients with massive hepatomegaly be managed initially with somatostatin analogs and definitively with liver transplantation but not hepatic resection. We do not dispute that liver transplantation is the only curative treatment option, but we do believe that our data do support hepatic resection and fenestration for selected patients.

We reported our experience to address the sparse literature and limited follow-up with resection-fenestration. These data reflect our evolving operative approach. Patient selection has been refined as our understanding of the polycystic liver and dimensional imaging has improved. Currently, only patients with relative cyst sparing of a hepatic sector with concomitant patency of its portal and hepatic veins are surgical candidates. Technical caveats were emphasized. Operative duration inclusive of anesthesia was prolonged and morbidity significant. However, mean liver volume reduction was approximately 60%, performance status normalized in approximately 75% of patients. Late liver transplantation was required in only 5 patients. Although postoperative periphe-\(\text{ratic adhesions undoubtedly occur, relevance is limited only to patients requiring repeat hepatic operations and, in fact, did not preclude transplantation.\)}

Drs. van Keimpema and Drenth noted that the impaired performance status of our patients was mild (ECOG level 0 and 1) in approximately 70% of patients. Although true, that data included patients who underwent cyst fenestration alone and reflects the limitation of applying a scoring system designed for cancer patients to PCLD. Quality of life measures have not been standardized for PCLD patients. In fact, for all patients undergoing hepatic resection and fenestration for massive hepatomegaly, life style was significantly compromised, though not infirm. Indeed we deferred resection until performance status precluded employment or homemaking. We agree that selective use of cyst aspiration with sclerosis and laparoscopic fenestration is indicated for patients with dominant symptomatic cysts. However, such patients do not have massive hepatomegaly from type C or D PCLD. We are unaware of outcomes quantitating liver volume reduction for laparoscopic fenestration comparable to resection-fenestration leading to durable improvement in quality of life for massive hepatomegaly. Indeed, based on our experience as a referral center such intervention was neither durable nor adhesion free.

Treatment with somatostatin analogs is attractive as suggested by our preclinical studies using in vitro and animal models of polycystic liver disease.2 Although 3 randomized controlled trials have been associated with a 2.9% to 4.45% decrease in liver volume over 6 months or a 4.95% reduction over 1 year,3–5 whether this preliminary beneficial effect will be sustained or the long-term administration of these drugs will be safe in patients with PCLD is unknown. Moreover, the reduction in liver volume from octreotide therapy is disparate from the 60% reduction achieved by resection-fenestration and the degree and duration of symptomatic relief from surgery.

Finally, although liver transplantation is the only definitive treatment, the literature search does not fully address the associated mortality and morbidity. The cited European Transplant Registry does not address operative morbidity and long-term immunosuppressive issues and 1-year patient survival was 85%.6 Furthermore, unless regionalization for specific diseases is implemented, the infrequency of patient-physician encounter will persist and organ allocation will remain a major issue for these patients because liver decapsulation is rare. Interestingly, the resection and fenestration procedure was applicable to majority of our patients with massive hepatomegaly for whom liver transplantation would have been recommended.

We believe that resection and fenestration has a role in the management of selected patients with massive hepatomegaly from PCLD. Operations for these patients should be undertaken in centers, which emphasize a team management approach of hepatologists, nephrologists, and hepatobiliary and liver transplant surgeons.

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Assessing the Quality of Surgical Trials
Further Insight

To the Editor:

Farrarhyer et al1 are > to be congratulated for drawing needed attention to the important subject of trial quality. All too often, we hear statements that suggest that the results of a trial—any trial—are valid by virtue of the study being a (randomized) trial. Farrarhyer et al1 refute this notion by establishing that there are standards, and that some trials are better than others, methodologically speaking. Yet, Farrarhyer et al1 may not have gone

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far enough in discriminating among trials on the basis of their methodological quality. It is pointed out, correctly, that the “method of randomization should always be reported”; yet, the authors are not fully aware of why this is, as they consider only the distinction between true randomization and pseudorandomization. It is then stated, incorrectly, that it “is possible to conceal the randomization sequence in every RCT [randomized control trial].” The fact that this statement is made routinely in no way mitigates the harm that comes from researchers actually believing it or absolves authors of their responsibility to fact-check their work. The reality is that there are 2 threats to allocation concealment, and only 1 of these (direct observation of the allocation sequence) can always be eliminated [Section 2.5]. Prediction of future allocations on the basis of knowledge of past ones, coupled with restrictions on the randomization procedure (such as permuted blocks), cannot be eliminated in any trial that may be unmasked or imperfectly masked, and which uses restricted randomization (as just about all do).

Surgical trials are especially notorious for problems with masking, so successful allocation concealment hinges on the precise methods used to generate the randomization sequence, and even among truly randomized designs, some are still better than others. For example, the maximal procedure is superior to the far more common permuted blocks design [Section 5.3.4]. Moreover, even when true randomization is used, the trial may still be fatally flawed by virtue of the wrong (true) randomization procedure being used. Far more attention needs to be paid to this key issue of trial quality. In addition, the authors completely missed the fact that some composite endpoints are better than others, and the best of them, the information-preserving composite endpoint, does not require the 3 conditions listed to be valid, reliable, or useful.

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Reply:

We note with interest the letter from Dr Berger concerning our recent publication. His concerns focused on the topic of allocation concealment in randomized controlled trials and the statement we made that—“it is possible to conceal the randomization sequence in every RCT.” Although it is always possible to conceal the allocation sequence from direct observation, Dr Berger correctly notes that researchers and clinicians may still be able to predict future allocations based on knowledge of past allocations in unblinded trials. This limitation is important for researchers to acknowledge, but in no way undermines the importance of concealing the allocation sequence from direct observation, a much more critical issue for researchers to address when designing RCTs.

Indeed, in a review of RCTs in orthopedic trauma surgery, only 3% of trials reported a concealed form of allocation. Surgeons designing trials should consult with a statistician to generate the most appropriate randomized sequence, ensure that the method used to allocate patients is adequately concealed, and report how both of these were done. A full discussion of the different methods of randomization (eg, urn, simple, blocked with fixed or random block sizes) is beyond the scope of this article, but interested readers may find an overview of these methods elsewhere.

With respect to composite endpoints, we agree with Dr Berger that some are certainly better than others. However, even information-preserving composite endpoints may be misleading and misinterpreted if the outcomes are not of similar importance to patients, do not occur with similar frequency, or yield different relative risks across the components. If any of these criteria are not met, we strongly urge researchers to measure and report the outcome that is most important to patients.

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Optimizing Medical Response to Large-scale Disasters: The Ad Hoc Collaborative Health Care System

During our recent experience in Haiti in the early aftermath of a major earthquake, we found that more optimal use of field hospitals could be achieved through increased coordination among the deployed medical resources. Moreover, if it were possible to standardize both the capabilities of these resources and their interoperational guidelines, further improvement in resource utilization could be achieved. We explain later the problems we identified, how we adapted to them, and how that led us to a model that could be implemented in future disasters in an effort to make more efficient use of available medical resources.

Hospitals and hospital staff are not immune to the destruction caused by earthquakes. Arriving field hospitals serve to replace temporarily and partially the destroyed health care infrastructure, perhaps especially important in places such as Haiti, where the infrastructure is already significantly challenged. The capabilities of field hospitals are quite variable, though they tend to fall into 2 categories: “light” and “advanced.” The former are generally capable of...
dispensing antibiotics, intravenous hydration, and minor bedside procedures, whereas the latter may have operating rooms, intensive care units, laboratories, and imaging facilities and appropriate specialists and staff. Each country or organization determines when and with which type of field hospital it wishes to deploy, leading to wide variation in available resources.

We brought an advanced field hospital to Haiti, including surgeons in various subspecialties. However, within 2 days of becoming operational, we were at full capacity and were faced with the stark prospect of allowing only 1 additional patient admission for each patient discharged. Because no recovery beds were available for patients who required potentially life-saving surgery, the operating room could have been brought to a standstill, severely curtailing our added value. We considered discharging postoperative patients prematurely to self-care, but the risk of complications, especially in the disaster setting, made it untenable.

Resolving the bottleneck was particularly crucial as the impact on mortality that specialized field hospitals may effect in disasters is observed primarily early on.4 Confronted with tremendous need in the face of massive devastation, we improvised a solution: For every patient requiring a higher level of care sent by a light hospital, the light hospital would have to take one of our patients in exchange. This arrangement allowed us to admit patients who had been screened by other health care professionals as requiring an acute intervention that we were in a unique position to provide and ensure that patients would remain under medical care (even if not our own) until they were stable enough to be discharged. (For example, a patient is not our own) until they were stable enough to be discharged. For every patient requiring a higher level of care sent by a light hospital, the light hospital would have to take one of our patients in exchange. This arrangement allowed us to admit patients who had been screened by other health care professionals as requiring an acute intervention that we were in a unique position to provide and ensure that patients would remain under medical care (even if not our own) until they were stable enough to be discharged. (For example, a patient is not our own) until they were stable enough to be discharged.

To better match resources with patients most likely to benefit from them, trauma experts could conduct twice-daily rounds at light hospitals to help the physicians there identify those patients who would most likely benefit from advanced procedures. The same experts could round in the advanced hospitals to identify patients ready either for transfer to light hospitals or for discharge. The level of acuity at which transfers would be recommended in either direction would depend on the mismatch between patient need and available resources.

The transportation of patients within the system presents a risk, just as in a standard hospital system with interfacility transfers. Judgment would be needed to determine whether the hazards entailed in moving a patient would be worth the potential benefit to that patient and/or to the patients who would then have access to the vacated resource. In addition, further dislocation of families should be minimized if possible, and clear communication from medical staff would be important in ensuring that transferred patients do not perceive that they are being abandoned.

The coordinated health care system would continue to play a role until sufficient, consolidated resources were available to meet local need. In Haiti, for instance, the United States Navy’s hospital ship Comfort arrived 8 days after the initial earthquake, bringing a 1000-bed hospital facility with 12 operating rooms. The coordinated health care system’s central command may still assist in triaging and directing appropriate patient transfers, though the flow at this stage would likely be unidirectional.

To achieve still further optimization of medical resources, the medical disaster response community could create a model based on the United Nation’s International Search and Rescue Advisory Group (ISARAG). The ISARAG uses the Urban Search and Rescue (USAR) team classification system to categorize available USAR teams into 3 levels, with agreed-upon requirements in terms of personnel, equipment, and capability. In the ISARAG guidelines and methodology state: “Teams are able to integrate effectively as they will have the same basic structure, comprise of the same components and will have standardised qualifications for the primary aspects of a USAR team response. This results in a safe, effective multinational operational response.”

A similar system, perhaps coordinated by the Global Health Cluster, would help to optimize the medical response in several ways. With standardized levels of field hospital capabilities, it would be much easier for the central command to incorporate available assets into the collaborative health care framework. More importantly, the rules for cooperation among the field hospitals would have already been assimilated by the individual teams as part of their training. With a common language, guidelines and methodology, and standardized expectations of other field hospital capabilities within the system, it would be much easier for interoperation among these entities to result in more optimal use of all available resources. This would be especially true during the first days of deployment when central coordination—and even regular communication—may not be fully functional. Finally, deployed clinics could also be incorporated into this system.

We believe that implementing a collaborative health care system would help to achieve more optimal use of all the medical resources available in a disaster. Further optimization could likely be achieved if participating countries and organizations adhered to a standardized classification and coordination system. The increased coordination at both the preparatory and deployment stages would very likely lead to decreased mortality, morbidity, and disability among the devastated population.

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