Parkview Regional Medical Cancer and Parkview Research Center

Comparison Study between 19 gauge EUS FNA BNX Needle vs. 22 gauge EUS FNA BNX Needle in Pancreatic Fiducial Placement to Treat Pancreatic Cancer

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1.0 Purpose

The primary purpose of this prospective multicenter study is to compare the cost, time, complications, and migration rate of two FDA approved needles; 19 gauge endoscopic ultrasound (EUS) fine needle aspiration (FNA) BNX needles to 22 gauge EUS FNA BNX needles.

2.0 Background

Pancreatic cancer is among the most deadly cancers in the United Sates. It is the ninth and tenth most common cancers among women and men respectively. Approximately forty-five thousand people were diagnosed with pancreatic cancer in 2013 in the United States. Only six percent of people with pancreatic cancer are expected to survive five years and it is responsible for seven percent of all cancer deaths.[1]

Treatment of non-resectable pancreatic cancer includes stereotactic radiotherapy which delivery methods include CyberKnife and Tomotherapy.[2, 3] The Cyberknife radiotherapy system and Tomotherapy radiotherapy system delivers noninvasive image-guided frameless radiosurgery, that is considered to be an alternative to conventional surgery.[2] Both delivery methods utilize the insertion of fiducial markers to facilitate accurate delivery of dose intensified radiotherapy. [3] This method of delivery relies on Image Guided Radiation Therapy (IGRT) to enable the delivery of a high dose radiation while having minimal effects on surrounding tissue, resulting in less adverse events by gating the respiratory motion and accommodating the tumor movement.[4] The fiducial markers are essential to ensure that there is interfractional certainty.[5]

Traditionally, percutaneous insertion of fiducial markers utilizing Computerized Tomography (CT) guided placement or surgery has been used to facilitate the delivery of stereotactic radiotherapy.[6] EUS-guided fiducial marker placement has been introduced as a safe and feasible alternate method to CT guided placement.[7, 8] Sanders et al., in a prospective study involving fifty-one patients evaluating safety, feasibility, and the ability to receive Stereotactic Body Radiation Therapy (SBRT) with EUS-guided marker placement using a nineteen gauge needle, found that fiducial placement was achieved in ninety percent of the cases with spontaneous migration found in seven percent of the cases requiring a second EUS-guided fiducial marker placement. Ninety-one percent of the patients successfully received SBRT, concluding that EUS-guide marker placement is safe and feasible for SBRT treatment of locally advanced pancreatic cancer.[9]

Both 19 gauge and 22 gauge needles are used to insert the markers per EUS-guided method. Ammar et al., noted that a 22 gauge needle may permit greater access, and also noted, that the need for a comparison trial of the two needles would be beneficial.[10] Khashab et al., compared the traditional fiducial marker to the coiled marker which differed in size. The use of a 19 gauge needle and a 22 gauge needle were utilized to accommodate the fiducial marker size. They noted the ideal needle characteristics

include the ability to incorporate multiple fiducial markers, good visibility, and ease of fiducial deployment.[11]

The intent of this study is to compare two commercially available needles, 19 gauge EUS FNA BNX needles vs. 22 gauge EUS FNA BNX needles in EUS-guided fiducial marker placement to treat patients with locally advanced pancreatic cancer who are not undergoing resection. Comparison of cost, time, complications, migration and the ability to receive SBRT will be evaluated.

3.0 Study Objectives

3.1 Primary Objectives

3.1.1 Determine the difference in cost between the utilization of using 19 gauge EUS FNA BNX needles to 22 gauge EUS FNA BNX needles for fiducial placement.

3.1.2 Determine the difference in the amount of time required to place pancreatic fiducials for pancreatic cancer between 19 gauge EUS FNA BNX needles to 22 gauge EUS FNA BNX needles.

3.2 Secondary Objectives

3.2.1 Determine the difference in rate of migration between 19 gauge EUS FNA BNX needles to 22 gauge EUS FNA BNX needles in patients in whom fiducial placement was performed.

3.2.2 Determine the difference in rate of post-procedure complications between 19 gauge EUS FNA BNX needles to 22 gauge EUS FNA BNX needles.

4.0 Study Design

This is a randomized prospective multicenter trial. A minimum of 14 patients and a maximum of 30 patients will be enrolled at up to ten participating sites. Enrollment is projected to be complete when enough data has been collected for statistical analysis.

Participating sites will consist of tertiary referral centers (either academic or community). The participating physicians are required to have experience as advanced interventional expert endoscopists as demonstrated by prior experience with endoscopic ultrasound based procedures involving the pancreas and prior experience of performing a minimum of five EUS guided fiducial marker placements in the pancreas. A Parkview Research Center (PRC) review committee will need to validate and approve the Principal Investigator before he/she may participate in this study. PRC will send a status letter of approval to the physician.

Adult subjects with a diagnosis of pancreatic cancer who will receive SBRT for pancreatic cancer via Cyberknife or Tomotherapy will undergo EUS guided fiducial

marker placement. The study duration will commence at the time of EUS guided fiducial marker placement and conclude at the time of last SBRT to the pancreas.

Subjects will be randomized to receive fiducial marker placement with either a 19 gauge EUS, FNA BNX needle or a 22 gauge EUS, FNA BNX needle. A single sheath and a single needle 19 gauge EUS, FNA, BNX needle using a Visicoil twin line with spacers will be utilized and a total of four fiducials (2 twin lines) will be placed in ARM 1. A single sheath and a total of four 22 gauge EUS, FNA, BNX needles will be used to place a total of four fiducials in ARM 2. Fiducial size will be per institutional standards. For all patients, standard hospital protocol will be followed for EUS procedures and patient care management.

Cost effectiveness will be evaluated by providing an itemized statement, including anesthesiologist, and endoscopist charges. Time in both arms starts when the first needle is loaded and sealed with bone wax. The patient is under anesthesia, in position, and staff is ready for the case. The time ends when last fiducial is placed. When using a 22 gauge needle, assistance to load blank needles is allowed if desired. Complications will be reported and may include but not limited to pain, bleeding, peritonitis, and pancreatitis. Migration will be reported during the timeframe from simulation to the last day of SBRT. The ability to receive SBRT from this EUS guided fiducial placement will be reported as simply a yes or no. Sites will provide a de-identified itemized statement for EUS guided fiducial placement procedure, prior to any discounted rate, including the endoscopist and anesthesiologist.

Follow up evaluations and treatment for pancreatic cancer will be performed in accordance with standard of care procedures and procedures deemed necessary by the attending physician.

Computerized Tomography Simulation (CT SIM) and set up will be performed per institutional policy and procedure.

There will be fiducials placed in the pancreas according to facility policy and procedure.

The participating site will obtain appropriate Institutional Review Board (IRB) approval prior to participating in any research activities. The participating site will provide PRC with a copy of their IRB approval prior to any study procedures. PRC will also need to collect the participating sites' IRB of records IRB registration and FWA to confirm compliance.

Once IRB approval has been confirmed by the coordinating site, the participating site will receive enrollment instructions, case report forms and the randomly assigned sealed envelopes.

5.0 Selection of Subjects

This study will include patients with pancreatic cancer who will receive fiducial marker placement in order to receive Cyberknife treatment to the pancreas.

6.0 Inclusion

6.1 Subjects that plan to undergo CyberKnife treatment for pancreatic cancer
6.2 Subjects that are deemed physically able to undergo anesthesia (either Monitored Anesthesia Care (MAC) or general anesthesia)
6.3 Subjects (or the subjects Legally Authorized Representative [LAR]) that have agreed to participate in the study and have signed Informed Consent
6.4 Subjects 18 years of age or older
6.5 Subject must be able to hold anticoagulants as per institutional standard of care
6.6 Women of child bearing potential who are not pregnant as proven by a negative pregnancy test

7.0 Exclusion

7.1 Subjects that are unable to tolerate anesthesia for the procedure
7.2 Subjects 17 or under
7.3 Subjects that refuse treatment for pancreatic cancer
7.4 Subjects whose anticoagulants cannot be held
7.5 Subjects who have distant metastatic disease
7.6 Subjects who cannot or refuse EUS guided procedures.
7.7 Subjects who are pregnant

8.0 Subject Confidentiality and HIPAA Compliance

To ensure that the confidentiality of subjects' identification is maintained and medical records are protected, subject names will not be used in the study. A unique subject identifier will be assigned to each subject enrolled in the study. Each participating site will maintain a list that cross-references subjects' identification. The participating site will control their own subject's identity. To ensure that subjects' identification and medical records are protected, the list will be kept confidential and only accessible to the PI, his/her staff, and the appropriate research representative responsible for ensuring the quality of the reported data. Subject's records may be reviewed by research representative to verify the quality of the reported data; however, confidentiality will be maintained.

Subjects will provide the appropriate authorization to allow the use and disclosure of their personal health records in accordance with the applicable laws and regulations including, but not limited to, HIPAA requirements.

9.0 Randomization

Subjects receiving EUS and fluoroscopic guidance for placement of fiducial markers into the pancreas will be randomized into two groups in a balanced manner to either the 19 gauge technique (ARM 1) or the 22 gauge technique (ARM 2) of EUS guided fiducial marker technique according to a predetermined computer generated randomization.

When the procedure has been scheduled the site should email the coordinating site at oncology.research@parkview.com for your randomization instructions.
Two sealed envelopes will be appended to each subjects folder they will be marked A and B. A sheet of paper inside the envelopes will indicate either "19" indicating 19 gauge technique (Treatment ARM 1) or "22" indicating 22 gauge technique (Treatment ARM 2).
The envelope will only be opened during the procedure after the endoscopy has been initiated.

10. Information Required

10.1 Prior to fiducial placement

10.1.1 Eligibility Checklist
10.1.2 Obtain Informed Consent
10.1.3 Patient information
- Gender
- Date of Birth
- Height
- Weight

10.1.4 Comorbidities
- Smoker
- Diabetes (type I or type II)
- Chronic Lung Disease
- Cardiac Disease
- Pancreatitis
- Hepatitis
- Hypertension
- Anticoagulation Status

10.1.5 Disease Characteristics
- Recurrent
- Stage
- Pathology
- Diagnostic Testing

10.1.6 History of chemotherapy and radiation

10.2 During Fiducial Placement

10.2.1 Time measurement

- Time in both arms starts when the first needle is loaded and sealed with bone wax. The patient is under anesthesia, in position, and staff is ready for the case. The time ends when last fiducial is placed. When using a 22 gauge needle, assistance to load blank needles is allowed if desired.

10.2.2 Needle type used
10.2.3 Number fiducials placed
10.2.4 Size of fiducials placed
10.2.5 Type of fiducials placed

10.3 Post Fiducial Placement

10.3.1 Cost

- Itemized charges to patient for procedure including anesthesiologist and endoscopist prior to any discounted rate.

10.4 Complications during/after the procedure:

10.4.1 Admission for pain
10.4.2 Need for laparoscopic or open surgery
10.4.3 Any additional endoscopic procedures to control bleeding
10.4.4 Peritonitis
10.4.5 Need for transfusion
10.4.6 Requiring hospital admission or emergency room visit
10.4.7 Pancreatitis

10.5 Migration of fiducials

10.5.1 Observation of fiducial migration from time of treatment planning to the last SBRT.

10.6 Ability to receive SBRT

10.6.1 Yes or No

10.7 Transmission of Case Report Forms (CRF) and other pertinent study material

10.7.1 Scanning
10.7.1.1 Scan to breck.hunnicutt@parkview.com
10.7.2 Faxing
10.7.2.1 Fax to 260-266-9169 c/o Breck Hunnicutt

10.8 Queries

10.8.1 All queries will be communicated through email
10.8.2 Query response is requested with two weeks of receipt

11.0 Adverse Event Reporting

11.1 Adverse events will be collected at the following time points:

- Baseline
- Completion of procedure, prior to discharge
- 72 hours post procedure
- Last day of SBRT treatment
- Migration of fiducial markers at any time prior to completion of SBRT treatment will be reported.

12.0 Serious Adverse Event (SAE) Reporting

All serious adverse events will be reported to Neil Sharma, M.D. by way of Breck Hunnicutt within 24 hours by calling 260-266-9168. This call should be followed by the SAE CRF submission within 10 days by faxing the submission to Breck at 260-266-9169 or email her at breck.hunnicutt@parkview.com
A monitoring board lead by Dr. Sharma will review all incoming SAE's.

12.1 Definition of an SAE: Any adverse event that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition

13.0 Data and Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a quarterly assessment of the number and type of serious adverse events.

14.0 Sample Size

A minimum of 14 subjects and a maximum of 30 subjects are expected to be enrolled. Approximately one half of the subjects receiving fiducial markers via 19 gauge EUS FNA needle and approximately one half of the subjects receiving fiducial markers via 22 gauge EUS FNA needle. The relatively small sample size will require the use of a non-parametric statistical test. Further, the detection of statistically significant results may be

difficult to detect due to the small sample size. [12] As such, the alpha level for all tests may be relaxed to the .10 level if significant effects are not detected at the .05 level.

15.0 Statistical Analysis Plan

15.1 Primary Endpoints

- The primary endpoint for this study is total cost and time of EUS guided fiducial placement in the pancreas to facilitate SBRT treatment of pancreatic cancer.

15.2 Secondary Endpoints

- The secondary endpoints for this study are the migration rate of fiducials between placement and SBRT treatment to the pancreas and the rate of immediate complications after placement of fiducials.

15.3 Enrollment

- Approximately 14 subjects and a maximum of 30 subjects are expected to be enrolled. With approximately one half of the subjects randomized to ARM 1 (19 Gauge EUS FNA needle technique) and approximately one half of the subjects randomized to ARM 2 (22 gauge EUS FNA needle technique).

15.4 Study Hypothesis

- This study is designed to test the null hypothesis that the 19 gauge EUS FNA BNX needles will have no variances related to cost, time, complication rate and migration rate to the 22 gauge EUS FNA BNX needles.

  $H_0: G_{19} = G_{22}$
  $H_1: G_{19} \neq G_{22}$

  G_{19}= 19 gauge EUS FNA BNX Needles
  G_{22}= 22 gauge EUS FNA BNX Needles

15.5 Interim Analysis

- Given that only a minimum of 14 subjects will be enrolled, a non-parametric statistical analysis technique is required.[12] Four separate areas will be examined: (1) cost; (2) time; (3) rate of migration, and; (4) complications. In all areas, the independent variable is a dichotomous nominal level indictor that identifies whether patients are enrolled in ARM 1 or ARM 2. The dependent variables of time, cost and migration are continuous markers of the concepts in question. Under normal circumstances, the use of an independent samples *t*-test is appropriate when the dependent variable is continuous in nature and the independent variable is a dichotomous nominal-level variable.[13] Under the current analysis scenario, the non-parametric equivalent of the t-test, which is the Wilcoxon-Mann-Whitney test,[12] is appropriate.

The dependent variable that will estimate the presence of immediate complications and complications after the surgery will be reduced to a series of dichotomous indicators that will indicate the presence of admission for pain, the need for laparoscopic or open surgery, any additional endoscopic procedures to control bleeding, peritonitis, the need for transfusion, pancreatitis, or the need for a hospital admission or an emergency room visit. These seven dependent variables will be juxtaposed against the independent variable that identifies whether a patient is enrolled in ARM1 or ARM2 through a series of cross tabulations. The Chi-Square statistic[13, 12] will then be used to determine if statistically significant differences in each of the seven dependent variables exists as a function of the independent variable.

16.0 Subject Withdrawal

A subject has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. The investigator and sponsor also have the right to withdraw subjects from the study in the event of comorbidities, adverse events, treatment failure, protocol deviation, or other reasons. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw; all efforts will be made to complete and report the observations as thoroughly as possible.

17.0 Data Collection and Management

For each subject for which informed consent has been obtained, a CRF must be completed by the PI or by their designee and signed by the PI, to certify that the data within each CRF is complete and correct. Every effort should be made to respond to all questions on each CRF page. All CRF's should be completed to identify the physician, subject number, and subject initials. At no time should the subjects name appear in the CRF. Every effort should be taken to protect the subject health information. Complete data is required in order to provide statistical analysis for each subject. All CRF's should be submitted to the coordinating site within 4 weeks.

18.0 Responsibility of Principal Investigator

- Conduct the study in accordance with the relevant, current protocol.
- Personally conduct or supervise the described investigation.
- Analysis of Complications and Adverse Events with respect to their clinical relevance and cause relation.
- Evaluation of necessary protocol amendments.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.
- Agree to maintain adequate and accurate records and to make those records available for inspection in accordance with regulations.

19.0 Responsibility of Participating Site

- The site will consist of the Principal Investigators and his/her research team.

- Each Investigator within the participating site is responsible to conduct the Study in full compliance with the protocol and assure that data collection is complete and accurate.

20.0 Conduct of Study

20.1 Ethical Conduct of the Study

This study will be conducted in accordance with applicable local, state, national laws and requirements.

20.2 Informed Consent

Informed Consent will be obtained from each subject and must be appropriately signed and dated. It is the PI or PI's designee's responsibility to obtain written informed consent from the subject or subject's legally authorized guardian prior to any protocol specific screening procedures being done. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The original signed copies of consent forms will be maintained by the participating site.

Subjects will provide the appropriate authorization to allow the use and disclosure of their Protected Health Information (PHI) in accordance with applicable laws and regulations, including but not limited to, HIPAA requirements.

20.3 Institutional Review Board/Ethics Committee

Written approval of the protocol must be obtained prior to subject enrollment. A copy of the letter indicating IRB approval must be provided to the sponsor. Annual updates must be submitted to the IRB by the PI for studies longer than one year or as dictated by the participating sites IRB. Serious or unanticipated adverse events occurring during the study must also be submitted as per the Institution's IRB policy.

SIGNATURE LINE

My name type below shall have the same force and effect and is as legally binding as my written signature.

Neil Sharma, MD — April 27, 2015

Principal Investigator — Date

List of References

1. American Cancer Society. Cancer Facts & Figures 2013 Atlanta: American Cancer Society; 2013.
2. Chang, S., Main, W., Martin, D., et al. An analysis of the accuracy of the CyberKnife: a robotic frameless stereotactic radiosurgical system. Neurosurgery. 2003 Jan;52(1):140-6; discussion 146-7.
3. Moseley, D., White, E., Whiltshire, K., et al. Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate. International Journal of Radiation Oncology*Biology*Physics. 2007 March;67(3): 942-953.
4. Chang, D., Schellenberg, D., Schen, J., et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. Cancer. 2009 Feb;115(3): 665-672.
5. Jayachandran, P., Minn, Y., Van Dam, J., et al. Interfractional Uncertainty in the Treatment of Pancreatic Cancer With Radiation. International Journal of Radiation Oncology*Biology*Physics. 2010 Feb;76(2): 603-7.
6. Sotiropoulou E., Stathochristopoulou, I., Stathopoulos, K., et al. CT-Guided Fiducial Placement for CyberKnife Stereotactic Radiosurgery: An Initial Experience. CardioVascular and Interventional Radiology. 2010 June;33(3): 586-9.
7. Park, W., Yan, B., Schellenberg, D., et al., EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. Gastrointestinal Endoscopy. 2010 March;71(3): 513-18.
8. Kim, J., Hong, S., Kim, J., et al. Safety and Efficacy of Ultrasound-Guided Fiducial Marker Implantation for CyberKnife Radiation Therapy. Korean Journal Radiology. 2012 May-Jun; 13(3): 307–313.
9. Sanders, M., Moser, A., Khalid, A., et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. Gastrointestinal Endoscopy. 2010 June;71(7): 1178-84.
10. Ammar, T., Coté, G., Creach, K., et al. Fiducial placement for stereotactic radiation by using EUS: feasibility when using a marker compatible with a standard 22-gauge needle. Gastrointestinal Endoscopy. 2010 71(3) 630-3.
11. Khashab, M., Kim, K., Tryggestad, E., et al. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. Gastrointestinal Endoscopy. 2012 Nov;76(5): 962–971.
12. Sprent, P. (1989). Applied Nonparametric Statistical Methods, Second Edition. Boca Raton, FL: Chapman & Hall
13. Ritchey, F. (2008). *The Statistical Imagination: Elementary Statistics for the Social Sciences, Second Edition.* Boston, MA: McGraw-Hill.

Appendix A

Optional Tool - Check List

Check List to be done in this order

1. Patient Scheduled for Pancreatic Fiducial Placement due to Pancreatic Cancer
2. Patient meets Inclusion/Exclusion Criteria
3. Informed Consent Obtained
4. Eligibility Checklist Completed
5. Email Coordinating Center for Randomization **Provide: Institution Name** **Date of Procedure** **Patient Initials**
6. Randomization Email from Coordinating Center **Information provided from them:** **Subject ID** **Randomization Code (Envelope A or B)**

Appendix B

Optional Tool - CRF Completion Guidelines

Case Report Form	Prior to Fiducial Placement or Baseline	During Fiducial Placement	Completion of procedure, prior to discharge	72 hours port procedure	Last day of SBRT treatment	Migration of Fiducial marker (if needed
Eligibility Checklist	**X**					
Subject Demographics	**X**					
Fiducial Placement		**X**				
Adverse Events	**X**		**X**	**X**	**X**	**X**
***Serious Adverse Events**	**X**	**X**	**X**	**X**	**X**	**X**

*All Serious Adverse Events to be reported to Dr. Sharma by way of Breck Hunnicutt within 24 hours by calling 260-266-9168. This should be followed by the SAE CRF submission within 10 days by faxing the submission to 260-266-9169