Danish guidelines for prevention of transmission of neoplastic diseases from organ donors to recipients

Organs from deceased donors with some cancers may be safely used for transplantation. On the basis of the current evidence, it is recommended that organs from deceased donors with some current and past cancers may be safely used.

European Committee on Organ Transplantation. Guide to the Quality and Safety of Organs for Transplantation. 7th ed: Council of Europe; 2018 has been entirely reviewed to provide current evidence for assessment of the risk of transplanting organs from donors with a past or present history of malignancies.

Grading of risk is provided for an extensive list of malignancies that may be identified in the donor history or be discovered at the time of organ procurement.

Risk of transmission of neoplastic diseases from the donor can be divided into:

- History of previous cancer in the donor
- Incidental cancer at time of procurement

Council of Europe 2018 categorized the risk of cancer transmission into:

- Minimal risk (<0,1% risk of transmission)
- Low to intermediate risk (>0,1% - <10% of transmission)
- High risk (>10% risk of transmission)
- Unacceptable risk

Council of Europe 2018 assesses *minimal risk as the donor being acceptable for all organs and all recipients*, whereas low to intermediate risk as the donor being acceptable justified by the specific health situation of their recipient or the severity of their clinical condition, based on a risk-benefit analysis.

Informed consent should be obtained from the recipient or their legal representative. Every recipient who receives an organ from a donor with a history of malignancy should be offered additional testing, monitoring and treatment as appropriate, in addition to routine follow-up care.

Recommendations on the use of organs from donors with
non-CNS cancers with minimal risk of transmission

1. History of previous cancer in the donor.

It is prerequisite that detailed exact histological reports, staging, grade of the tumour and imaging studies as well as all information and actual diagnostic findings are documented on the donor information form prior to acceptance.

Predonation CT-TAB is mandatory. Histo-pathological diagnosis are found in the web-based module "Patobank".

- **In situ carcinomas:** E.g. uterine cervix, colon, breast (only low-grade), non-melanoma skin, vocal cord – and confirmed pancreatic intra-epithelial neoplasia in the absence of invasive cancer may be considered minimal risk. Transplantation of the pancreas itself in the case of pancreatic intra-epithelial neoplasi is considered questionable.

- **Skin:** Basal cell and squamous cell carcinoma of the skin.

- **Thyroid**: Solitary papillary carcinoma (<0.5cm) and minimally invasive follicular carcinoma (<1.0cm).

- **Urothelial neoplasia:** non-invasive papillary urothelial carcinoma of the urinary bladder (pTa/G1-2, without uCIS anywhere or pTa in upper urothelial tracts) are considered minimal risk for non-renal transplants. pTaHG > 5 years prior are considered minimal risk for non-renal transplants. Any epithelial neoplasia is considered questionable for renal transplants, except for donors with a few small TaLG in the bladder.

- **Kidney:** Small radically removed solitary renal cell carcinoma (pT1a, low risk Leibovich score 0-1) is considered to represent minimal risk for transplantation. Papillary carcinoma type2 or tubulo-papillary carcinoma are considered questionable at any pT stage.

- **Prostate:** Curatively treated prostate cancer ≤ pT2 and Gleason 3 + 3 (radical prostatectomy, tumor confined to prostate) and very small prostate cancers and Gleason 3 + 3 under 'active surveillance' (not observation) is considered to represent minimal risk for transplantation at any time after diagnosis with the prerequisite of non-suspicious follow-up. Prostate cancer ≤ pT2 (confined to the prostate) and Gleason grade 3+4 (not 4+3), PSA< 0,1ng/ml and cancer-free period of 5 years after radical prostatectomy is considered minimal risk. In any case, current PSA values should be obtained to compare to former ones and to assess the actual situation.

2. Incidental cancer at time of donor procurement

It is prerequisite that frozen sections for preliminary diagnosis; subsequent work-up and imaging studies are done for definite diagnosis prior to acceptance.

Predonation CT-TAB is mandatory.

- **Skin:** Basal cell and squamous cell carcinoma of the skin.

- **Thyroid:** Solitary papillary thyroid carcinoma < 0.5 cm and minimally invasive follicular thyroid carcinoma < 1 cm.

- **Kidney:** Exofytic small solid cT1a renal tumors (no contact to renal sinus on CT, < 4 cm, conventional non high grade renal cell carcinoma subtypes) are considered to represent minimal risk for transplantation of other organs including contralateral kidney. If it is technically possible to reconstruct the kidney after macroradical resection of tumor (no frozen section of resection margin) and the quality of the remainder kidney is expected to contribute with an eGFR of ≥ 30, then the kidney is suitable for transplantation with minimal risk of local recurrence of cancer. Cystic renal cell carcinomas >T1a are considered minimal-risk for all organs.

- **Prostate**: Newly diagnosed very small intra-prostatic, low-grade (Gleason score ≤ 6) tumours are considered minimal-risk.

Recommendations on the use of organs from donors with CNS tumours

Extraneural metastases from CNS neoplasms are rare but have been described, the most common sites being the lungs, pleura, cervical lymph nodes, bone, liver and intra-thoracic and intra-abdominal lymph nodes. The WHO classification provides a grading system (I to IV) for each type of tumour, depending on its biological behaviour and, hence, dictates the choice of therapy and predicts prognosis.
To date, the two most important factors in assessing CNS tumour transmission risk via organ transplant are:
1. The histologically determined WHO grade of a CNS tumour,
2. Any performed interventions (surgery, shunting, chemo and radiotherapy).
A higher grade of tumour (> WHO grade III) and more interventions will lead to increased transmission risk. The specific tumour diagnosis adds important detail.

Classification of risk for central nervous system tumours
Drawing on the available information and the variable estimates of disease transmission derived from registries, there is a widely accepted qualitative classification of CNS malignancies, based on the risk of tumour transmission, as shown below.

- **WHO grade I and II tumours** – minimal risk of tumour transmission.
- **WHO grade III tumours** – should be accepted as low to intermediate risk if no risk factors are present (resection, ventriculo-peritoneal or ventriculo-atrial shunt, chemo-/radiotherapy).The risk is increased to high risk in the presence of any risk factors.
- **WHO grade IV tumours** these neoplasms should only be accepted with some caution on a case-by-case basis as intermediate to high risk. The risk is increased particularly in the presence of ventriculo- peritoneal or ventriculo-atrial shunts, as well as previous resection or chemo-/radiotherapy.

Review of specific tumours of the central nervous system

1. Medulloblastoma
Organs from potential donors with medulloblastomas (WHO grade IV) are considered intermediate to high risk for tumour transmission. They should be used exclusively for transplants where the recipient's risk of dying while on the waiting list is greater than the risk of tumour transmission.

2. Glioma
Gliomas comprise astrocytomas, oligodendrogliomas and ependymomas.
- **Pilocytic astrocytoma (WHO grade I):** Potential donors may be considered for organ donation with minimal risk of transmission.
- **Low-grade astrocytomas (WHO grade II)** Extraneural metastases are rare, and have been associated with resection and ventriculo-peritoneal shunts. In the absence of these risk factors, the donor may be considered minimal-risk.
- **Anaplastic astrocytomas (WHO grade III)** Potential donors with can be accepted as organ donors. Transmission risk is considered low to intermediate for tumours without any risk factors.

- **Glioblastoma (WHO grade IV):** Potential donors are considered intermediate to high risk for transmission,
- **Low-grade oligodendrogliomas (WHO grade II)** represent a minimal risk of tumour transmission.
- **Anaplastic oligodendrogliomas (WHO grade III)** without any risk factors are considered low to intermediate risk.
- **Anaplastic oligodendrogliomas (WHO grade III):** Donors with who have previously undergone interventions such as tumour resection, ventriculo-peritoneal/-atrial drainage and/or cranial chemo-/radiotherapy, are associated with an increased risk (high risk) of tumour transmission.
- **Ependymoma:** low-grade (WHO I or II) ependymoma represents minimal risk of transmission, whereas an anaplastic ependymoma (WHO III) will be associated with low to intermediate risk if there are no additional risk factors. The risk is high in case of previous interventions (se above)

3. **Meningioma**

- **Benign meningiomas:** Organs from potential donors with these types of tumour have a minimal risk of transmission.
- **Anaplastic or malignant meningiomas (WHO grade III)** are more aggressive meningeal tumours that can occasionally be associated with extraneural metastases. Organs from potential donors with these tumours are considered low to intermediate risk if no risk factors are present. In case of risk factors the risk is increased (high).

4. Haemangioblastoma
Due to the usually benign behaviour, organs from potential donors with this diagnosis may be considered minimal risk for tumour transmission, provided that coincidental neoplasms and the existence of Von Hippel-Lindau syndrome are ruled out.

4. Primary cerebral lymphomas
Organs from donors with primary cerebral lymphomas have an unacceptable risk for tumour transmission and should not be considered for transplantation.

For other more rare specific tumors please see European Committee on Organ Transplantation. Guide to the Quality and Safety of Organs for Transplantation. 7th ed: Council of Europe; 2018. (https://www.edqm.eu/en/news/new-release-7th-edition-guide-quality-and-safety-organs-transplantationlink)

Guidelines from the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), 2014.

Table 1. Recommendations on the use of organs from donors with CNS tumours

Absolute contra-indications

- Primary cerebral lymphoma
- All secondary intracranial tumours.

Intracranial tumours with an intermediate risk of cancer transmission (2.2% with an upper 95% CI of 6.4%) include WHO grade 4 tumours and equivalents:

- Glioblastoma
- Giant cell glioblastoma
- Gliosarcoma
- Pineoblastoma
- Medulloblastoma
- CNS primitive neuroectodermal tumour
- Medulloepithelioma
- Ependymoblastoma
- Atypical teratoid/rhabdoid tumour
- Malignant peripheral nerve sheath tumour
- Germinoma
- Immature teratoma
- Teratoma with malignant transformation
- Yolk sac tumour
- Embryonal carcinoma
- Choriocarcinoma.

Intracranial tumours with a low risk of transmission (<2 %) include WHO Grade 3 and equivalents:

- Anaplastic astrocytoma
- Anaplastic oligodendroglioma
- Anaplastic oligoastrocytoma
- Ependymoma
- Choroid plexus carcinoma
- Anaplastic gangliomyoma
- Pineal parenchymal tumour of intermediate differentiation
- Papillary tumour of the pineal region
- Malignant peripheral sheath tumour
- Anaplastic/malignant meningioma
- Papillary meningioma
- Rhabdoid meningioma
- Haemangiopericytoma.

References

European Committee on Organ Transplantation. Guide to the Quality and Safety of Organs for Transplantation. 7th ed: Council of Europe; 2018.

NHS Blood and Transplant, British Transplantation Society. NHSBT BTS Responsibilities of clinicians for the acceptance of organs from deceased donors. 2012. Available from: http://www.odt.nhs.uk/pdf/nhsbt_responsibilities_acceptance_organs_deceased_donors.pdf.

SaBTO UK guidelines
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/304261/Transplantation_of_organs_from_deceased_donors_with_cancer_or_a_history_of_cancer.pdf

These recommendations were proposed by the Danish Society of Transplantations working group on November 2020.

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