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Current Practice Regarding the Use of Fatty Livers: A Trans-Atlantic Survey

Charles J. Imber, Shawn D. St. Peter, Inigo Lopez, Lynden Guiver, and Peter J. Friend

A strong association exists between the presence of steatosis in a donor liver for transplantation and the development of primary nonfunction in the recipient. Despite this, appraisal of the donor remains one of the least scientific aspects of the transplantation process, and many centers base their practice on subjective opinion, rather than objective data. We conducted this survey to illuminate controversial issues and highlight the variation of opinion and practice policies both between and within the United Kingdom and the United States. A simple, anonymous, one-page, 10-question survey with tick-box answers was sent to every practicing liver transplant surgeon in the United Kingdom. The same form was sent by E-mail to liver transplant surgeons in the United States with a current E-mail address listed in the American Society of Transplant Surgeons registry. In the United Kingdom, 16 of 19 surgeons polled responded (84.2%) and thus were considered representative. From the United States, there were 78 respondents from 52 centers, representing all 11 United Network for Organ Sharing regions. We found that current practice policies differ not only between nations, but also among centers in each country. US surgeons generally follow a more conservative approach, with greater emphasis on histological assessment. Dichotomous opinions exist on the significance of microvesicular steatosis in both countries. Most evident from this survey is that more research in the field is required to help answer these questions and allow for the safe use of all viable livers. (*Liver Transpl 2002;8:545-549.*)

One of the least scientific aspects of the liver transplantation process is appraisal of the donor liver. This is particularly true with regard to steatosis, in which preretrieval liver function test results are seldom elevated to a clinically significant level, and the subjective opinion of the surgeon determines the fate of the organ. The fear of transplanting a fatty liver is based on the strong association with primary nonfunction (PNF) after a period of cold preservation, initially described by Todo et al[1] from the University of Pittsburgh. However, if a valid and standard method of assessment could be developed, it may be possible to maximize the use of fatty livers while simultaneously minimizing the risk to the recipient.

In the present climate of evidence-based medicine, clinical practice should be supported by sound experimental and clinical data. Many controversies exist regarding the transplantation of fatty livers because of the use of inconsistent and often confusing nomenclature. The situation is confused further by differing practices among institutions based on personnel experience and highly subjective opinion.

If meaningful audit of best practice is to be established with the aim of improving standards, it is imperative that an accurate impression of current clinical practice within the international transplant community be established. This survey was designed for this purpose and also to identify differences between United States (US) and United Kingdom (UK) practice.

Methods

A simple, anonymous, 10-question survey with tick-box answers was sent to every practicing liver transplant surgeon in the United Kingdom. An identical proforma was sent by E-mail to every liver transplant surgeon with a current E-mail address listed in the American Society of Transplant Surgeons registry in the United States. These results have been categorically compiled.

Results

In the UK, 16 of the 19 practicing liver transplant surgeons responded (84.2%); therefore, this was considered representative. From the US, there were 78 respondents from 52 centers, representing all 11 United Network for Organ Sharing (UNOS) regions. Using data from the UNOS Web site based on 1999 statistics, these centers accounted for 82.6% of liver transplantations performed that year. Results are shown in Figure 1, with percentages of respondents listed for both UK and US data.

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		0-20%	20-40%	40-60%	60-80%	Unsure
Can you estimate the percentage of livers retrieved in your region that show evidence of steatosis?	UK	25	44	19	0	12
	US	29	49	14	3	5
		Looks bad	**Risk factors**	**Never**	**Always**	**Both**
Under what circumstances do you seek histological appraisal of a donor liver?	UK	38	6	50	6	
	US	47	27	0	14	12
		1	**2**	**3**	**4**	**0**
How many biopsies do you take?	UK	44	6	0	0	50
	US	78	19	3	0	0
		Retrieval	**Backbench**	**Either**	**Don't**	
When do you take them?	UK	19	31	0	50	
	US	79	14	7	0	
		Most fat	**Same spot**	**Random**	**Don't**	
Where do you take the biopsy?	UK	6	38	6	50	
	US	19	33	48	0	

		H&E	Oil red O	Sudan III	TBS	Unsure	None	Both 1&2
What staining technique is used for evaluation of fatty change?	UK	25	0	6	0	19	50	-
	US	71	10	6	0	5	0	8

		Never	Sometimes	Always
Do you use CT/MRI/ultrasonography to assess fatty change prior to retrieval?	UK	94	6 (LRD)	0
	US	86	14	0
		Yes	**No**	**Unsure**
Do you consider microvesicular fat a risk factor for Primary Non- Function?	UK	38	38	24
	US	27	54	19

		20%	30%	40%	50%	60%	No limit	N/A
Above what level would you always reject a donor liver, irrespective of other variables?	UK	0	0	6	18	43	19	14
	US	3	30	26	27	6	-	8

		Yes	No
Would you accept a higher degree of macrovesicular fat in case of a urgent recipient?	UK	50	50
	US	68	32

Figure 1. Comparison of UK and US responses to Fatty Liver Survey.

Discussion

The most common answer concerning the prevalence of steatosis, with 44% of UK and 49% of US respondents, estimated the percentage of steatotic livers retrieved in their region to be between 20% and 40% of the total. A wide disparity exists in the literature regarding the prevalence of fatty change in livers from brain-dead adult and pediatric donors. This ranges from 13% to 26% in cases in which biopsy specimens are stained with hematoxylin and eosin (H&E).[2] This large discrepancy among centers may be caused by genuine variations between donor pools, as well as variable definitions of fatty change.

The use of fat-specific staining has been shown to identify greater levels of steatosis than seen by H&E.[3-5] Markin et al,[4] using Oil red O, found steatosis in 51% of 187 livers. The investigators dismissed this figure by stating that Oil red O is unreliable for fatty change in the liver because it stains sinusoids, as well as vacuoles. Another series of 83 consecutive donor wedge biopsies showed greater than 30% steatosis in 49% of sections stained with toluidine blue.[5]

The most commonly used means of predicting function of a liver after transplantation is surgical assessment by the retrieval surgeon. This is based on the combination of appearance and texture, but is inevitably subjective. This is the only method of liver appraisal currently applied by 50% of UK respondents who never incorporate histopathologic assessment into their decision-making process. This is in direct contrast to the United States, where 100% of transplant surgeons use liver biopsy under some circumstances. Although the reasoning behind this dissimilarity may be caused by greater awareness of the threat of litigation within the United States, it would appear from objective scientific data to be the correct one.

Attempts at practical assessment of the degree of steatosis have not proved reliable. In one series, 66% of steatotic livers were described as normal on macroscopic appearance by a surgeon, with predictive values of 71%, 46%, and 17% for massive, moderate, and mild change, respectively.[6] In another study, 38% of livers judged to be normal macroscopically showed fatty change on histopathologic appraisal.[3] Certainly, severe steatosis can be identified by yellow discoloration after flushing, rounded edges, and a greasy firm texture. However, this is obviously a highly subjective test that becomes less sensitive with lesser degrees of steatosis.

Three quarters of US respondents perform a biopsy when an organ appears macroscopically steatotic or such adverse donor risk factors as age and body mass index prejudice the use of the organ. Forty-four percent of UK surgeons perform a biopsy if macroscopic change exists, whereas only 6% perform a protocol biopsy regardless of other factors. Both groups take one or two specimens, predominantly on the backbench in the UK and at the time of retrieval in the US. They also differ in relation to the position of their biopsy sampling; US teams predominantly obtain random samples as opposed to sampling the same position in the UK. The area of greatest macroscopic change is chosen for biopsy less commonly in both countries (19%, UK; 6%, US).

Fatty infiltration of the liver has been shown to have a nonuniform distribution by radiological assessment.[7] It therefore appears intuitive that one or two biopsy specimens from an entire liver may provide inaccurate and misleading information. Variation of biopsy interpretation between pathologists at different centers also is a confounding factor. Chinnakotla et al[8] recently reported the successful transplantation of livers deemed severely steatotic at other centers, but acceptable by their own pathologist. However, at present, this appears to be the only widely available and logistically acceptable technique that offers an objective method of quantifying steatosis and a framework on which to base decisions. It is suggested in the literature that protocol biopsies performed regardless of other donor factors can improve outcome. This was exemplified by Markin et al,[4] who reported a reduction in PNF rates from 8.4% to 1.4% after instituting a policy of protocol biopsy and discarding livers with greater than 45% steatosis.

We attempted to determine what severity of macrovesicular change was considered an absolute contraindication for acceptance of a donor liver when biopsies had been performed. In both groups of respondents, the acceptable range of steatosis varied widely (Fig. 2). US respondents tended toward a more conservative approach, with a larger proportion of surgeons accepting only livers with less than 50% macrovesicular change. Conversely, 43% of UK surgeons would accept up to 60% change.

Fifty percent of respondents in the UK do not perform a biopsy at all, which explains the high proportion of these surgeons not responding to this question (20%), as well as 19% who reported no upper limit on histological grounds.

Ploeg et al[9] originally suggested a classification of fatty change as mild (<30% of visualized hepatocytes involved), moderate (30% to 60%), and severe (>60%), a system approximately applied by most centers. In the early 1990s, four studies examined the relationship of fatty change to PNF.[2,4,6,9] The largest of these assessed 390 frozen section biopsy specimens and found that 13% of grafts showing greater than 30% steatosis showed PNF compared with 2.5% of nonsteatotic grafts.[6] Progressive deterioration in graft survival was observed from mild to massive steatosis; thus, it was concluded that grafts with severe steatosis should be discarded, and those with moderate change should be evaluated in conjunction with other criteria, such as the condition of the recipient and availability of organs at that time. The institution involved, in line with most others worldwide, found no contraindication to transplanting livers with minimal change. This concurs with the findings of Ploeg et al,[9] who found PNF rates as high as 80% in severely steatotic organs, but more wor-

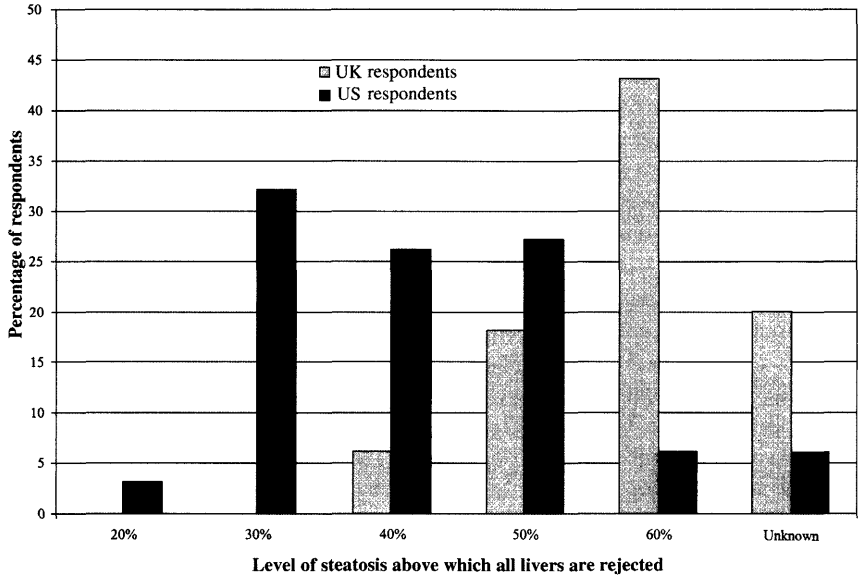

Figure 2. Maximum percentage of steatosis considered acceptable by UK and US respondents before acceptance of a donor liver.

ryingly, initial poor function rates as high as 30% in moderately steatotic livers.

These studies suggest that mild to moderate steatosis is not a contraindication for transplantation, but merely a risk factor for eventual graft loss. This was not borne out in our study because 50% and 68% of UK and US respondents stated they would consider greater degrees of steatosis in urgent or superurgent recipients, who by definition are the sickest. Although this would appear from published data to be a dangerous practice, no study to our knowledge has specifically examined this controversy.

No published data address the correlation between number or position of biopsies and their accuracy in assessing steatosis. Liver density assessed by computed tomography (CT) accurately reflects the presence of steatosis throughout the liver, and techniques to convert Hounsfield units into real fat volume fractions have been developed.[10,11] Given that hepatic steatosis is not homogeneous and macroscopic estimation by the retrieval surgeon is not accurate, it would seem intuitive that a more accurate estimation of steatosis throughout the entire organ potentially could be achieved by radiological assessment of each donor. However, although a positive finding on CT or magnetic resonance imaging (MRI) has correlated positively with steatosis on biopsy, the converse recently was not shown to be the case, with 30% of negative scans on MRI and 24% of those on CT associated with greater than 10% steatosis.[12]

Given these recent data, together with logistic difficulties and cost of performing CT or MRI on potential donors, it is not surprising that so few respondents are currently using radiological assessment to evaluate potential cadaveric donor livers. Considering the catastrophic outcome of PNF and enormous consumption of resources associated with urgent retransplantation, radiological assessment possibly could be considered in the future if diagnostic sensitivity could be improved. More studies investigating the application of available technology to the evaluation of steatosis clearly are required.

The most common stain used on both sides of the Atlantic is H&E, although fat-specific stains are used at some centers in both countries. H&E identifies fatty change by the presence of nonstaining vacuoles. Fat-specific stains, such as Oil red O and Sudan IV, require a positive color change. Several studies analyzed the various merits of each technique and determined that H&E can underestimate microsteatosis, whereas Oil red O staining can generate false-positive results, especially after University of Wisconsin storage.[4,5] From the available information, it seems that a standard method of staining and pathological assessment needs to be introduced before meaningful worldwide comparisons of clinical and experimental data can be made.

Several studies have shown that microvesicular steatosis in donor livers should not be considered a risk factor for PNF. Urena et al[5] found high-grade microvesicular steatosis present in 31% of 72 donors, although none showed features of PNF after transplantation. These livers resulted in significantly greater patient and graft survival rates compared with a group with high-grade macrovesicular change.

Fishbein et al[13] reviewed 426 transplantations and identified 40 cases containing moderate to severe microvesicular steatosis (>30% steatosis). Donor obesity (42%) and traumatic death (68%) were the most commonly associated risk factors. In this study, the incidence of PNF and poor early graft function in these livers was 5% and 10%, respectively. This was not significantly different from their results using normal livers. The investigators concluded that high-grade microvesicular steatosis (>60%) in a donor organ should not be considered a contraindication to transplantation.

This has not been accepted by 38% of UK and 27% of US respondents, who maintain that microvesicular change is a risk factor for PNF, with a large proportion of surgeons (24% and 19%, respectively) admitting that they remain unsure of the relationship. However, the literature on this point suggests that use of livers with microvesicular steatosis should no longer remain controversial, and pure microvesicular change in a donor biopsy specimen can be safely ignored.

In conclusion, we attempted to highlight some of the controversial issues regarding the use of fatty livers for transplantation and discuss how the existing literature might be applied to clinical practice. It is evident from this survey that current opinions differ, not only between the UK and the US, but also among centers in both countries. On the whole, US respondents adopt a more conservative approach, with greater emphasis on histological assessment than their UK counterparts. It is clear from this survey that more evidence from clinical trials is needed so that some of these questions can be answered and safe use of all viable livers achieved.

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