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CRITERIA FOR PREVENTING THE TRANSMISSION OF NEOPLASTIC DISEASES IN ORGAN DONATION

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CONSENSUS DOCUMENT

Criteria for Preventing the Transmission of Neoplastic Diseases in Organ Donation

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I. INTRODUCTION

It is recognized that neoplasias can be transmitted to immunosuppressed patients and animals when organs from donors with neoplastic diseases are unknowingly transplanted in recipients[1].

The malignant tumor donor frequency and the donor-recipient tumoral transmission risk are not known with any exactitude. However, today we have available abundant information in regards to this subject thanks to the UNOS's[2,3] (United Network for Organ Sharing), IPTTR's[2] (Israel Penn Transplant Tumor Registry), the Italian experience through the Centro Nazionali di Trapianti[4] and the Organización Nacional de Trasplantes (ONT) registries.

On the other hand, the accidental transmission risk of a tumoral disease of a cadaver donor to a recipient should be examined with perspective, since the majority of the cases reported until now correspond to the primary era of the transplants. Although there are now some published transmission cases[5,6], after more than 300.000 solid organ transplants performed only a minimum percentage of the recipients have developed a transmitted malignant disease. Nevertheless, due to the serious consequences that this entails, it is obligatory to carefully select all the potential donors with the intention of avoiding the transmission of these types of diseases.

Also, we cannot forget that the progressive increase of the need for organs for transplant along with the shortage of donors available forces us to reconsider the concepts admitted until now that guide the acceptation of donors diagnosed with tumors[7]. In this sense, the transplant coordinators and the members of the transplant teams need guidebook procedures that provide them with security in the management of such complex situations, although ultimately the treatment of each case will be individualized.

Until now the consensus document "The Standardization of the Organ Donation Criteria for the Prevention of Transmission of Neoplastic Diseases," [8,9] subsequently approved by the European Council, has been a tool of great use for coordinators and transplant teams. Also other documents have been elaborated, including regulations, like the "Security and Quality Guide for Organs, Tissues, and Cells" by the European Council[10] or the Directive 2004/23/CE of quality and safety in human cells and tissues[11]. These specify what pathological conditions invalidate donors and in which circumstances they can be used.

II. GENERAL RECOMMENDATIONS TO FOLLOW IN THE DONATION PROCESS TO PREVENT THE TRANSMISSION OF TUMORS

Clinical History of the Donor

During the process of obtaining an organ, a complete clinical history of the donor should be made taking into consideration the following basic points:

1. Records of any previous treatment of neoplasias or tumors removed without registering the definitive diagnosis.
2. History of menstrual irregularities after pregnancies and/or miscarriages of women of a fertile age as clinical evidence of a metastatized choriocarcinoma.
3. The origin of a tumor should always be excluded in donors diagnosed with intracranial hemorrhagia, especially if no evidence of hypertension or arteriorvenous malformation exists.

Laboratory Determinations. Tumoral Markers.

Standard laboratory tests should be conducted on all potential donors with the objective to detect specific diseases that may contraindicate the organ donation. The human chorionic gonadotropin (HCG) beta in the urine should be determined since this hormone appears augmented in females with choriocarcinoma and in males with testicular germinal tumors. Furthermore since in males the HCG may be undetectable in the urine and has a pathological value in the blood, it is recommendable in these cases to also determine the hormone in the blood.

The usefulness of other specific tumoral markers is questionable. With regards to prostate specific antigen (PSA) as screening the adenocarcinoma of the prostate different studies have shown its limited or null usefulness for a premature diagnosis[12]In the ONT registry, there are 38 donors (period 1997-2004) with high PSA of which only 3 present adenocarcinoma of the prostate; furthermore, the three were older than 60 years old. When selecting donors older than 50 Frutos[13] finds that only 11 of them (5.9%) had high PSA and only 2 out of those that had high PSA confirmed the presence of adenocarcinoma of the prostate. There is a consensus to advise against indiscriminately carrying PSA and other tumoral markers. PSA should only be carried out on donors with a history of prostate disease[14,15,16].

In any case, when possible a new sample of serum or plasma will be stored in the hospital's serum bank to investigate laboratory tests and/or tumoral markers in the future.

Radiological Tests

Radiological tests along with a complete clinical history and physical examination will help us to carry out a thorough donor study especially in those

we suspect may have greater chances of tumoral presence. More specifically, both the abdominal ultrasound and the CT thoracoabdominal may become important tools for diagnostic support.

Organ Revision During Extraction

During organ extraction, surgeons should examine the solid intrathoracic and intraabdominal organs to detect possible hidden tumors or pathological lymphadenopathies.

If a microscopic test reveals pathological findings, an intraoperatory ultrasound could be useful to locate hidden tumors. Obviously, none of these examinations rule out metastasis or micro metastasis.

Special emphasis should be made on the examination of kidneys due to the great number of tumors found in kidneys after their extraction.

Anatomicopathological Exam

We should distinguish three situations:

a) If during the extraction process a mass or a lymphadenopathy with a malignant appearance is found, an anatomopathological test will be performed through a cytologic smear and/or with frozen cuts before any organ is transplanted. The results of this histological test could be available in 30 min. to an hour.

b) The decision to be taken regarding a potential donor with a intracranial space occupying lesion (ISOL) will be carried out according to the clinical and neuroradiological data. However, if it is suspected that the donor's cerebral death was caused by a malignant ISOL, a histological diagnosis should be performed before any organ is transplanted. Furthermore in tumors in which different histological degrees of malignancy may coexist, a complete anatomicopathological test should be performed.

For some pathologists the extraction of CNS, its in situ macroscopic study and the performance of frozen section analysis to determine the histogenesis and the histological degree of malignancy, can be done in 2-3 hours. Nevertheless, this is not always the case and it might be necessary to embed the material in paraffin for 24 hours so that the histogenesis of the tumor can be more accurately determined.

If no precise histological diagnosis of the donor's intracranial process can be obtained, the donor should be excluded from the donation.

c) If the presence of elevated levels of PSA, the finding of a nodule in the examination or any other reason lead to suspect there might exist a

malignant tumor growing in the prostate, it must be wholly extracted and an anatomopathological study through freezing of the specimen and a complete anatomopathological study afterwards should be performed before implanting any organ.

For a thorough study of the prostate, thin cuts (with a maximum thickness of 1mm) should be made.
If an autopsy of a donor is performed, the hospital coordination team should collect the results and reveal to those in charge of the transplant teams any discovery made that could put the safety of the transplant patient at risk.

III. PREVENTION TO AVOID THE TRANSMISSION OF NEOPLASIAS

A. Background of Neoplastic Diseases and Transmission Risk

Although the exact frequency of donors with a malignant tumor nor the donor-recipient tumoral transmission risk is accurately measured, today there is information about this subject based on the following facts:

1. The ONT Registry: In the ONT registry the frequency of donors with an undetected tumor in the last 15 years has been 6.1 per thousand donors. Of these donors with a tumor, only 5 (2.9 per 10,000 donors) transmitted the tumor to the receptor. Only 10 recipients out of the 155 that received a donor graft with a tumor developed tumoral transmission (6.4%), which means 2.2 per 10,000 transplants performed in our country in the time period mentioned. The tumors transmitted from the donors to the recipients were a soft tissue sarcoma, a germinal cell carcinoma, an undifferentiated carcinoma, and two renal carcinomas (these last two cases correspond to two kidneys that were implanted and that presented a renal adenocarcinoma and papillary carcinoma; in both cases the diagnosis was made through a post-implant biopsy).

2. UNOS Registry: The first UNOS[3] (1994-1996) report presented a 1.7% frequency of donors with a history of cancer and a 4.3% frequency of transmission of the tumor from the donor to the receptor. A more updated report of this registry[17] (1994-2000 period) presented 14 of the 35,503 donors had a tumor (4 per 10,000 donors), and there was tumoral transmission in 15 of the 109,749 recipients transplanted (1.3 per 10,000 transplants) during this period. The tumors transmitted were the following: 4 melanomas, 1 neuroendocrine tumor, 1 adenocarcinoma, 1 cancer of the pancreas, 1 nondifferentiated squamous carcinoma, 2 lung cancers, 1 small cell carcinoma, 1 oncocytoma, 1 papillary tumor, 1 breast cancer, 1 prostate cancer).

3. The Danish Registry Experience. Bikerland studied a group of donors for 27 years and found 13 malignant tumors among 626 donors (2% of the donors), of which in 8 the tumor was detected after the organs were implanted (1.3%). From those donors, only one transmitted neoplasia (a melanoma) to the receptor (2 per thousand donors) [18].

4. The Italian National Transplant Center Registry (CNT). Since 2002, the CNT have put in practice a new strategy to evaluate the safety and acceptability of the donors[4]. This new strategy analyzes donors with tumors and infections and establishes some donor risk criteria (unacceptable, high but acceptable, calculated, not acceptable, and standard) in the transmission of neoplastic or infectious diseases. Analysis of the years 2001-2002 showed 2.9% of the donors with tumors of which approximately half were ruled out as donors before the extraction, a fourth of them were detected between extraction and implantation and the rest were detected after the implant.

5. IPTTR[2] Registry. The I Penn Registry presents greater frequencies of neoplastic transmission than those previously stated. During the years 1994-2001 68 recipients of organs from donors with renal carcinoma were registered. Tumoral transmission took place in 43 (63%) of them. Of 30 recipients from melanoma donors, tumoral transmission took place in 23 (77%). Of 14

recipients of organ donors with choriocarcinoma, there was tumoral transmission in 13 (93%). Other tumors transmitted were: lung (41%), colon (19%), breast (29%), prostate (29%) and Kaposi's sarcoma (67%). No tumoral transmission of thyroid, head, neck, lymphoma-leukemia or testicular cancer or hepatobiliary tumors from the donors took place. The discrepancy between the results of this registry and those of the other registries might be explained by the fact that this registration is voluntary while the other are active and stem from the follow-up of all donors and recipients.

Penn and cols[1] suggest that donors with a history of neoplastic diseases who after a 10 year period of strict monitoring do not demonstrate a recidive of original tumor could be considered for organ donation with the exception of those with breast carcinoma, soft tissue sarcoma and cutaneaous melanoma because these tumors more often develop late metastasis. However, the consensus of this issue is not generalized and most authors believe that donors who have had a history of neoplastic disease should not be considered under any circumstances for the donation while others believe that with certain tumors a period of 3-5 years[19] free of the disease is sufficient.

The present data indicate that although the risk of tumoral transmission exists, the frequency of donors with tumors and the frequency of transmission is low. Generally, tumors of high degree of malignancy are more often transmitted from donor to recipient. Whereas, the transmission of tumors of low degree of malignancy or localized tumors is much less frequent. On the other hand, not enough evidence exists to set a period of time in which a donor must be free of the neoplastic disease before being accepted as a donor. This depends on the type and features of the tumor, meaning that decisions should be specific to each case.

B. Solid Organ Tumors

1) Renal Tumors:

In 1995, Penn[5] reported 14 kidney transplants from donors with renal carcinomas of < 2 cm completely removed without observing tumor transmission after a 55-57 month monitoring. Therefore he concluded that kidneys which come from donors with renal tumors < 2cm completely removed could be used for transplantation with a low risk of local recurrence or metastasis, but specified that it was important to make a close follow-up of the receptor. Likewise, Nalesnik[19] referred another 14 renal transplant cases from donors who had a renal tumor $\leq$ 4 cm (average 2 cm) detected and extirpated with negative margins and Fuhrman grade I-II/VI. After a monitoring period of 69 months, a transmission of the tumor was not detected in any of the cases.

Nor has the ONT Registry detected any tumoral transmission among those donors registered with renal tumors. Specifically, 47 donors were detected with renal tumors from which 59 organs (15 kidneys, 29 livers, 7 hearts, and 5 lungs) were implanted. Prophylactic transplantectomy was done in 9 kidneys, 2 livers and a heart. After three years of follow-up, tumoral

transmission has not appeared in any of the cases (as it was previously referred to in two of the cases a kidney with a tumor had been implanted).

Furthermore, in relation to the use of other organs from donors with kidney cancer, Carver[20] refers a liver and a contralateral kidney transplant from a donor of this type without evidence of a tumor after four years of monitoring[20]. In our country, as mentioned before, 28 liver grafts from donors with renal carcinoma were implanted and presently there is no appearance of tumoral transmission.

However, transmission cases do exist. In 1997, Seeck[21] reported the transmission to a cardiac receptor that died of metastatic renal cancer 12 months after the transplant. Similarly, in 2001 Bernoit Barroul[6] refers to the execution of a contralateral kidney transplant and another heart transplant from a donor with a 17 mm tubulepapillary carcinoma. The kidney receptor underwent transplantectomy four months later, due to tumor infiltration of the kidney and the heart recipient died 7 months later because of metastatic renal cancer. These authors recommend not using these types of donors.

In summary, renal cancer donors would be acceptable if the tumor is 4 cm or less in size, the margins are free and present a Fuhrman histopathological grade I-II.

2) Prostate Cancer: Given the increase in the average age of donors and that prostate cancer increases with age it is certain that in many of the organ transplants that are now being performed, organs of donors with undiagnosised prostate cancer are being used. It has been estimated that in Spain 28.5% males between 50-59 years old, 33.3% between 60-69 years old and 45.4 % between 70-79 years old show malignant intraepithelial neoplasia[22].

Although in both the IPTR and the UNOS registry there are case descriptions of prostate cancer transmission from donor to recipient, these are isolated cases; furthermore, in the ONT registry there has never existed a donor to receptor prostate cancer transmission case.

A consensus does not exist in literature 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.

3) Carcinomas in situ: According to some authors, donors with colon carcinomas in phase 0 and I could be considered for donation, if they have received adequate treatment for their tumor[19]. Also donors with breast cancer in phase 0 (except those with high risk factors like extensive carcinoma in situ) can be considered for organ donation in anytime after the treatment. Women with phase I (T1a or T1b) breast cancer can be considered as donors if after 10 years they do not show a relapse of the tumor. Women with phase T1c or greater of breast cancer should not be considered for organ donation[19,23]. Other authors consider that donors with thyroid carcinoma in situ can also be considered for donation. On the other hand, there is an understanding that incredibly aggressive tumors like melanoma, sarcoma lung cancer and choriocarcinoma should not be considered as donors regardless of their phase[19,23].

Donors with carcinomas in situ could be considered valid except extensive breast cancer in situ, choriocarcinoma, melanoma, lung cancer and sarcomas.

5) Tumors with a high risk transmission: Donors with choriocarcinoma with a 93% transmission rate and a 64% recipient mortality rate, or with melanoma — with a 74% transmission rate and a 60% recipient mortality rate—as well as those that have lung cancer or sarcomas should not be used as donors due to the tumors' high risk of malignancy[19,23].

Metastatic carcinomas hold a high transmission risk and also should not be used as donors.

Sufficient evidence exists to reject as donors those who are diagnosed with choriocarcinoma, melanoma, lung cancer and metastatic carcinomas.

C. Primary Tumors of the Central Nervous System

Primary tumors of the central nervous system represent 3-4% of the causes of brain death of the organ donors. On the other hand, although the central nervous system[24,25] neoplasias rarely develope extraneural metastasis, these have been described in 0.4-2.3% of the cases[26,27]. These metastases can develop themselves in order of frequency in: the lungs, pleura, lymphatic glands, bone, liver, suprarenals, kidneys, mediastinum, pancreas, thyroids and peritoneum[26,28].

Rubinstein analyzed 116 tumor cases published until now and found that the type of tumor that produces more metastasis was glioblastoma (41.4%), followed by meduloblastoma (26.7%), ependymoma (16.4%), astrocytoma (10.3%) and lastly oligodendroglioma (5.25%)[28].

It has been shown that malignant CNS tumors can grow in the extracranial spaces through the lymphatic drainage of the cephalorhachidian fluid and the invasion of the veins[29,30]. Among the classically implicated factors in the extraneural disemmination of these tumors we can feature: a) histological type and malignancy grade; b) peripheral intracranial location; c) history of craniotomy or stereotactic surgery; d) presence of ventricle-systemic derivations; e) previous history of chemotherapy or radiotherapy; f) duration of the disease and survival time after the surgery[19,26,31].

In any case, the extraneural dissemination of these tumors implies the access of these tumoral cells to the blood vessels once they have infliltrated the tissues outside the leptomeninges. With respect to the histological type, the neuroectodermic tumors that metastasize with greater frequency out of the cranial cavity are the multiform glioblastoma and the meduloblastoma[32], although several forms of gliomas have also been described (different grades of astrocytomas, malignant ependymomas, and anaplastic olgodendrogliomas) as well as malignant meningiomas and germinal cell tumors[32]. Although the craniotomies and prior derivations are the principal cause of dissemination of the CNS tumors, there are plenty of examples of spontaneous dissemination to the cranial and cervical lymphatic glands, and even distant metastasis[26,33,34,35,36]. It is estimated that 10% of the metastasis of these tumors occurs without prior surgical intervention and even within 3-6 months of the diagnosis[26].

Classically the Israel Penn Transplant Tumor Registry (IPTTR) [31] has described the following as *risk factors for transmission of primary CNS tumors* through transplant: 1) high grade malignancy tumors, 2) the presence of

peritoneal ventricle or artrial ventricle derivations, 3) the previous craniotomies, 4) systematic chemotherapy and 5) previous radiotherapy[31].

At least 12 organ recipients with CNS primary tumor transmission from 8 donors have been described in literature since 1987 until 1998. The tumors referred to are: 5 multiform glioblastomas (4 of them having undergone previous craniotomies and 1 radiotherapy), 1 meduloblastoma (having undergone a craniotomy, radiotherapy and previous ventriculo-peritoneal shunt), 1 malignant meningioma and 1 CNS primary lymphoma[3,26,37,38,39,40,41].

On the other hand, some series in which tumoral transmission has not been detected from donors with primary CNS tumors have been published. That is the case in the series published by the New Zealand Registry (1999) of 46 donors with primary CNS tumors (28 malignant and 18 benign) in which none of the 153 recipients showed signs of tumoral transmission. Neither did 91 organ recipients from the 41 donors with CNS tumors referred to by the Czech Republic Registry in 2001 showed signs of tumoral transmission[23,31,38].

Similarly the UNOS registry published in 2002 a series of 397 donors with history of primary CNS tumor from which 1,220 organs were transplanted. Following a 36-month monitoring period no tumoral transmission to the recipients was registered. According to the UNOS, the tumoral transmission risk from donors with primary CNS tumors is small. However, the UNOS itself warns that some tumors like the multiform glioblastoma and the meduloblastoma can entail a high transmission risk and that they should not be used as donors. The UNOS concludes that the tumoral transmission risk of each donor should be carefully considered for each case, bearing in mind the risk of death that the potential recipient incurs on while on the waiting list for a transplant[37]. However it is suggested this UNOS study presents a whole series of problems: 1) it only includes anatomopathological data of 35 (7%) donors, 2) data regarding possible tumoral transmission risk factors are not collected 3) it is probable that all the tumoral transmission cases have not been reported to the UNOS and 4) in practice, nowadays donors with risk factors of tumoral transmission are not usually used. All this could mean that the UNOS Registry has not detected cases of tumorals transmission in the recipients[31].

On the contrary, in 2003 the IPITTR published data about 62 organ recipients from 36 donors diagnosed with primary CNS tumors: (16 astrocytomas, 15 gliomas or glioblastomas, 3 meduloblastomas and 2 cerebellar tumors). The results were the following:

1) Of the 25 organs transplanted from donors with astrocytoma, 14 had risk factors for tumoral transmission (4 had high grade III/IV astrocytomas, 5 had a previous craniotomy, 4 had a previous radiotherapy and 4 had a previous chemotherapy). There was one tumoral transmission case 20 months after the transplant in which the donor presented a high grade (III/IV) astrocytoma as the sole risk factor.
2) Of the 26 organs of the donors with gliomas/glioblastomas, (8 grade III/IV gliomas and 18 gliomas), 15 had some factor of risk (10 previous craneotomies and 9 were high grade III/IV gliomas) and there were 8 tumoral transmissions within 2-15 months after the transplant.
3) Of the 7 organ recipients from donors with meduloblastomas (all with a previous ventriculo-peritoneal shunt) three showed tumoral transmission.

4) The 2 organ recipients from donors with cerebellar tumors also presented tumoral transmission.

The IPITTR states that the rate of transmission from donors with primary CNS tumors to organ recipients when there is no risk factor is 7%. However when one or more of the risk factors described arise, the rate of transmission to recipients is raised up to 36%-43%[23,31]. The IPITTR concludes that organs from donors with low-grade malignant or benign primary CNS tumors can be used for transplant. Nevertheless, donors that show one or more risk factors should be avoided as donors or used only when there is a need for a vital emergency transplant[31].

Primary CNS tumors can be classified in the following way:

Group I. Tumors that do not contraindicate organ donation

Benign Meningioma
Pituitary adenoma
Acustic schwannoma
Craniopharyngioma
Pilocytic astrocytoma (astrocytoma grade I)
Epidermoide cyst
Colloid cyst of the third ventricle
Choroid plexus papilloma
Isolated hemangioblastoma (unrelated to the Von Hippel-Lindau phakomatosis)
Ganglion cell tumors (ganglioglioma ganglioctytoma)
Pineocytoma
Low-grade oligodendroglioma (A y B Schmidt). As it happens with the astrocytomas, in these tumors a greater degree of malignancy and/or relapse with a greater histological grade might coexist. Therefore, the same considerations as in the astrocytoma grade II will be observed.
Conventional ependymoma (non-anaplastic)
Mature teratoma.
Pleomorphic Xanthoastrocytoma, subependymal giant cell astrocytoma, desmoplastic astrocytoma of childhood, subependymoma, astroblastoma, dysplastic cerebellar gangliocytoma, central neurocytoma, blood vessel malformation, benign mesenchymal tumors, cysts

Hamartoma of the hypothalamus, nasal glioma, meningiomatosis (are tumors that do not contraindicate donation, but that for its uncommoness are not quoted in the text)

Grupo II. Tumors that can be considered for organ donation in the absence of other risk factors

Astrocytoma grade II. Can be considered for organ donation depending on the histological findings and the local invasive behavior. A complete histological study of high histological malignancy should be performed. If it is a low-grade astrocytoma relapse, a new histological study to rule out a higher degree of malignancy should be performed.
Gliomatosis cerebri

Group III. Tumors that contraindicate organ donation and would only be used for the recipient in case of a vital emergency, after individually assessing each case and having previously informed the patient.

Anaplastic astrocytoma (astrocytoma grade III).
Multiform glioblastoma.
Meduloblastoma and variants.
Anaplastic oligodendroglioma (Schmidt grade C and D).
Malignant ependymoma
Pineoblastoma
Malignant and anaplastic meningioma.
Intracranial sarcoma.
Intracranial germinal tumor (except mature teratoma).
Cordoma.
Primary cerebral lymphoma
Plexo choroidal carcinoma, primordial neuroectodermic tumor, ependymoblastoma, hemangiopericytoma, papillary hemangioma, melanoma

In conclusion, donors diagnosed with a central nervous system primitive malignant tumor that rarely metastatizes out of the central nervous system (groups I and II) can be considered for donation. The donors in Group III present a significant transmission risk and could only be used should a vital emergency arise and after having previously informed the recipient.

IV. FINAL CONSIDERATIONS

In general and after analysis of knowledge accumulated in the last decades, the majority of authors think that given the shortage of donors and the limited tumoral transmission risk with certain tumors, an individualized assessment of each case should be made weighing the donor *tumoral transmission risk* with the *degree of emergency of the recipient* and the risk of him dying while on the waiting list[26,37].

SPECIFIC RECOMMENDATIONS

1. The accidental transmission risk of neoplasias from donors to recipients is rare; however, due to serious consequences that may result, a careful study of all the potential donors should be performed to avoid the unnoticed transmission of neoplastic diseases.
2. Donors diagnosed with neoplasias should not be considered for organ donation, except those with:
    - Low-grade skin tumors with little metastatization capacity like basocellular carcinoma.
    - Carcinomas *in situ.*

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- Primary central nervous system tumors that rarely metastatize outside the central nervous system.
- Low malignancy grade kidney tumors.

3. CNS tumors:
   - Group I tumors do not contraindicate organ donation
   - Group II tumors can be considered for organ donation when there is an absence of other risk factors
   - Group III tumors that contraindicate organ donation and would only be used for the recipient in case of a vital emergency, after individually assessing each case and having previously informed the patient.

ANNEX. A REVIEW OF THE PRINCIPLE CENTRAL NERVOUS SYSTEM PRIMITIVE TUMORS

NEUROECTODERMIC TUMORS

1).- Meduloblastoma

Meduloblastoma represents 6% of all the intracranial gliomas and 44% of the gliomas in children. Normally, it originates in the fourth ventricular layer and invades the cerebellar vermis. The tumor that mestastasizes outside the core of the central nervous system[42] with greater frequency is the one that occurs during childhood. In 7% of the cases extraneural metastases have been observed and some authors suggest that this prevalence could be augmented. If a peritoneal ventricular derivation has been previously performed, risk increases by 20%[43,44]. Risk also increases when prior surgery or radiotherapy has been performed[45]. Berger and cols[44] found a 2% extraneural metastasis effect on kids with central nervous system primitive tumor of which all were meduloblastomas. The meduloblastoma metastasizes more frequently in bones, bone marrow and lymphatic glands and less frequently in the lungs, pleura, liver and breast.

Neoplastic transmission from organ donors with meduloblastomas to recipients has been observed. Lefrancois[46] (1987) published the transmission from a donor with meduloblastoma to a hepatic, renal and a kidney-pancreas recipient 4 months after the transplant. The IPITTR[2,31] has 7 organ recipients from 3 donors with meduloblastoma (all with prior ventriculo-peritoneal shunt) registered. 3 out of the 7 recipients had transmission of the tumor within 5-7 months after the transplant. Of these three, 2 died of metastasic disease and third lived but with scattered tumoral disease. The UNOS Registry as well as the IPITTR contraindicates the use of these types of donors because of the high risk of transmission raised to the recipients.

In summary, the meduloblastoma is the central nervous system primitive tumor that occurs during childhood and that metastatisizes outside of the central nervous system with greater frequency. The risk increases if prior peritoneal ventricular derivations or surgeries have been performed.

Therefore, potential donors with meduloblastomas should not be considered for donation and can be used exclusively in cases of life-threatening emergency transplants in which the recipient's risk of dying while on the waiting list is greater than the probability of tumoral transmission. In these cases, it is recommended to not use donors who have previously undergone craniotomies and/or peritoneal ventricular derivations.

2). Gliomas:

The incidence of extracranial glioma dissemination is calculated at 0.4-2.3%, predominantly in the lung, pleura, lymphatic glands, bone and liver[47].

2.1.- Astrocytomas

Astrocytomas are divided into 1) malignant astrocytomas (anaplastic astrocytoma or grade III and multiform glioblastoma or grade IV) and 2) low degree disease astrocytomas (pilocytic astrocytomas or grade I and diffused astrocytomas or grade II) represent, respectively, 55% and 20% of all of the intracranial gliomas[48].

a) Pylocitic astrocytoma (grade I) and low degree astrocytomas (grade II)

Low-grade astrocytomas are normally found in young adults[53,62]; they rarely mestastasize through the cephalorrhachidian fluid and often do not necessarily continue with the local invasion of the leptomeninges, the latter being a frequent find. Furthermore, they occur with greater frequency if the tumoral growth reaches the ventricular apendima or it is followed by anaplastic changes, therefore acting as a malignant glioma. Rubienstein[49] noted occasional distant dissemination in histologically benign astrocytomas[50,51,52]. While diagnosing Pollock and cols[50] found multisystemic disease in 2 cases, one of which developed peritoneal dissemination after having underwent a peritoneal ventricular derivation. Up to 30% of low-grade astrocytomas maybe associated to histological degrees of greater malignancy[49]. These tumors have a tendency to relapse and with frequency show in the recidives a degree of malignancy greater than that of the prior tumor.

Potential donors with astrocytoma pilocytic could be considered for organ donation.

Low degree extraneural astrocytoma metastases, although rare, have been described; therefore, potential donors with this diagnosis can be considered for organ donation depending on the histological results of the tumor and the local invasive performance.

A complete histological study should be performed in which areas of greater malignancy are ruled out. Since they have a tendency to relapse with a higher degree of histological malignancy, a new histological study should be performed on the recidives also.

If the tumor coexists with histological areas of greater malignancy or shows a very invasive conduct at a local level, it will not be considered low-grade.

b) Anaplastic astrocytomas (Grade III astrocytoma) and multiform glioblastoma (grade IV)

At least 80% of the malignant gliomas are multiform glioblastomas and represent the most undifferenciated type of tumor of all the tumors of the central nervous system in adults. It can be located in any part of the brain, but it normally affects the cerebral hemispheres. Anaplastic astrocytomas appear more frequently between the 4^{th}-5^{th} decades of life and the multiform glioblastomas between the 6^{th}-7^{th}. A majority of the malignant astrocytomas are sporadic, but they can be associated to diseases like type 1 and 2 neurofibromatosis, the Li-Fraumeni syndrome, and the Turcot syndrome[53]. Although direct dissemination rarely occurs through the dura mater without prior surgical decompression, the transgression of the dura mater takes place with greater ease[49] when peritoneal ventricular derivations or radiotherapy of tumor have been performed. The dissemination of a multiform glioblastoma through the cephalorrhachidian fluid is not uncommon, and generally occurs because of invasion or a rupture within the ventricular cavity[49]. In the absence of prior surgeries extracranial malignant astrocytomas metastasis and multiform glioblastomas[33,34,35,35,54] have been observed, although they have been registered with greater frequency when prior surgery or peritoneal derivations were made[48,52,55]. Pasquier notes that out of 750 astrocytomas and glioblastomas, the incidence of extracranial metastasis was 0.5%[3]. Bone metastases have been observed in anaplastic astrocytomas and multiform glioblastomas[52], although they metastasize with greater frequency in the lungs, liver[54] and cervical lymphatic glands.

Transmission of neoplastic diseases from donors with malignant CNS[56,57,58] tumors has also been noted. From 1987 to 1998, at least 15 transplants (2 hearts, 3 livers and 10 kidneys) from 5 donors with glioblastomas (4 of them having undergone prior craniotomies and 1 radiotherapy) have been noted in literature. The 3 liver recipients died of tumoral invasion. Of the 10 kidney recipients, tumoral transmission took place in 5 with a nephrectomy being carried out on all of them and returning them to hemodialysis. Transmission to heart recipients was not observed[37,40,41,54,59].

Fecteau published a case of a patient with peritoneal metastasis 9 months after a ventriculo-peritoneal shunt.

Similarly, the IPITTR describes a series of 25 organ transplants from 16 donors with astrocytomas during the period 1970-2002 and 14 of those transplants had risk factors for tumoral transmission: (4 high grade III/IV astrocytomas, 5 prior craniotomies, 4 prior radiotherapies and 4 prior chemotherapies). There was 1 case of tumoral transmission 20 months after transplant in which the donor presented a sole risk factor (astrocytoma grade III/IV). And, of the 26 organ transplants from 15 donors with gliomas or glioblastomas, 8 were high grade III/IV glioblastomas and 18 gliomas. Out of these, 15 had some risk factors (10

prior craniotomies and 9 high grade III/IV gliomas), and there were 8 tumoral transmissions between 2-15 months after transplant.

Recently it has been suggested that 70% of the glioblastomas exhibit elevation of certain growth factors (Akt and mTOR). This would favor the development of extraneural metastasis and the possible benefit of Sirolimus (Rapamune) and/or its derivatives like as immunosuppressant in the recipients of these organs, since Rapamune would block the activity of mTOR[14,47].

Spontaneous extraneural metastases of anaplastic astrocytomas and multiform glioblastomas are rare, but have been observed, and have been associated with greater frequency to prior surgical treatments and/or peritoneal ventricular derivations.

Potential donors with anaplastic astrocytomas and multiform glioblastomas should not be considered for organ donation and could only be of value in cases of life-threatening emergency transplants in which the recipient's risk of dying while on the waiting list is greater than the probability of tumoral transmission[31,61].

In these cases, donors with a high tumoral transmission risk like those who have previously undergone craniotomies and/or peritoneal ventricular derivations, should not be used.

2.2.- Oligodendrogliomas

Given the recent discovery of the chemosensibility of oligodendrogliomas, today a great effort is being made in the recognition of these types of tumors. As a result, it is now estimated that oligodendrogliomas represent 20% of the gliomas[53]. There are four types according to the degree of histological malignancy: low degree (Schmidt grade A and B) oligodendrogliomas and anaplastic oligodendrogliomas (Schmidt C and D)[49].

Low degree oligodendrogliomas are the most frequent and difficult to distinguish from the astrocytomas. They appear between the 3rd-4th decades of life. They grow slowly and infiltrate the cortex and even the leptomeninges. It is an incredibly vascularized tumor and often calcifies. Low degree oligodendrogliomas are known for appearing in many cases as spontaneous cerebral hemorrhages. Some low degree oligodendrogliomas could progress to become malignant oligodendrogliomas.

Anaplastic oligodendrogliomas are very aggressive tumors that behave like a multiform glioblastoma. Extracranial metastasis of anaplastic oligodendrogliomas[28,63,64,65] has been observed after multiple craniotomies and massive infiltration of extracranial tissues. Until now, no case of oligodendroglioma tumoral transmission to organ recipients has been published.

Potential donors with low degree oligodendrogliomas could be considered for organ donation.

Anaplastic oligodendrogliomas will not be considered for organ donation and could only be used in cases of life-threatening emergency transplants in which the recipient's risk of dying while on the waiting list is greater than the probability of tumoral transmission[31].

In these cases it is recommended not to use donors who have previously undergone craniotomies and/or peritoneal ventricle derivations in which the tumoral transmission risk is greater.

2.3- Mixed gliomas:

These gliomas are grade II/III and have anatomopathologic data of oligodendrogliomas and astrocytomas[47].

3). Ependymomas

The ependymomas represent 6% of all the intracranial gliomas. 50% of the ependymomas are infratentorials located in the IV ventricle and manifest in the first two decades of life. The supratentorials can appear at any age and grow in the ventricular cavities or invade the nervous parenchyma, especially in the parieto-occipital region. They are highly vascularized and infiltrating tumors and glial neoplasias that generally settle in the rear cavity and rarely metastasize outside of the central nervous system[28,49]. However, extraneural metastasis of the cranial and spinal ependymoma have been observed[66,67,68], although the majority were recurrent neoplasias in which the extraneural dissemination followed the tumoral invasion of the adjacent soft tissues. Newton and cols[66] found a 6% incidence of extraneural metastasis (in their series of 81 ependymomas, 5 had extracranial dissemination). Two tumors were histologically anaplastic and 3 were benign and a majority of them had been treated with surgical removal plus radiotherapy and/or radiation plus chemotherapy. Only one patient who had not received prior therapy presented extracranial metastasis since the diagnosis. Newton and cols[66] report that the extraneural metastases did not correlate to the histological degree of the tumor. The tumor metastasized in the lungs, thoracic lymphatic glands, pleura, peritoneum and liver. The case that produced peritoneal metastasis was preceded by a peritoneal ventricular derivation. Schreiber and cols[67] and Wakabayashi and cols[68] describe a case of ependymoma with extracranial metastasis in which multiple surgical interventions, radiotherapy and various chemotherapy cycles were performed.

Extraneural ependymoma metastases are rare and the cases observed correspond to recurrent neoplasias or those treated with radiotherapy and/or chemotherapy.

Therefore, donors with ependymomas can be considered for organ donation.

4).- Plexus choroid tumors

Plexus choroid tumors represent less than 1% of all intracranial primitive tumors. In children they are more often found in the supratentorial levels, while in adults it is more frequent in the IV ventricle and in the cerebello-pontine angle. Those located in the cerebello-pontine angle are more often benign.

The plexus choroid papillomas are the most frequent and are histologically benign tumors.

Plexus choroid carcinomas are aggressive malignant tumors that can metastasize outside of the central nervous system[69].

Potential donors with plexus choroid papillomas could be considered for organ donation.

However, those with plexus choroid carcinomas are not considered for donation.

5). Pineocytomas and pineoblastomas

The pinecytomas are derived from relatively mature pineal parenchyma cells. Little is known about the behavior of these tumors, since some remain well delimitated without exhibiting an aggressive behavior while others metastasize through the cephalorrhachidian fluid and behave like pineoblastomas[49].

The pineoblastoma is a rare tumor that corresponds to a more primitive form of pineocytoma. These tumors are highly malignant and biologically behave similarly to the meduloblastoma[49], showing a clear tendency to disseminate in the cerebral-spinal core. Lesoin and cols[70] have reported 3 extraneural metastasis cases out of a series of 81 cases with pineal tumors.

Potential donors with pinecytomas can be considered for organ donation.

However, potential donors with pineoblastomas should not be considered for organ donation.

OTHER INTRACRANIAL PRIMITIVE TUMORS

Benign meningiomas, anaplastic meningiomas and malignant meningiomas

Meningiomas represent 20% of all the intracranial tumors[53] that can manifest at any age. Typically they are neoplasias in adults and more frequently in women[48,49,53]. Less than 10% are multiple meningiomas that can appear sporadically or associate to type 2 neurofibromatosis[53].

Normally meningiomas are *benign* in behavior, and although invasion of the adjacent tissues is frequent, the dissemination outside of the affected organ is less frequent. However although a majority of tumors that originate in the meninges are benign[53], occasionally they behave in an invasive manner with a

prognosis significatively worse than the histologically benign meningiomas [71,72]. Approximately 5% of the meningiomas are *atypical* and 2% are *frankly malignant*[53].

Anaplastic meningiomas and malignant meningioms are two meningeal tumors aggressive in behavior that frequently associate with multiple recurrences and extracranial metastasis[71]. Younis and cols[71] presented a series of 18 patients with aggressive meningeal tumors (12 malignant meningiomas and 6 anaplastic meningiomas). Three (16%) of the 18 patients developed extracranial metastasis (2 malignant meningiomas and 1 anaplastic meningioma). Pulmonary and bone metastases were the most frequent. All of the cases, besides the surgical resection, had received radiotherapy and chemotherapy. Younis and cols[71] define what the main histological results found in these tumors were, but generally they are neoplasias that show a high degree of cellularity, abundant mitotic activity and pleomorphic cellular forms, all of which indicate aggressive growth. Sato and cols[73] describe extraneural metastases in an anaplastic meningioma case. In this event the tumor was surgically extirpated, but part of it was not removed because it invaded the main vessels. Postoperatory radiotherapy was administered. Seven months after the surgical intervention bone metastasis were detected.

There has been literature published[39] about a tumoral transmission case of a kidney recipient that showed peritoneal invasion from a donor with malignant meningioma.

There is no report of well-documented extraneural metastases in meningiomas histologically benign. Potential donors with these types of tumors could be considered for donation.

Anaplastic and malignant meningiomas are aggressive meningeal tumors that could pass on extraneural metastasis; therefore, they will not be considered for donation.

Malignant mesenchymal tumors: non-meningeal intracranial sarcomas, meningeal sarcoma and hemangiopericytomas

The intracranial sarcomas represent 1% of all the tumors of the central nervous system. The most anaplastic forms of sarcomas metastasize through the cephalorrhachidian fluid; however, extraneural metastases are rare (in general due to the fact that the rapid development of the tumor does not provide sufficient time for the extraneural metastasis to develop). Metastasis of polymorphic sarcoma has been observed in the leptomeninges, liver, lungs and bone marrow, but in one of these cases there was a massive local recurrence of a primitive tumor with invasión of the muscle and fascia, and in another the dissemmination was preceded by an exploratory craniotomy[49]. Cerame and cols[74] describe the existence of extracranial metastasis in gliosarcomas.

Meningeal sarcomas and hemangiopericytomas are two aggressive meningeal tumors that frequently associate with extraneural metastasis and multiple recurrence. Younis and cols[71] in their aggressive meningeal tumors series

describe 4 cases of hemangiopericytoma and 3 meningeal sarcomas. 3 out of the 7 cases (43%) showed extracranial metastasis (1 meningeal sarcoma and 2 hemangiopericytoma). The meningeal sarcoma developed metastasis in multiple organs 3 months after the first intervention.
Potential donors with sarcomas of the central nervous system and hemangiopericytomas should not be considered for organ donation.

Hemangioblastomas

Hemangioblastomas are benign tumors of the blood vessels that with greater frequency settle in the cerebellum[48]. Dissemination out of the hemangioblastoma capillaries is rare, although Hoffman and cols[75] observed 2 spontaneous extraneural metastasis cases.

In 20% of the cases it may appear associated to other disseminated tumoral lesions, becoming von Hippel-Lindau's phakomatosis.

Due to the usually benign behavior of the hemagioblastomas, potential donors with this diagnosis could be considered for organ donation, as long as they show isolated neoplasia and the existence of von Hippel-Lindau's phakomatosis is ruled out.

Germinal cell tumors

The pineal region tumors are infrequent[49]. Approximately half of the tumors that settle in this area are germinal tumors which include: germinomas, mature teratomas, immature teratomas, teratocarcinomas, choriocarcinomas, breast endodermic tumors and embryonic carcinomas[48,75]. The pineal gland is where intracraneal germinomas most frequently settle. They are histologically malignant and infiltrating tumors that habitually disseminate through the third ventricle. Out of the gland metastasis has been observed after craniotomies, cranial-spinal radiotherapy or peritoneal ventricular derivations[76,77,78,79]. Although these cases presented an increment of chorionic beta-gonadotropina level in the serum.

The choriocarcinoma is a type of teratoma that settles in the pineal region. They are highly malignant tumors with a tendency to invade the adjacent structures. Extracranial metastases have been especially observed in the lungs[49].

Potential donors with mature teratomas can be considered for organ donation. Donors with other germinal cellular tumors should not be considered for organ donation.

Chordomas

Chordomas are aggressive tumors that lead to extracranial metastasis in 5-43% cases[49,80,81].

Potential donors with chordomas should not be considered for organ donation.

Primary cerebral lymphomas

The primary intracranial lymphomas appear with greater frequency in immunosuppressed patients, like for example those diagnosed with AIDS. Their prognosis is bad and they go on to extracraneal dissemination[82].

Those with primary cerebral lymphomas should not be considered for organ donation.

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