Neuroendocrinology Letters Volume 35 No. 7 2014
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Complications of MRI-guided stereotactic biopsy of brain lymphoma

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Submitted: 2014-08-20 Accepted: 2014-10-30 Published online: 2014-12-27

Key words: **brain lymphoma; brain tumor; stereotactic biopsy; mortality; morbidity**

Neuroendocrinol Lett 2014; **35**(7):613–618 **PMID:** 25617885 NEL350714A07

Abstract

OBJECTIVES: Stereotactic biopsy is a suitable method for sampling intrinsic brain lesions. Although this method is considered to be a safe procedure, some risk of complications still exists. The aim of the study was to retrospectively assess the morbidity and mortality of MRI-guided stereotactic biopsy of lesions which were histologically proven to be brain lymphoma.

METHODS: We retrospectively studied all accessible medical records for patients who had undergone MRI-guided stereotactic biopsy of brain lesions with histologically proven brain lymphoma from January 2007 to December 2012. Our cohort included 45 patients, 27 males and 18 females, aged 23–84 (63±14) years.

RESULTS: Forty-nine biopsies were carried out on 45 patients; the average number of tissue specimens was 3±1. The diagnostic yield of the stereotactic biopsy was 92%. Overall major morbidity directly related to stereotactic biopsy of brain lymphoma was 6.1% (3 cases) including 4.1% mortality (2 cases). Both deaths after the stereotactic procedure were due to intracranial hemorrhage and subsequent complications and both these patients had a history of treatment of systemic lymphomas. In one patient the stereotactic biopsy was complicated by a brain abscess which was successfully treated.

CONCLUSION: Stereotactic biopsy is still a mandatory diagnostic procedure for primary brain lymphomas, with an acceptable risk of complications. However, according to our results, the risk of complications can be higher in patients who have previously been treated for secondary lymphomas.

INTRODUCTION

Nowadays CNS lymphoma is a more common brain neoplasm than it was in the past (Liscak *et al.* 1998). Brain lymphoma may be secondary or may arise directly from the brain tissue itself, which is called primary central nervous system lymphoma (PCNSL). PCNSL is a subtype of extranodal non-Hodgkin lymphoma that involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. It has been reported in both immunocompetent and immunocompromised patients. Though in HIV-positive patients the rate of occurrence of PCNSL is 3,600-times higher than

ORIGINAL ARTICLE

in general population (Schabet, 1999), most PCNSL lymphomas in the Czech Republic occur in immunocompetent adults. The majority of PCNSL tumors are of the highly aggressive diffuse large cell subtypes, usually of B-cell phenotypic origin (Montesinos-Rongen *et al.* 2008), though other histology (Burkitt's lymphoma, peripheral T-cell lymphoma, or even indolent lymphoma types) may also present as PCNSL. PCNSL accounts for approximately 1% of non-Hodgkin's lymphomas and 3–4% of newly diagnosed central nervous system (CNS) tumors (Hoffman *et al.* 2006). According to a study by Villano *et al.* (2011) the overall incidence rate of PCNSL was 0.47 per 100,000 person-years and the incidence was significantly higher in males compared with females.

CT/MRI guided stereotactic biopsy is a suitable method that allows sampling of intrinsic brain lesions. As there is no role for surgery in the treatment of CNS lymphomas, stereotactic biopsy is the method of choice to obtain histological material. The decision to proceed with stereotactic biopsy instead of a more radical procedure is further supported by the fact that the diagnosis of brain lymphoma is frequently suspected from diagnostic MRI. Although stereotactic biopsy is considered as relatively safe procedure, it has its inherent risks, which may be greater in more fragile patients, either immunocompromised due to HIV infection or after previous treatment for systemic lymphoma. The need for a biopsy for secondary lymphoma as invasive diagnostic procedure with its inherent operational risks should therefore be evaluated carefully, as diagnosis in these patients has already been established. This situation is similar to histological verification of brain metastases in patients with other known primary tumors, which is usually not performed, when MRI is typical for suspected diagnosis.

To evaluate the risk/benefit ratio of stereotactic biopsies for brain lymphoma, we analyzed a cohort of patients who were diagnosed in our center during last 5 years.

CLINICAL MATERIALS AND METHODOLOGY

Patient selection data

During the period from January 2007 – December 2012 we performed MRI-guided brain biopsies in 240 consecutive patients. We selected cases with histologically proven brain lymphoma from biopsy samples and retrospectively studied all available clinical data and medical records pertaining to these. All patients provided signed informed consent with the procedure.

All stereotactic biopsies were indicated on the basis of brain MRI findings. Apart from MRI, all patients with enhancing lesions, which also includes brain lymphoma, underwent cerebral digital subtraction angiography to exclude any pathological vascularization of lesions. Normal standard blood test values, including platelet count, prothrombine time and activated partial thrombin time, were mandatory for biopsy indication. The clinical neurological status of patients was usually assessed immediately after the biopsy, then several hours after the procedure, the second day after the procedure and/or before discharge. CT follow-ups were not provided as standard. The CT examination was only indicated in cases of blood appearance in the biopsy probe after the sample of the tissue was obtained, or in cases showing new alteration of neurological or general patient status during or after the biopsy. All patients were observed for at least 24 hours before they were discharged.

MRI technique

Suggested standard diagnostic MRI protocol included TSE T2 WI axial, T2 WI turbo FLAIR axial, DWI (ADC maps included) axial, native SE T1 WI sagittal plane and post-gadolinium SE T1 WI (3 planes examination was preferred, but 2 planes examination was considered satisfactory).

Pre-operative stereotactic MRI scanning for stereotactic biopsy was performed on a 1.5 T whole body MRI system (Siemens Symphony or Avanto). We used a three dimensional (3D) volume acquisition sequence after intravenous gadolinium contrast administration with the following parameters: voxel size 1.0×1.0×1.0 mm, slab 1, slices per slab 176, slice thickness 1 mm, distance factor 50%, phase encoding R to L, rotation 90 degree, phase oversampling 0%, slice oversampling 45.5%, FoV read 256 mm, FoV phase 81.3%, TR 2030 ms, TE 3.54 ms, averages 1, concatenations 1.

Stereotactic biopsy technique

Stereotactic biopsies were carried out under local anesthesia and mild sedation in all patients. The Leksell stereotactic system (Elekta Instrument, Sweden) was used and the coordinate frame was attached to the patient´s head. MRI was performed with an indicator box using a 1.5 T (Siemens Symphony or Avanto) MRI system with a three-dimensional volume acquisition sequence and the administration of an intravenous gadolinium contrast agent to visualize the enhancing lesion and cortical vessels. The entry point was placed according the anatomical localization of the enhancing lesion and the trajectory of the biopsy probe was planned using Surgi Plan (Elekta Instrument, Sweden). The target point of the trajectory was located in the center of the enhancing tumor and the trajectory itself was planned to avoid the ependymal surface of the ventricles and the cortical vessels.

Stereotactic biopsy was performed in analgosedation. A circle of hair was shaved around the entry point and a percutaneous drill hole was made under local anesthesia (diameter of drill 4 mm), and the dura mater was penetrated with the coagulating tip of the probe. The biopsy was carried out with a Sedan biopsy needle with the diameter of the side opening measuring 4 or 8

Tab. 1. Characteristic of patients (N=45).

History of systemic lymphoma 9 pts (20%)			No history of systemic lymphoma (PCNSL) 36 pts (80%)		
NHL	**NHL and HL**	**HIV-positive and Burkitt lymphoma**	**No history of serious disease**	**MS**	**Cancer treatment**
7 pts	1 pt	1 pt	32 pts	1 pt	3 pts
Complications					
2 dead	0	0	1 abscess		

NHL- Non-Hodgkin´s lymphoma, HL- Hodgkin´s lymphoma, MS - multiple sclerosis

mm (depending on the localization and the volume of the enhancing lesion). Samples of the tissue were sent for pathological examination in a formol solution.

RESULTS

Patient selection data

We included 45 patients (19% of all patients sampled), 27 males and 18 females, aged 23–84 (63±14) years with histologically proven diffuse large B-cell lymphomas of the brain. Twenty-nine percent of patients had internal comorbidities. Seven patients had a previous history of systemic Non-Hodgkin´s lymphoma (NHL) (range 9 months to 17 years before the brain affection), 1 patient had history of both NHL (11 years before) and Hodgkin´s lymphoma (1 year before). However, at the time of the brain affection they did not show clinical or imaging signs of systemic lymphoma. The only patient who showed signs of systemic lymphoma was an HIV-positive patient suffering from Burkitt lymphoma with a massive abdominal manifestation. This patient had completed 6 cycles of chemotherapy when neurological symptomatology occurred. We found one coincident brain lymphoma and multiple sclerosis. Three patients had a history of cancer treatment (2 renal and 1 rectal cancers). See also Table 1.

Forty-nine biopsies were carried out on 45 patients; the average number of tissue specimens obtained by biopsy was 3±1. The diagnostic yield of stereotactic biopsy was 92%. In 4 cases the biopsy was repeated due to inconclusive histological samples – all these patients underwent corticosteroid therapy before the first biopsy. The localization of sampling lesions is shown in the Table 2.

MRI findings

MRI examinations were retrospectively assessed by one experienced radiologist. Solitary lesions were present in only 7 patients (15.6%); most solitary lesions (n=6) were supratentorialy localized. In most cases multiple lesions (38 patients; 84.4%) were also localized supratentorialy (n=24), in 4 cases infratentorialy and in 10 cases lesions were localized both supratentorialy and infratentorialy. Twelve patients (26.7%) had involvement of the corpus callosum; in 7 patients (15.6%) we found a butterfly pattern. The involvement of intracranial nerves was present in 7 patients (15.6%). Ependymal involvement was also present in 7 patients (15.6%). Tumor lesions or infiltrations enhanced after the gadolinium contrast intravenous administration. In cases examined using the DWI MRI scan, we found restriction of diffusion in at least one of the lesions present. In 20 patients who were treated by corticoids before biopsy we found regressive changes at least in one of the present lesions or infiltrations (size regression or diminishment of lesions, lack of diffusion restriction, regression or lack of enhancement).

Tab. 2. Localizations of sampling lesions.

The site of biopsy	No. patients	No. symptomatic complications	Mortality cases
Basal ganglia, hypothalamus	4	0	0
Periventricular	11	1	1
Suprasellar, chiasmatic or optic tract regions	4	1	1
Other supratentorial lesions	25	1	0
Cerebellum	1	0	0
Brain stem	0	0	0

Complications

Stereotactic procedure-related mortality was 4.1%: two patients died after stereotactic biopsy due to intracranial hemorrhage and following complications.

The first death case was a 23-year-old male, who had a history of systemic B-cell NHL from the age of 13. Since that time no signs of systemic disease were present. Neurologic symptomatology and MRI findings were present for 6 months. The patient had undergone stereotactic biopsy without conclusive diagnostic results in another institution 3 months previously. He was treated by corticosteroid therapy. He suffered from neuropsychiatric symptoms, amaurosis, bilateral mydriasis, incontinence and limb spasticity. The target site for biopsy was a tumorous infiltration in the

suprasellar region affected the optic chiasm. During the procedure the patient lost consciousness, arterial hypertension developed together with tachypnoea and miosis. Orotracheal intubation and mechanical ventilation was necessary. The CT examination revealed a subarachnoid hemorrhage (SAH). Neurosurgical intervention was not indicated. The SAH did not progress and by the third day the patient had regained consciousness. Several hours after extubation he again lost consciousness. The CT examination showed a diffuse brain edema. The general status of the patient was complicated by pneumonia and the patient´s serious condition resulted in death on the ninth day after the stereotactic procedure.

The second death case was a 77-year-old female also with the history of systemic B-cell NHL nine months previously, treated by chemotherapy with complete systemic remission; the body PET-CT was negative. She suffered from personality changes and neuropsychiatric symptoms for one month. MRI revealed multiple intraventricular lesions. The target lesion for biopsy was located in the right frontal lobe close to horn of the lateral ventrical. A follow-up CT was indicated due to the appearance of blood in the biopsy probe after obtaining a sample of the tissue. The patient´s general status was good during the procedure and immediately after the biopsy. The CT examination revealed a mild hemorrhage in the puncture channel and in the target tumor. After 3 hours the patient lost consciousness and an orotracheal intubation with mechanical ventilation was necessary. The CT scans showed massive intracerebral hemorrhage (ICH) with hemocephalus. ICH was evacuated from the frontal craniotomy. Three days after the open neurosurgical operation re-bleeding occurred, the hemocephalus was treated by the ventricular drainage, after regression of the hematoma a new spontaneous hematoma developed in the left thalamus. The patient died due to complications involving systemic sepsis (MRSA) 3 months after the biopsy.

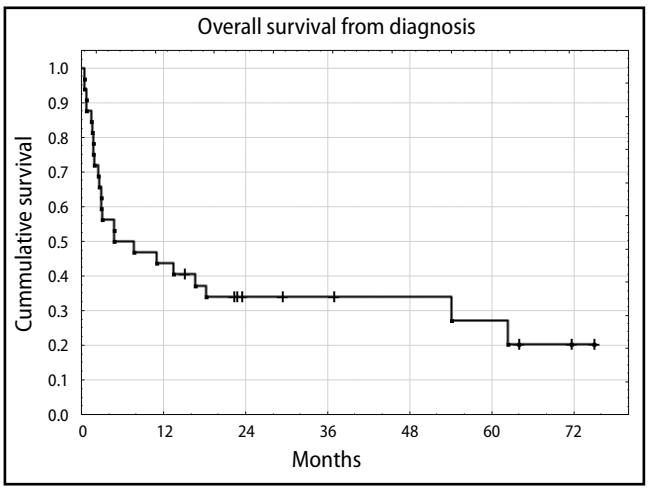

Fig. 1. Survival of 29 patients treated at hematooncology.

We detected 3 cases of clinically asymptomatic bleeding in other patients, in whom the biopsy samples contained blood coagula. CT revealed limited bleeding inside the targeted structure, no intervention was needed and the patients were treated conservatively. We cannot exclude another asymptomatic bleeding because we did not indicate standard CT follow-ups in asymptomatic patients.

The last complication that we found retrospectively was 1 small brain abscess (2%) in the site of the probe trajectory, which was again proved by stereotactic biopsy, and was treated by antibiotics leading to complete recovery.

Patients' survival

Twenty-nine of the 45 patients (64%) were transferred to hematooncology department for further treatment. Of them, 25 (55% of all diagnosed patients) received treatment with curative intent: Fourteen patients underwent a combination of chemotherapy and radiotherapy, 11 patients underwent chemotherapy only. Four patients received only palliative treatment. For 26 patients where survival data are available, the median survival was 4.8 months. Nine patients (20% of all patients, 36% of patients treated with curative intent) are alive, making overall survival 27% at 5 years, after a median follow-up of 29 months for living patients (Figure 1).

DISCUSSION

CT/MRI guided stereotactic biopsy is a well-established method for the sampling of intrinsic brain lesions. In our study the diagnostic yield was 92%. Other authors reported an overall diagnostic yield of stereotactic brain biopsy of between 89% and 96% (Alkhani *et al.* 2008; Chen *et al.* 2009; Dammers *et al.* 2008; Grossman *et al.* 2005). However, in these studies, a range of tumors and non-tumoral diagnoses were included. In 4 patients the biopsy was repeated. Those patients mentioned were treated by corticosteroids before biopsy, therefore brain lesions samples were affected by regressive changes. This is not surprising, because the dramatic temporary response to corticosteroid therapy is well known (Bhagavathi & Wilson, 2008). In the case of a complete resolution of a contrast enhancing lesion, the biopsy has little chance of obtaining a positive diagnostic result and the biopsy should be postponed until recurrence of tumor enhancement is detected.

CT/MRI guided stereotactic biopsy is considered to be a safe procedure. However, the risk of hemorrhage related morbidity/mortality is often reported in the literature. The mortality rate in retrospective study by Bernstein & Parrent (1994) was 1.7%, all these patients suffered from glioblastoma multiforme. Mortality or major morbidity with persistent neurological deficit was seen in 3% of patients. The rate of symptomatic non-fatal hemorrhage was 4.7%. These authors included 18 subjects with brain lymphomas taken from 300 cases,

and 1 of them suffered non-fatal hemorrhage. In the retrospective study by Hall (1998), the mortality rate was 0.7% (1patient with pinealoblastoma) from the 122 patients included. In this study only 13 cases of brain lymphomas were included. In the prospective CT controlled study by Kulkarni *et al.* (1998) the rate of non-silent bleeding was 10%, the rate of silent bleeding was a high 67.9%. This is contrasted by another prospective CT controlled study by Kreth *et al.* (2001), where the rate of clinically silent bleeding after stereotactic biopsy was 9.6%. However, hemorrhage related morbidity was only 0.9% with 0% mortality. These authors included 24 patients with brain lymphoma (from 326 patients) and they did not find any bleeding in them. In the study conducted by Grossman *et al.* (2005) bleeding occurred in 7% of patients, 3.6% of them were symptomatic with 0.6% mortality. Chen *et al.* (2009) observed 4.4% hemorrhagic complications in 299 brain biopsies in 246 patients. They included 31 patients with brain lymphoma and in 1 of them symptomatic bleeding occurred.

All stereotactic biopsies in our series were done under the MRI navigation, which is more precise than CT navigation. The MRI scan for the stereotactic navigation was also done after the administration of intravenous gadolinium contrast for the visualization of cortical vessels. This helps to avoid cortical vessel damage during the biopsy. All our patients underwent cerebral DSA before biopsy to exclude strong pathological vascularization. Voges *et al.* (1993) considered preoperative angiography and intra-operative Doppler investigation as useful for increasing the safety of stereotactic biopsy. In our study the rate of symptomatic bleeding after stereotactic biopsy of brain lymphoma occurred in 4.1% with the same 4.1% biopsy-related mortality. This is significantly higher than the usual complication rate of other brain tumor biopsies (Bernstein & Parrent, 1994; Chen *et al.* 2009; Dammers *et al.* 2008; Grossman *et al.* 2005; Kongkham *et al.* 2008; Kreth *et al.* 2001; Kulkarni *et al.* 1998). Moreover, we have not experienced other life-threatening complications after stereotactic biopsies of other histological lesions in our institution during the last 5 years.

The rate of silent bleeding is not clear, because our patients did not undergo the CT follow-up after MRI-guided stereotactic biopsy as standard. According to the opinion of some authors, the risk factors for operative complications from stereotactic biopsy would be expected to be histology, localization and presence of increased intracranial pressure (Bernstein & Parrent, 1994; McGirt *et al.* 2005). Malignant lesions with neovascularization and/or abnormal blood vessel structures, such as malignant gliomas and lymphomas, should be more prone to bleeding and/or produce increased edema following manipulation (Bernstein & Parrent, 1994; Kongkham *et al.* 2008; Kreth *et al.* 2001; McGirt *et al.* 2005). However, usually there is no pathological vascularization of lymphomas on DSA, in some patients mild "blush" can be visualized in the region of the tumor, which does not usually preclude an indication for a biopsy.

Also HIV-positive patients might be expected to have a high risk of deterioration following needle biopsy. In a study by Bernstein & Parrent (1994) the neurological deficit worsened in 12.5% of those patients. However, as we mentioned above, in our series only one of our patients was HIV-positive and his biopsy was uneventful. However, both patients who died had a history of treatment for systemic lymphomas. We cannot definitely state from our data that secondary brain lymphomas are more prone to bleeding than PCNSL, because this subgroup was very small in our series. However, those patients who succumbed to postoperative bleeding were in a debilitated condition with an affected immunological system relating to the previous intensive oncological treatment of their systemic lymphoma.

An important secondary finding of our study is the fact that not all patients after biopsy were referred for specialized center for antilymphoma treatment. In overall terms, the survival rate for our cohort is very poor, though this would not necessarily apply to patients who received appropriate therapy. Better selection of patients who can benefit from a histological diagnosis may spare those who would derive no profit from the unnecessary invasive procedure. On the other hand, a quick referral to a specialized center after a lymphoma diagnosis may improve these patients' chances of long-term survival.

CONCLUSION

Stereotactic biopsy is a widely used, effective and relatively safe procedure for sampling intrinsic brain lesions. However, it is necessary to be aware of possible complications related to the procedure and all the pros and cons should be considered, especially in immunocompromised patients, who have limited capacity to recover from complications, which are overcome without sequel in immunologically fit patients. In our study overall major morbidity directly related to stereotactic biopsy of brain lymphoma was 6.1% (2 hemorrhagic mortal cases and 1 brain abscess); the rate of symptomatic hemorrhage was equal to 4.1% mortality. The risk of stereotactic biopsy of secondary brain lymphomas may be higher than in the sampling of other lesions, which may be related to immunodeficiency of those patients. These patients might be spared the invasive diagnostic procedure, if MRI findings are conclusive enough.

ACKNOWLEDGEMENT

Supported by MH CZ - DRO (Na Homolce Hospital - NNH, 00023884).

The authors declare that they have no conflict of interest.

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