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Expanding the Criteria of Organ Procurement from Donors with Prostate Cancer: The Application of the New Italian Guidelines

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Prostate cancer (CaP) represents the most prevalent malignancy in men more than 60-year-old, posing a problem in organ procurement from elderly subjects. However, most of the currently diagnosed CaP are low-grade and intraprostatic, with low metastatic risk, and there is recent evidence that most patients are over-diagnosed. The Italian National guidelines about organ acceptance from neoplastic donors changed in March 2005, extending the pool of potential candidates with CaP and introducing the function of a second opinion expert. Between 2001 and February 2005, 40 candidate donors with total PSA≥10 and/or positive digital rectal examination underwent histopathological analysis of the prostate: 15 (37.5%) donors harboured CaP, and 25 (62%) were judged at 'standard risk'. After the introduction of the new guidelines in 2005, the second opinion expert judged at 'standard risk' 48 of 65 donors, while 17 of 65 needed histopathological analysis. Four (6.2%) donors harboured CaP, and 61 (94%) where judged at 'standard risk', with a significant increase of donated and actually transplanted organs. The application of the new guidelines and the introduction of a second opinion expert allowed a significant extension of the 'standard risk' category also to CaP patients, decreasing the histopathological examinations and expanding the donor pool.

Key words: Histopathology, organ donation, prostate cancer, second opinion expert

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Introduction

Prostate cancer (CaP) represents the most prevalent malignant neoplasia in men more than 60-year-old. Prevalence of CaP in Italy is estimated about 4% of the male population (1). The progressive implementation of prostate-specific antigen (PSA) screening in the male population caused a steady decrease in the number of CaP diagnosed in advanced stage. Currently, most of the diagnosed CaP are small, low-grade and organ-confined posing little risk to the life and the health of the patients (2). Even among those patients who undergo radical prostatectomy the risk of death from other causes greatly exceeds prostate cancer-specific mortality (3).

The Gleason grade is the measure of CaP differentiation and currently represents the stronger predictor of tumor clinical recurrence and overall survival (4). The Gleason grade is tiered from 1 to 5 and is generally heterogeneous throughout the prostate. The Gleason score is the sum of the primary (most predominant) and the secondary (the second most predominant or the highest of the less predominant patterns) Gleason pattern and therefore ranges from 2 to 10. For practical purposes, CaPs are generally classified in low (score $\leq$6), intermediate (score = 7) and high (score $\geq$8) Gleason's score groups that are associated with significant outcome differences (5).

Nomograms based on the Gleason grade, the levels of PSA and the clinical stage and the number of positive biopsies have been introduced in the clinical practice (6,7). In particular, Conrad et al. predicted the likelihood of lymphatic spread based on the Gleason pattern of a systematic sextant biopsy by means of classification and regression tree analysis (8). This algorithm (known as the 'Hamburg' algorithm) categorized CaP patients into three risk groups for the development of lymph-node metastases: high risk when >3 sextant biopsies with Gleason pattern 4 or 5, intermediate risk when at least 1 sextant biopsy contained a Gleason pattern 4 or 5 were present, low risk in all the other cases (9). More recently, Makarov et al. showed that a nomogram (also called 'Partin tables') combining preoperative PSA, clinical stage and Gleason score was able to predict pathological stage after radical prostatectomy (10). Although these nomograms do not reliably predict prostate cancer-specific death, they currently represent the most

effective tools to predict prostate cancer outcome and relapse.

The progressive increase of the transplant waiting lists and the general organ donor shortage enforced the transplantation teams to extend the multiorgan donor pool also to elderly subjects with consistent higher risk of CaP in men over 60-year-old. These new perspective led the Commission of the European Community on organ transplantation to require a careful screening of all the potential organ donors in order to avoid any kind of donor/recipient cancer transmission and thus to override most of the previous guidelines on the acceptance of donors bearing malignancies (http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_directive_en.pdf). Despite the high risk of using organs from elderly donors, there are few reported single cases of donor/recipient transmission of CaP in the literature and confined to donors with metastatic disease (11–13). In the United States, the voluntary-based Cincinnati Transplant Tumor Registry recorded from 1968 to 1997 a 29% rate of CaP transmission although no clinical data were available for each single event (14).

In Italy, the National regulations on the acceptance of organs from donors with cancer stratify candidates in three categories at 'standard', 'nonstandard' and 'unacceptable' risk of tumor transmission (15). The guidelines for the use of donors with CaP have recently changed to meet the increasing organ demand. These new guidelines introduced the judge of a second opinion expert for organ donor safety and applied at a National level the experience acquired in the Emilia-Romagna region to redefine the three risk categories of transmission (16). The novelty of the new regulations lies in the inclusion in the 'standard risk' category of all donors with localized and Gleason score $\leq$6 CaP and the restriction of the whole-prostate histological examination only to the candidate donors with suspect digital rectal examination (DRE).

Here, we report on the benefits in terms of donor gain after the application of the new National guidelines and the introduction of the second opinion expert to the CaP donor screening in the Emilia-Romagna Region of Italy.

Methods

Italian national regulations

The first regulations on the acceptance of organs from donors with CaP have been first introduced in the Emilia-Romagna Region of Italy in 2001 (15). Until that time, all candidate donors with CaP were excluded from donation according to the 1997 European guidelines. With the 2001 regulations all donors with suspect CaP (i.e., with total PSA $\geq$10 ng/mL, free/total PSA ratio <25%, doubtful DRE and/or available suspect transrectal ultrasound [TRUS]) were screened with frozen section examination of the whole prostate and therefore categorized at 'standard', 'nonstandard' and 'unacceptable' risk of tumor transmission (15). The 'standard risk' category included donors with no evidence of CaP at frozen section examination. Donors with confined CaP with Gleason score 3 + 4 or lower were considered at 'nonstandard risk' and organs from such donors were used pending informed consent in case of clinical urgency. Donors with extraprostatic tumors and/or Gleason's score 4 + 3 or higher were judged at 'unacceptable risk' of CaP transmission and therefore excluded from donation. In March 2005, the National guidelines on donation safety have changed to meet the increasing organ demand and introduced the judge of a second opinion expert. The National Transplant Center nominated a dedicated surgical pathologist as the reference for the second opinion in organ donation safety for neoplastic diseases, on call for the entire country 7/24/365. The second opinion expert was supported in his decision making by a team of other professionals that in the case of prostate cancer also included a urologist who actually performed the DRE or the TRUS. The new guidelines introduced the application of the clinical nomograms to stratify donors with CaP, including in the 'standard risk' category donors with abnormal PSA but negative DRE. Histological examination of the whole prostate was restricted just to those candidate donors with positive or doubtful DRE and only the donors with at least one area of Gleason pattern 4 or with evidence of extraprostatic extension fell into the revised 'nonstandard risk' category. CaP donors with prevalent Gleason pattern 4 and/or ascertained metastases at the time of donation were qualified at 'unacceptable risk'. The changes to the risk groups before and after 2005 are summarized in Table 1.

Table 1: Differences in donor risk category assignment between the old (until February 2005) and new guidelines (effective in March 2005)

	Old guidelines	New guidelines
Standard risk	1. No CaP	1. No CaP 2. Intraprostatic CaP GS $\leq$6
Nonstandard risk	2. Intraprostatic CaP GS $\leq$6	3. Intraprostatic CaP Gleason 3 + 4 4. Extraprostatic CaP Gleason 3 + 3
Unacceptable risk	3. CaP with any Gleason 4 4. Any extraprostatic CaP 5. CaP with prevalent Gleason $\geq$4	5. CaP with lymph nodal or distant metastasis 6. CaP with lymph nodal or distant metastasis

CaP = prostatic cancer; GS = Gleason score.

Screening protocol

All candidate donors presenting in the 16 Intensive Care Units (ICU) of the Emilia-Romagna Region underwent the multiorgan donor cancer screening protocol as previously described (15). DRE, total PSA and free/total PSA ratio were assessed for all male candidates with age $\geq$50 years and/or strong familiarity for CaP. TRUS was performed in DRE positive donors in selected cases depending on the availability of a TRUS facility in the ICU where the donors presented. Frozen section examination of the whole prostate was performed as previously described (16) in the cases selected according to the criteria described below. In case of CaP, detection of the tumor grade (Gleason's score) and the tumor stage according to the American Joint Committee on Cancer were assessed (17).

Risk assessment

Each candidate donor was assigned to one of the above-mentioned risk groups according to the flowchart described in Figure 1. Briefly, the second opinion expert was contacted by the transplant reference center in

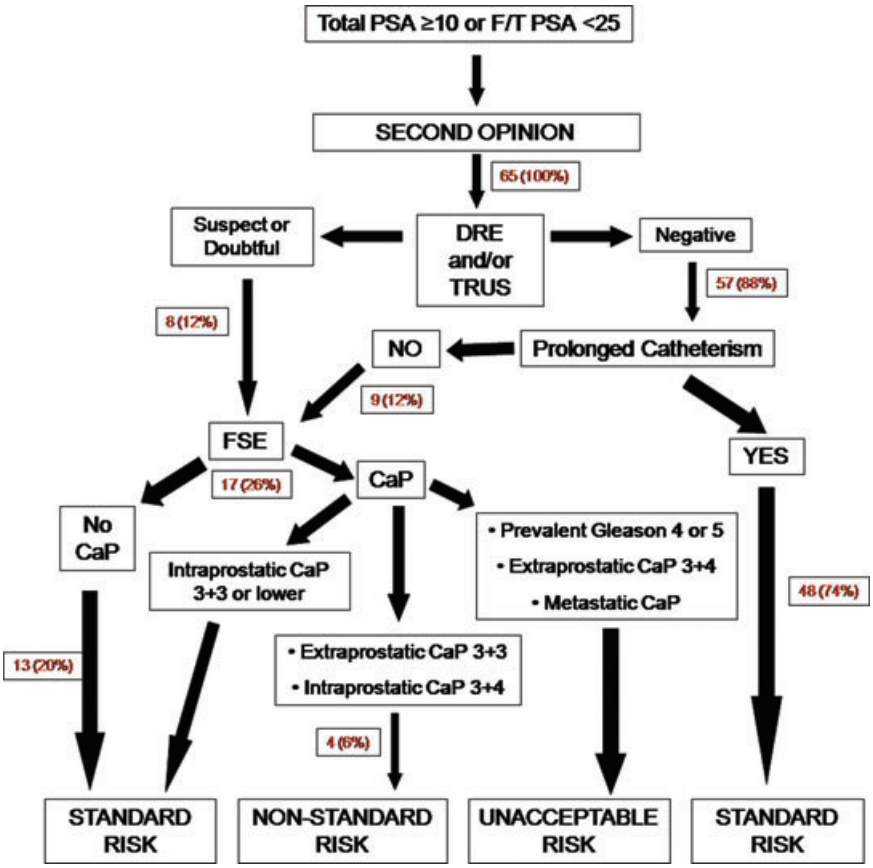

Figure 1: Flowchart depicting the diagnostic algorithm applied to the 65 candidate donors with suspect prostate cancer since 2005 according to the introduction of the second opinion expert. PSA = prostate specific antigen; CaP = prostate cancer; DRE = digital rectal examination; TRUS = transrectal ultrasound; FSE = frozen section examination.

any case of male donors with total PSA ≥10 ng/mL, free/total PSA ratio <25% or doubtful DRE. Frozen section examination of the whole prostate was limited to donors with clinical CaP suspicion and without prolonged catheterism (>5 days) in ICU. The latter condition is a well-known cause of total PSA increase and free/total PSA ratio alteration (18). Assignment to each risk group was decided by the responsible transplant reference center (who acted as the legal representative) together with the second opinion expert and the information regarding the donation safety transferred to the transplantation teams. Donors belonging to the 'unacceptable risk' category were discarded *a priori*. The final decision for the utilization of the organs from all the other donors was taken by the transplant team and the informed consent of the recipients was collected only in case of 'nonstandard' risk donors.

Results

The protocol raised the suspicion of prostate cancer in 105 (mean age 69.54 ± 10.13 years, range 40–97) candidate donors presented in the Emilia-Romagna Region, 40 (38.1%) before February 2005, and 65 (61.9%) between March 2005 and March 2009 after the introduction of the new guidelines. The total PSA was suspect (≥10 ng/mL) in 62 (59%) candidates while DRE was suspect in 43 (41%) and the free/total PSA ratio was ≤25% in 48 of 83 (58%) available donors. TRUS examination was available for 30 (29%) candidates. Combined assessment of PSA, free/total PSA ratio DRE and TRUS had 50% sensitivity and 79% specificity for the detection of CaP at frozen section examination.

Before 2005, frozen section histopathological analysis of the whole prostate was performed in all the 40 presenting donors with suspect CaP among which 25 (62%) were deemed at 'standard risk' (cancer-free) for donation, 14 (36%) at 'nonstandard risk' and 1 (2%) at 'unacceptable risk' due to extraprostatic tumor extension. After the application of the new guidelines 48 (73.8%) of the 65 suspect donors were judged at 'standard risk' by the second opinion expert without histological examination. Thirteen (20%) of the remaining 17 donors who underwent histological frozen section examination were cancer-free while 4 (6.2%) harboured CaP judged at 'nonstandard risk'. No donors at 'unacceptable risk' were encountered after 2005. Therefore, the number of 'standard risk' donors over the total number of suspect candidates shifted from 25/40 (62%) to 61/65 (93.8%) with the application of the new guidelines (Table 2).

Among the 14 donors judged at 'nonstandard risk' for histologically diagnosed CaP before 2005, only 2 were actually utilized for liver transplantation (OLT) and 12 discarded by the transplantation teams. After the introduction of the new guidelines, the four donors included in the 'nonstandard risk' risk group were all utilized for OLT. Furthermore,

Table 2: Donor/recipient characteristics before and after the application of the new guidelines

	2001–2004	2005–2009	p (Mann–Whitney Test)
No. of suspect donors	40	65	
Mean age (years)	68.55	70.15	$p = 0.474$
Mean PSA (ng/mL)	23.48	30.87	$p = 0.771$
Donor risk category			
'Standard'	25 (63%)	61 (94%)	$\mathbf{p < 0.001}$
'Nonstandard'	14 (35%)	4 (6%)	
'Unacceptable'	1 (2%)	0	
Diagnosed CaP	15 (38%)	4 (6%)	$\mathbf{p < 0.001}$
Transplanted livers	21 (53%)	60 (92%)	$\mathbf{p < 0.001}$
Transplanted kidneys	9 (23%)	36 (55%)	$\mathbf{p = 0.001}$
Transplanted hearts	1 (2%)	4 (6%)	$p = 0.395$

the 48 suspect donors included in the 'standard risk' category by second opinion alone together with the 13 histologically negative donors permitted between 2005 and 2009 the actual transplantation of 56 livers, 36 kidneys and 4 hearts (Table 2). Notably, none of the organs discarded by transplantation teams after 2005 was excluded for tumor-related reasons.

The six OLT recipients (four males and two females) who had received the organs from donors with histologically proven CaP underwent the routine follow-up procedures after OLT without a specific protocol for CaP transmission. At the time of last available follow-up (mean 23 months, range 12–56), all the six recipients were clinically free from tumor transmission.

Discussion

The issue of donor/recipient cancer transmission is critical in Europe and Italy where organ procurement is mainly based on voluntary donation. A careful evaluation of the risk/benefit ratio of using organ donors with neoplastic diseases is needed in order to expand the donor pool while maximizing donation safety. The combination of the increasing age of organ donors, the high prevalence of CaP in the male population over 60 and the relatively mild aggressiveness of the majority of CaP led to the modification of the guidelines for organ donation from donors with prostate cancer in Italy. Currently, according to the European guide for safety and quality assurance for the transplantation '*There is no written consensus regarding the procedure for donors with prostate carcinoma. The procedure should be individualized assessing the characteristics of the donor and the condition of the recipient*' (19).

Our results demonstrate that the inclusion in the 'standard risk' category of donors with organ-confined CaP allowed a significant gain in the number of donated—and actually transplanted—organs with negligible risks of cancer transmission at least in the setting of the Emilia-Romagna region of Italy. This raise in the 'standard risk' group has been made possible with the introduction of a second opinion expert able to provide a judgement on the potential risk of transmission of a specific tumor limiting histopathological analyses only to selected cases. The judge of the second opinion expert mainly relies on the presence of positive or suspect DRE. In the specific field of organ transplantation, there is evidence that DRE might be even more relevant than PSA to contraindicate organ harvesting (20). The expansion of the donor pool obtained in our setting after 2005 represents a substantial progress over the previous guidelines that were based exclusively on the histological features of the tumor (pathological stage and grade obtained after frozen section examination). In addition, the introduction of the new guidelines led to a substantial change in the willingness of the transplant centers to actually utilize organs from donors with CaP. Our data clearly show that the number of 'nonstandard risk' discarded donors dropped from 86% to 0% with the application of the new regulations. This reflects the acknowledgment by the transplantation teams that the benefits coming from the utilization of organs from donors with organ-confined, low-grade CaP greatly exceed the risks of potential tumor transmission.

A pivotal role in the application of the clinical predictive criteria for CaP to the donors is played by the second opinion expert. This institutional consultant was designated by the National Transplant Center and the addition of its judge represents a major advancement of the National guidelines on organ donation safety issued in 2005. A surgical pathologist was chosen for this role due to the skill of this professional in the recognition of a wide spectrum of malignant diseases and cancer mimickers. In the specific case of histologically diagnosed CaP, the second opinion expert translates the criteria coming from clinical nomograms to deceased donors and helps the transplant reference center in deciding the risk category in which each donor falls. The final decision on the donation is taken with the agreement between the legal representative of the reference center and the second opinion expert. The second opinion system is also useful to homogenize decisions across the Country and to supervise the activity of each local center.

We realize that with the new guidelines many CaP in the donors will remain undiagnosed and that clinical criteria cannot be completely informative of the actual histological features of each CaP. Results from the recent reports on the failure of the screening with PSA clarified that most of CaP patients are currently overtreated (2,3). Unlike other epithelial malignancies the favorable clinical behavior of organ confined CaP is well recognized. The follow-up of the six recipients who received organs from donors with CaP in our series is short (23 months) especially considering the long terms usually required to follow CaP patients. However, the few cases described of donor/recipient cancer transmission were characterized by an extremely rapid tumor progression due to the posttransplant immunosuppressive regimens, leading to early death of the recipient.

Therefore, we believe that the chance of CaP recurrence in our recipient series after more that 1 year is almost negligible, especially in the female recipients. In conclusion, in view of the chronic shortage of organ donors and of the increasing transplant waiting list, we think that the current Italian guidelines provide a reasonable risk/benefit ratio for the utilization of organs from donors with prostate cancer.

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