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NCCN Guidelines Panel: Adult Cancer Pain Panel

On behalf of *InSightec*, I respectfully request the *NCCN Adult Cancer Pain Panel* to review the enclosed data for inclusion of the Magnetic resonance-guided focused ultrasound (MRgFUS) in the following lists: *intervention for cancer pain syndromes considered for local bone pain* and *interventional strategies*. And update the *Discussion* to reflect evidence from the pivotal phase III trial.

Specific Changes:

- Add MRgFUS as a treatment alternative for local bone pain in the list *Intervention for cancer pain syndromes considered for local bone pain* (PAIN-D).
- Add MRgFUS as a treatment alternative in the list *Interventional strategies* (PAIN-M)
- Update the wording in the *Discussion* that describe the evidence, to reflect the outcomes of the pivotal study:
 - *Management of bone pain without an oncologic emergency* (MS-22)"Ablative strategies such as RF ablation or MRgFUS ~~US~~ ablation may also be performed to reduce pain and prevent SREs. RF ablation of bone lesions has proven successful in pain management, especially for those failing to achieve adequate analgesia without intolerable effect. ~~Several small studies have also demonstrated the palliative effects of high intensity focused US (HIFU) treatment of bone lesions.~~ MRgFUS ablation has proven successful in rapid and sustainable pain relief in a single procedure that is radiation-free and non-invasive. The effect of pain relief by this technology can be achieved by endocortical denervation, or local debulking of the tumor"
 - *Interventional strategies* (MS-24)" Interventional therapies that can be useful in the relief of cancer pain include nerve blocks, vertebroplasty, kyphoplasty, regional infusion of analgesics, RF ablation, MRgFUS ablation and other techniques"

FDA Clearance: ExAblate[®] system is FDA-cleared for pain palliation of Metastatic Bone Cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy. The bone tumor to be treated must be visible on non-contrast MR and device accessible.

Rationale: solid evidence of the efficacy and safety profile of MRgFUS for pain palliation of bone metastases support its routine use in the clinic, allowing patients to achieve their QoL goals in a non-invasive, non-ionizing, single procedure, and allow patients who are not eligible for radiation to have another effective and safe treatment option.

The following articles are submitted in support of this proposed change.

- 1. Hurwitz MD et al. Magnetic Resonance-Guided Focused Ultrasound for Patients with Painful Bone Metastases: Phase III Trial Results. JNCI 2014;106(5):dju082.**
The pivotal phase III trial with the ExAblate[®] system demonstrated superiority of treatment with MRgFUS compared to a sham procedure. Pain relief without increase in medication consumption was significantly better as soon as 1 day and lasted for 90 days. This rapid response far surpasses the response time of radiation palliative treatment, and the response rate of 64.3% was similar to response rates reported for radiation therapies. This is in line with the NCCN treatment goals of adult pain: optimize activities of daily living. The safety results reflect sub-optimal sedation/analgesia in the trial population with relatively high intra-procedural pain. This issue has been addressed with the FDA labeling mandating proper sedation/analgesia during the procedure to eliminate this side effect.
- 2. Huisman M et al. International consensus on use of focused ultrasound for painful bone metastases: Current status and future directions. Int J Hyperthermia. 2015;31(3):251-9.**
This consensus paper reviews the clinical results published at the time of this publication. It concludes that the treatment is safe and effective for pain palliation of bone metastases via two potential modes of action: endocortical denervation and debulking/ local tumor control. Consensus has been reached that MRgFUS is an acceptable secondary treatment option for patients who have painful bone metastases in a non-spinal site, for whom radiotherapy has not been effective and that it can be considered a primary palliative treatment option in patients for whom radiotherapy may be contraindicated (e.g. due to prior radiation to the same site) or has been refused.
- 3. Gianfelice D et al. Palliative treatment of painful bone metastases with MR imaging-guided focused ultrasound. Radiology. 2008;249(1):355-63.**
This study shows the preliminary results of rapid and sustained pain relief with the ExAblate[®] system (InSightec).
- 4. Catane R et al. MR-guided focused ultrasound surgery (MRgFUS) for the palliation of pain in patients with bone metastases--preliminary clinical experience with the ExAblate[®] system. Ann Oncol. 2007;18(1):163-7.**
This study shows the preliminary results of rapid and sustained pain relief with the ExAblate[®] system (InSightec).
- 5. Huisman M et al. Feasibility of volumetric MRI-guided high intensity focused ultrasound (MR-HIFU) for painful bone metastases. Journal of Therapeutic Ultrasound 2014, 2:16. doi: 10.1186/2050-5736-2-16. eCollection 2014.**
This study shows the preliminary results of rapid and sustained pain relief with the Sonalleve system (Philips Healthcare)
- 6. Chan M et al. Magnetic Resonance-Guided High-Intensity-Focused Ultrasound for Palliation of Painful Skeletal Metastases: A Pilot Study. Technology in Cancer Research & Treatment 2016. DOI: 10.1177/1533034616658576**
This study shows the preliminary results of rapid and sustained pain relief with the Sonalleve system (Philips Healthcare)