HEPATIC STEATOSIS ASSESSMENT:
a comparative study between surgeon evaluation and forward histopathologic findings

Aline M. A. **MARTINS**[1,2]*, Gustavo R. **COELHO**[2]*, Geraldo A. **MARQUES**[1], Manoel O. **MORAES**[1], José Telmo **VALENÇA Jr.**[3] and José Huygens P. **GARCIA**[2]

ABSTRACT - *Context* - Liver transplantation is one of the last viable resources for patients with end-stage liver disease. Many strategies are been used to improve the number of available organs and overcome waiting list delay. However, hepatic steatosis is one of the mainly concerns when organs are consider to transplantation due to it is importance as a risk factor for primary dysfunction. Surgeons play an important role to decide each organ will be accept or decline and its righteous allocation. *Objective* - Retrospectively evaluate the surgeon assessment of steatosis degree and its confrontation with further histopathologic findings. *Methods* - We analyzed 117 patients underwent deceased liver transplantation for end-stage liver disease in University Hospital Walter Cantideo, Fortaleza, CE, Brazil. A matrix table was organized to estimate the categorical data observed. We clustered the subjects into mild (0%–30%) and moderate (30%-60%) steatosis degree under the clinical criteria of organ suitability for transplantation. We categorized the organs as suitable organ for transplant and as non-suitable organ for transplant. Evaluations between the two first assessments, before perfusion (pre-perfusion) vs biopsy findings and after perfusion vs biopsy findings observations were analyzed and also a comparison between pre-perfusion and after perfusion data was performed. *Results* - On the first assessment, we obtained a 93% of agreement (n = 109) between the two evaluations. On the second assessment, we had an 8% (n = 9) of mistaken allocation. Comparing the observation before (pre-perfusion) and after (after perfusion), we obtained a strong agreement between the surgeons. *Conclusions* - Although our experienced surgeon team, we have wrongly evaluated feasible organs for transplantation. Nonetheless, our faulty percentage is low comparing to worldwide percentage.

HEADINGS - Fatty liver. Liver transplantation. Tissue and organ procurement. Tissue and organ havesting.

INTRODUCTION

Nowadays, liver transplantation is one of the last viable resources for patients with end-stage liver disease, including those ones with acute liver failure and metabolic disorders. In order to respond to this rising demand, surgeons have been adopting strategies to maximize donor organ utilization, minimizing waiting list delay[10].

Worldwide, many strategies are been used to improve the number of available organs and overcome this discrepancy. Those include governmental programs regarding to organ donation campaigns, training medical staff to improve evaluation on possible donors and the usage organs from expanded criteria donors[4]. This last approach, is been widely discuss among surgeons and the scientific community, because this definition remains controversial and prediction of organ function still a challenge remain[11].

Hepatic steatosis is one of the mainly concerns when organs are consider to transplantation due to it is importance as a risk factor for primary dysfunction after liver transplantation[9]. Although represents a relevant feature of donor organ, incidental liver steatosis is a relatively common finding in the deceased donor[3] and its prevalence could ranges from 13% to 26%, approaching 50% when very sensitive histological techniques are used[6]. It seems an agreement between surgeons, that livers with mild to moderate steatosis cannot be discharged, however an accurate evaluation on clinical situation of each potential recipient must be fulfill. Grafts with severe steatosis (>60%) are recommended to be excluded, due to high risk of primary nonfunction[2]. Nevertheless, in extreme situations, as

*These authors contribute equally to this work.
[1]National Experimental Oncology Lab – LOE – Federal University of Ceará, Brazil. [2]Liver Transplantation Center – Federal University of Ceará, Brazil [3]Pathology and Forensic Department – Federal University of Ceará State, CE, Brazil.
Correspondence: – Dr. Aline M A Martins - Av. Cel. Nunes de Melo, 1127 - Rodolfo Teófilo - 60430-270 - Fortaleza, CE, E-mail: alinemartins@ufc.br

fulminant liver failure, organs with steatosis could be used, as a last source of survival, to this kind of end-stage patients.

In this matter, surgeons play an important role to decide each organ will be accept or decline, relying on clinical and gross morphological information, assessed at harvesting site, about its suitability for potential further liver transplantation. In Brazil, the lack of day-round histopathologic support on transplantation centers and logistic difficulties due to surgery conditions, make the microscopically evaluation of donor organs a challenging obstacle, dispatching this assessment to further verification. Therefore, the procurement surgeon's estimation is a very relevant, and many times, the only feasible tool to righteous organ allocation.

The aim of this study was to retrospectively evaluate the surgeon assessment of steatosis degree at the harvesting time, and its confrontation with further histopathologic findings.

METHODS

From May 2008 to August 2009, we analyzed 117 patients underwent deceased liver transplantation for end-stage liver disease at the Liver Transplantation Center – Walter Cantídeo University Hospital – Federal University of Ceará, Fortaleza, CE, Brazil. The assessment was performed by the main surgeon according to gross morphology inspection and palpation. The grafts were grouped according steatosis level: mild steatosis (0%-30%), moderate steatosis (30%-60%) and severe steatosis (>60%) during harvest. A 60% of steatosis cutoff limit value was used to discharge the organ for liver transplantation. The procurement surgeon evaluation where noted before perfusion (PREPER) and after perfusion (AFTPER), as also the biopsy (BX) findings as show on Table 1.

Liver biopsies were performed after perfusion for histological confirmation of donor liver steatosis. All specimens were graded and reviewed by an independent pathologist. Fat droplets displacing the hepatocyte nucleous and occupying the majority of the cytosol were considered macrovesicular steatosis and organ was discharged. Donor clinical data as age, sex, body mass index (BMI), blood group, cause of death and hepatic enzymes were also noted but not consider to analysis here, regarding the goals of this study.

We organized a matrix table with our findings to estimate the categorical data observed. Due to clinical purpose and relied on cited literature above, we clustered the mild (0%–30%) and moderate (30%-60%) steatosis degree under the clinical criteria of organ suitability for transplantation. We recognized as SOT (suitable organ for transplant) all the organs that display until 60% of steatosis with no macrovesicular droplets and as N-SOT (non-suitable organ for transplant) all the organs that display more than 60% of steatosis and/or macrovesicular droplets. To analyze the data, we applied the kappa index for statistical test (PREPER x BX; AFTPER x BX; PREPER x AFTPER). This test aimed to analyze the degree of agreement between the groups, in which case it was compared the ability of the organ to be transplanted. Furthermore, to be considered an excellent degree of agreement, the kappa index must have a value between 0.81 to 1. All the data followed guidelines of the Ethics Committee of our Hospital.

RESULTS

On the first scenario, when we evaluated the surgeon findings PREPER against the histopathologic findings from BX, we obtained a 93% of agreement (n = 109) between the two evaluations. In four situations the organ was evaluated by the procurement surgeon at harvesting site as SOT with less than 60% of steatosis, but when confronted with the biopsy findings, it was placed as a N-SOT due to high degree of steatosis, and discharged (Table 2A).

On the second scenario, we have a 8% (n = 9) of mistaken allocation, in which five organs were wrongly discharged by the procurement surgeon at harvesting site, as those present a high steatosis degree and classified as N-SOT. Further histopathologic findings confirm that, in the events described above, the organs present steatosis degree no higher than 60%, and the organ could be used to transplant, due to its

TABLE 1. General clinical data of all patients evaluate under this study, including gross evaluation of the steatosis degree at harvesting site and biopsy findings

Gender %	Age average (min-max)	PREPER %	AFTPER %	BX %	Suitability* %
M (67.0)		0%-30% (89.66)	0%-30% (81.90)	0%-30% (91.38)	SOT (91.44)
	34.74(4-75)				
F (33.0)		30%-60% (6.03)	30%-60% (12.93)	30%-60% (4.31)	N-SOT (8.56)
		>60% (4.31)	>60% (5.17)	>60% (4.31)	
NE (in numbers)		1	1	1	0

F = female; M = male; PREPER = before perfusion;
AFTPER = after perfusion; BX = biopsy; SOT = suitable organ for transplant;
N-SOT = non-suitable organ for transplant; NE = non evaluated

TABLE 2. Representation of the matrix table for three conditions (PREPER x AFTER x BX) in disctinct situations (SOT and N-SOT)

A		BX (histopathologic findings)		
		SOT (0%-60%)	N-SOT (>60%)	TOTAL
PREPER (surgeon evaluation)	SOT (0%-60%)	108	4	112
	N-SOT (>60%)	4	1	5
	TOTAL	112	5	117
B		BX (histopathologic findings)		
		SOT (0%-60%)	N-SOT (>60%)	TOTAL
AFTPER (surgeon evaluation)	SOT (0%-60%)	107	4	111
	N-SOT (>60%)	5	1	6
	TOTAL	112	5	117
C		AFTPER (surgeon evaluation)		
		SOT (0%-60%)	N-SOT (>60%)	TOTAL
PREPER (surgeon evaluation)	SOT (0%-60%)	111	1	112
	N-SOT (>60%)	0	5	5
	TOTAL	111	6	117

mild lipid content. In those cases, the liver was discharged by the surgeon at the harvesting site, and the transplant never took place (Table 2B).

In order to compare the observation PREPER and AFTPER and evaluate the agreement among the two scenarios, we used the kappa index value[7]. The obtained K value was 0,90 which displays a strong agreement between the surgeons, in the two independent moments (Table 2C).

DISCUSSION

The unfair ratio between availability of donor organs and waiting list still a major concern of public health. The utilization of organs from donors with expanded criteria is an uneven reality that must be undertaken by procurement surgeons in other to avoid dismissing reliable organs. The ability to predict graft function before transplantation has proven to be a hard issue and the equalization between offer and demand has become a crucial matter. We cannot deny that these grafts allow a significant increase in organ pool that counterbalances the negative outcome, in those cases where orthotopic liver transplant is not a feasible option. The large experience surgeon team is an important factor to liver allocation. Worldwide, gross examination appears to be fairly reliable in determining the presence of severe steatosis, but it seems to fails to detect moderate or mild steatosis.

Even though our transplantation center have been conduct more than 500 liver transplants, with an experienced surgeon team, wrong evaluations of feasible organs for transplantation and misguided discharges occur summing, at least, until 8% of mistaken allocations. Wrongly allocated livers can increase the mortality rates in the waiting list recipients or, even so, play an important role in the mortality rates after surgery. Thus, understanding the relevancy of the studies that characterize in which situation these mistaken allocations would take place, it could help to optimize and avoid flaws along those process.

Despite the fact that our faulty percentage is low comparing to worldwide percentage, which ranges about 20% mislead organ placement[3], an accurate clinical assessment is needed, if we account that each organ is a relevant source (and sometimes, the unique treatment) for end-stage liver patients.

As recognized worldwide, the histopathologic evaluation of donor biopsies prior to liver transplantation, continuous to be the golden standard to classify steatotic organs[5]. Thus, is a fact that, at least, on particular doubtful cases, this investigation is the only reliable source of information[1, 8]. Regardless, most of the Brazilian centers does not provide a day-around histopathologic facility to evaluate the grafts, and occasionally, the procurement surgeon's estimation of liver gross pathology is the only possible evaluation.

An important finding of this study was the high index agreement between the surgeons (K = 0.90), regarding the graft conditions; therefore allowing appropriate organ allocation for transplant. The results present in this work also show the surgeons ability to identify organs suitable for transplantation, demonstrated by the fact that there was no statistical differences between BX x PREPER (P >0.05) and BX x AFTPER (P >0.05).

It is relevant to emphasize that frozen-biopsies, the fasten method used in histopathologic evaluation, are not suitable to assess liver steatosis degrees, enforcing even more

the importance of surgeon's assesment, before transplantation[5, 8]. So therefore, the prospective characterization on data at harvesting site and its comparison on histopathologic findings might be an important tool to estimate the surgeon team experience and accuracy on accessing steatosis degree, and also to evaluate the allocation process, in those occasions where the receptor's life is in a greater risk.

Martins AMA, Coelho GR, Marques GA, Moraes MO, Valença Jr. JT, Garcia JHP. Comparação do grau de esteatose hepática: estudo entre a avaliação do cirurgião e os achados histopatológicos. Arq Gastroenterol. 2013;50(1):15-8.

RESUMO - *Contexto* - O transplante ortotópico de fígado é considerado um dos últimos recursos terapêuticos viáveis para os pacientes hepatopatas, em estágio terminal da doença. Muitas estratégias têm sido usadas para aumentar o número de órgãos disponíveis e diminuir a demora em lista de espera. No entanto, a presença de esteatose hepática é uma das principais limitações quanto ao uso de órgãos para transplante, devido a sua importância como relevante fator de risco para disfunção primária pós-transplante. Neste cenário, a avaliação do órgão pelo cirurgião, no momento da captação no doador, é de grande importância para a correta alocação do mesmo. *Objetivo* - Avaliar retrospectivamente o grau de esteatose estabelecido pelo cirurgião e confrontar estes dados com os achados histopatológicos da biopsia. *Métodos* - Analisaram-se 117 pacientes hepatopatas terminais submetidos ao transplante de fígado no Hospital Universitário Walter Cantídeo, Fortaleza, CE. Uma tabela matriz foi organizada para avaliação dos dados categóricos observados. Os indivíduos foram classificados quanto ao grau de esteatose apresentado pelo órgão: leve (0%-30%) e moderada (30%-60%) e agrupados sob os critérios clínicos de adequação de órgãos para transplante. Os órgãos foram descritos como adequado para transplante de órgãos e como não adequado para transplante de órgãos. As avaliações entre as duas primeiras situações, antes da perfusão vs biopsia e após a perfusão vs biopsia foram analisadas; bem como realizada comparação entre as duas situações de perfusão (antes e após). *Resultados* - Na primeira avaliação, obtiveram-se 93% de concordância (n = 109) entre as duas observações, mostrando grande grau de concordância entre as classificações do órgão antes da perfusão e na biopsia. Na segunda avaliação, obteve-se um grau de discordância de 8%, levando a erros de alocação em nove situações. Na comparação entre as avaliações realizadas entre antes e após a perfusão, obteve-se forte concordância através do índice kappa entre os espectadores. *Conclusões* - Embora a equipe deste estudo seja constituída de cirurgiões experientes, em alguns casos os mesmos, foram induzidos a erros de alocação. No entanto o percentual encontra-se bastante abaixo da média mundial.

DESCRITORES - Fígado gorduroso. Transplante de fígado. Obtenção de tecidos e órgãos. Coleta de tecidos e órgãos.

REFERENCES

1. Adani GL, Baccarani U, Sainz-Barriga M, Lorenzin D, Bresadola V, Risaliti A, Risaliti A, Avellini C, Trevisan G, De Candia A, Bresadola F. The role of hepatic biopsy to detect macrovacuolar steatosis during liver procurement. Transplant Proc. 2006;38:1404-6.
2. Briceño J, Padillo J, Rufián S, Solórzano G, Pera C. Assignment of steatotic livers by the Mayo model for end-stage liver disease. Transpl Int. 2005;18:577-83.
3. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. Liver Transpl. 2003;9:651-63.
4. D'Alessandro AM, Kalayoglu M, Sollinger HW, Hoffmann RM, Reed A, Knechtle SJ, Pirsch JD, Hafez GR, Lorentzen D, Belzer FO. The predictive value of donor liver biopsies for the development of primary nonfunction after orthotopic liver transplantation. Transplantation. 1991;51:157-63.
5. D'Alessandro E, Calabrese F, Gringerib E, Valente M. Frozen-section diagnosis in donor livers: error rate estimation of steatosis degree. Transplant Proc. 2010;42:2226-8.
6. Garcia Ureña MA, Colina Ruiz-Delgado F, Moreno González E, Jiménez Romero C, García García I, Loinzaz Segurola C, Gonzalez-Pinto I, Gómez Sanz R. Hepatic steatosis in liver transplant donors: common feature of donor population? World J Surg. 1998;22:837-44.
7. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1997;33:159-74.
8. Markin RS, Wisecarver JL, Radio SJ, Stratta RJ, Langnas. AN, Hirst K, Hirst K, Shaw BW Jr. Frozen section evaluation of donor livers before transplantation. Transplantation. 1993;56:1403-9.
9. Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, Sasaki T, Sollinger HW, Belzer FO, Kalayoglu M. Risk factors for primary dysfunction after liver transplantation - a multivariate analysis. Transplantation. 1993;55:807.
10. Starkey G, Buckels J. Birmingham liver unit: use of marginal donors for liver transplantation. Clin Transpl. 2008;137-42.
11. Yoo HY, Molmenti E, Thuluvath PJ. The effect of donor body mass index on primary graft nonfunction, retransplantation rate, and early graft and patient survival after liver transplantation. Liver Transpl. 2003;9:72-8.