I would like to formally request for the NCCN Pancreatic Adenocarcinoma Panel to review the referenced articles and associated data detailing the survival benefit of irreversible electroporation as an accepted mode of treatment for locally advanced pancreatic adenocarcinoma (LAPC).

Specific Changes

Irreversible electroporation, as is currently omitted from the Guidelines as an accepted approach to treatment, should be recommended as an effective form of therapy to patients who have previously undergone unsuccessful chemo/radiotherapy for the downstaging of unresectable LAPC.

FDA Clearance

The NanoKnife System has received FDA clearance for the surgical ablation of soft tissue. It has no clearance for the therapy or treatment of any specific disease or condition, such as LAPC.

Rationale

LAPC is the fourth leading cause of cancer mortality in the United States\(^1\). Because preliminary symptoms can be silent, those afflicted often go undiagnosed for long periods, and by the time the disease is diagnosed it is considered unresectable in the majority of patients (\(~85\%)\(^2,3\). Standard treatments, such as chemotherapy and/or radiation, have been used to treat pancreatic cancer and yield quantifiable benefits. In a study by Yoo et al examining the efficacy of FOLFIRI and FOLFOX in the treatment of gemcitabine-refractory pancreatic cancer, median overall survival (O.S.) was found to be 3.8 and 3.4 months respectively\(^4\). However, a study by Hammel et al involving 449 patients found there was no significant difference in O.S. between chemoradiotherapy compared with chemotherapy alone, nor between gemcitabine and gemcitabine paired with erlotinib\(^5\).

Irreversible electroporation (IRE) is a non-thermal technique that utilizes electric pulses to induce the formation of nanopores in the cellular membrane. The formation of these nanopores destabilizes the phospholipid bilayer leading to cell death similar to apoptosis. This mechanism of action provides notable safety benefits; as the procedure does not rely on thermal energy, there is no heat-related damage done to surrounding tissues or critical structures nor does the heat sink effect limiting efficacy. This targeted tissue destruction preserves critical structures and surrounding healthy tissue

IRE is associated with high survival rates and low recurrence, including in patients who are unable to proceed with aforementioned standard treatments. In a study by Martin et al\(^6\) involving 200 Stage III LAPC patients treated with IRE, 37% of patients sustained complications with a mean grade of 2 (range
and only 3% have experienced local recurrence. O.S. was 24.9 months (range 4.9-85 months). A study conducted by Kwon et al involving 48 patients found a similarly low recurrence rate (6%) with only 11% of patients presenting with complications. O.S. was 22.4 months. IRE is well tolerated and patients often do not have to undergo repeat treatments. Complications are generally transient and mild, and include infection, thrombosis, pancreatitis, and bleeding. The following peer-reviewed publications are submitted to support this proposed change.

Sincerely,

Kathleen Pietrovito
Director, Medical Affairs and Clinical Operations
