Experimental Computed Tomography-guided Vena Cava Puncture in Pigs for Percutaneous Brachytherapy of Middle Mediastinal Lymph Node Metastases

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Abstract

Background: Percutaneous brachytherapy is a valuable method for the treatment of lung cancer and mediastinal lymph nodes metastasis. However, in some of the metastatic lymph nodes in the middle mediastinum, the percutaneous approach cannot be used safely due to possible damage to surrounding anatomical structures. We established an animal model (group of 12 pigs) to assess the safety and feasibility of computed tomography (CT)-guided vena cava puncture.

Methods: Under CT guidance, an 18G needle was used to puncture the anterior wall of the anterior vena cava (AVC) in 12 pigs. The 18G needle was chosen as it is similar in size to the needles employed for clinical application in brachytherapy. The incidence of complications and vital signs was monitored during the procedure. Thoracotomy was performed to remove AVC specimens, which were analyzed for histological evidence of vessel wall damage and repair.

Results: Following postoperative enhanced CT, two animals were found to have a small pneumothorax (one being hemopneumothorax). The intraoperative oxygen saturation of both animals was not significantly decreased and was maintained at 93–100%. No animals developed mediastinal hematoma. Preoperative, intraoperative, and postoperative changes in blood pressure, heart rate, hemoglobin, and blood oxygen saturation were not significant. Histological evaluation of AVC specimens showed that by 7 days following the procedure, the endothelial layer was smooth with notable scar repair in the muscularis layer.

Conclusions: CT performed after the procedure and histological preparations confirmed the safety of the procedure. This indicates that percutaneous brachytherapy for metastatic middle mediastinal lymph nodes can be carried out via the superior vena cava.

Key words: Anterior Vena Cava; Brachytherapy; Computed Tomography-guided Puncture; Imaging-based Procedures, Swine

Introduction

Mediastinal lymph node metastases are common in lung and esophageal cancer and rare in the primary extrathoracic malignancy.[1] Treatment possibilities include surgery, external beam radiotherapy (EBRT), chemotherapy and from the 90's brachytherapy. Surgical procedures such as mediastinal lymphadenectomy, anterior mediastinotomy, and more recently, video-assisted thoracic surgery has significant morbidity and even mortality.[2-4] EBRT cannot avoid adjacent normal tissues and may cause radiation pneumonitis, esophagitis, and medullitis.[5,6] EBRT requires long treatment cycles (20–50 days), which can be very inconvenient for patients due to daily treatment and travel distances. Three-dimensional conformal radiotherapy and intensive modulation therapy significantly improve radiation delivery but require sophisticated equipment. Intravenous (iv) chemotherapy can be employed only as part of multimodality treatment.[7-10]

Computed tomography (CT)-guided radioactive seeds implantation combines the high accuracy of CT and the advantages of brachytherapy. However, the percutaneous approach to some metastatic lymph nodes in the middle mediastinum is difficult or impossible due to their closeness to the aorta, superior vena cava (SVC), trachea, and esophagus without enough space for the safe passage of the needle. Therefore, we propose the use of CT imaging with the implantation of radioactive ^{125}I seeds via SVC for

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therapy of metastatic middle mediastinal lymph nodes when the conventional approach is not possible.

To determine the feasibility and safety of this approach, we provide experimental evidence using a pig model mainly to determine the potential risk of mediastinal bleeding. In the pig, the term anterior vena cava (AVC) due to animal posture is more correct and, therefore, is preferred to SVC. In some nomenclatures, "posterior vena cava" is used in place of "inferior vena cava (IVC)".

Methods

Twelve 6-month-old Chinese experimental pigs (Jiangsu Taizhou Taihe Biotechnology Co. Ltd., Taizhou, China) with an average weight of 27.51 ± 1.72 kg (25–30 kg) were selected for this study. Animals were managed according to the "Laboratory Animal Science" manual and fulfilled the "National Standards of Experimental Animals" (1994) and "Animal Management Ordinance" (1988) requirements of the Ministry of Health.[11] This study was approved by the Experimental Animal Ethics Committee of our hospital.

Equipment and supplies

Spiral CT imaging was performed with a GE LIGHT SPEED 16 (General Electric, Connecticut, USA) with scanning parameters of 120 kV, 280 mA, 5 mm. Gas anesthesia was performed with GE Aespire (General Electric, Connecticut, USA), and anesthetized pigs were monitored with an ECG model (Philips, Ende von Richthofen, The Netherlands) and pulse oximeter (Philips, Ende von Richthofen, The Netherlands). The puncture needles (18G, 15 cm) used were similar to brachytherapy needles used in humans (TRUSCO Ltd., Tokyo, Japan).

Procedure techniques

Pigs were fasted for 8 h prior to performing the procedure, and first sedated with diazepam (0.8 mg/kg, im). This allowed for placement of a catheter in the auricular vein and administration of the preanesthetic drug propofol (2 mg/s, iv).

Animals were placed in dorsal recumbency. After endotracheal intubation and initiation of gas anesthesia (isoflurane, 10 ml/kg), ECG leads and pulse oximeter (Philips, Ende von Richthofen, The Netherlands) were connected for appropriate monitoring. The chest was then imaged with enhanced CT to identify the location of AVC and to select the puncture site and angle of insertion [Figure 1].

The skin at the selected site of puncture was aseptically prepared and an 18G core needle was used to puncture the AVC under CT guidance by slowly advancing the needle in 2–3 small steps at a time until about 0.5 cm of the needle tip was observed entering the AVC [Figure 2]. In two animals, the needle was inserted through and through the AVC (both anterior and posterior walls) as we intended to perform clinical brachytherapy in human patients. Upon completion of the procedure, the needle was removed, and the puncture site was compressed and bandaged. Enhanced CT imaging was repeated to monitor the possible development of any complications such as mediastinal hematoma, pneumothorax, or hemothorax [Figure 3a and b]. The incidence of complications was recorded. Vital signs were monitored throughout the procedure which was followed by administration of etamsylate (0.8 g, qd for 24 h).

Monitoring for complications

Enhanced CT scans were performed during and after the procedure to determine the presence of any abnormalities in AVC as well as in the surrounding vital tissues and organs.

Monitoring of vital signs

Blood pressure (BP), including systolic (S) BP and diastolic (D) BP, heart rate (HR), and blood oxygen saturation (SO_2) were monitored in all animals from 30 min before to 30 min after the procedure. In addition, 2 ml of venous blood was drawn for hemoglobin (Hgb) analysis 30 min before the puncture, immediately after the puncture and 30 min after the procedure.

Tissue specimen acquisition and analysis

Experimental animals were randomly divided into four groups (1–4) and euthanized with the infusion of 10% potassium chloride (25 ml) in auricular vein at the end of the procedure, 24 h, 48 h and 7 days after the procedure. Thoracotomy was performed to remove AVC specimens. The puncture site was identified macroscopically. All samples were fixed in 4% formaldehyde and taken to the histology laboratory for processing and staining with hematoxylin/eosin (Biomart, Wuhan, China). Slides were analyzed for histological evidence of vessel wall damage and repair by light microscopy at 1000× (CX41/Olympus, Tokyo, Japan).

Statistical analysis

Measurements of BP, HR, SO_2, and Hgb before, during and after the procedure were compared by ANOVA using SPSS software 12.0 (IBM Corporation, New York, United States). When significant differences were detected, Student–

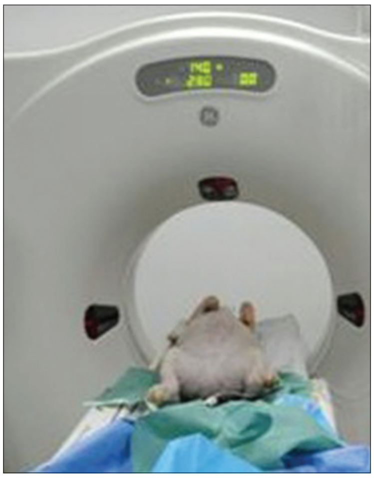

Figure 1: Identification of the puncture site under computed tomography guidance.

Newman–Keuls test was applied for mean separation. Significance was considered at $P < 0.05$.

Results

Outcome and monitoring results

All 12 procedures were successful, 10 following a single puncture attempt and 2 requiring some minor needle reposition adjustments to reach the lumen of the AVC. Postoperative enhanced CT identified a small pneumothorax in each of two animals (one being a hemopneumothorax). The intraoperative oxygen saturation of these two animals was not significantly decreased and was maintained at 93–100%. No animals developed mediastinal hematoma.

Preoperative, intraoperative, and postoperative changes in blood pressure, heart rate, hemoglobin, and blood oxygen saturation

As shown in Table 1, there were no significant changes detected in any of the blood values monitored. The intraoperative HR and BP were slightly increased but not significantly different from preoperative values ($P > 0.05$).

Macroscopic assessment of organs and histologic evaluation of anterior vena cava specimens

Thoracotomy and subsequent examination of euthanized animals confirmed the absence of congenital macroscopic heart, lung, or vascular disease. The AVC was normally developed, and as expected, the puncture site was easily visualized [Figure 4a]. In one animal, a small hemothorax, approximately 20 ml, was present on the right side of the thorax. Moreover, histologic evaluation of vascular tissue in this and other animals in Group 1 revealed no abnormal findings. Conversely, samples of animals euthanized 24 h after the procedure (Group 2) showed clear endothelial migration at the puncture site with no pronounced endothelial defects but with visible damage to the muscularis layer [Figure 4b]. Tissue from Group 3 indicated endothelial cell proliferation, structure of muscle cells in disorder and formation of granulation tissue [Figure 4c]. However, 7 days following the procedure (Group 4), the endothelial layer appeared smooth with notable scar repair in the muscularis layer [Figure 4d].

Discussion

The value of brachytherapy was recognized early at beginning of 20th century. Following initial interest, the procedure declined in the middle of the 20th century due to the amount of radiation exposure to the operator from the manual application of radioactive sources. The successful development of radioactive ^{103}Pb, ^{125}I, ^{192}Iridium, ^{198}Au, and after loading technology renews the interest in clinical application of brachytherapy.

The new imaging technique CT and ultrasound with guided procedure and three-dimensional treatment planning in the 1980's allows and extends the application of brachytherapy. Radioactive seeds may be delivered by intracavitary

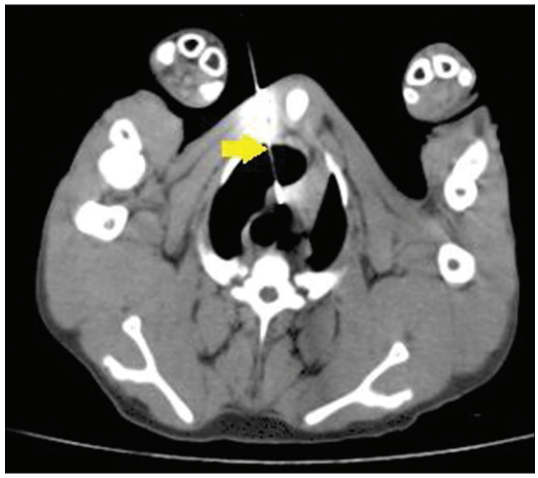

Figure 2: Computed tomography-guided 18G core needle puncture of the anterior vena cava in an anesthetized pig. The arrow shows the needle and the puncture tract.

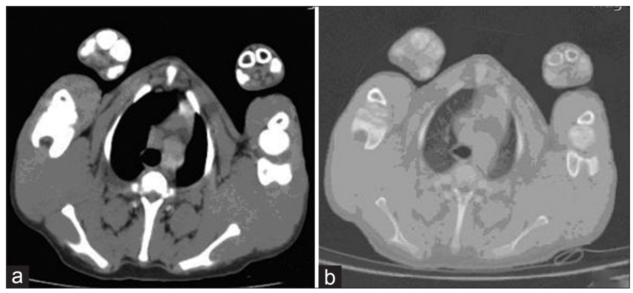

Figure 3: Enhanced computed tomography scan following needle removal after puncture through the lumen of the anterior vena cava; (a) Mediastinal view shows no hemothorax or pneumothorax; (b) Lung view showing no obvious pneumothorax.

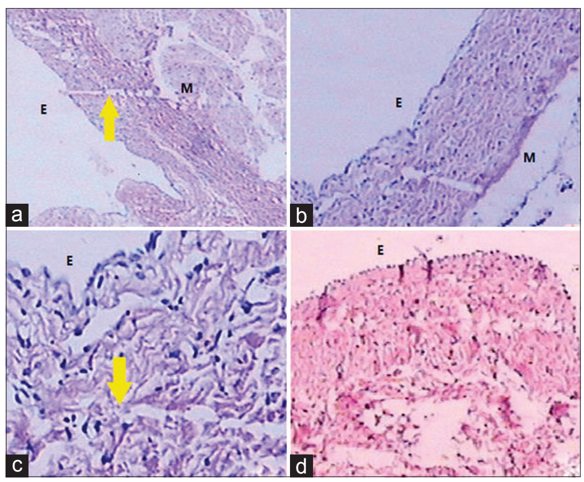

Figure 4: Anterior vena cava with puncture stained by H and E. The arrow shows the puncture tract. (a) Group 1: The puncture path was clearly observed through the endothelial and muscularis layers (arrow); (b) Group 2: Migration of endothelial cells was obvious at the puncture site with no visible track in the muscularis layer; (c) Group 3 showing endothelial cell proliferation, structure of muscle cells in disorder and formation of granulation tissue (arrow); (d) Group 4 showing smooth endothelium and visible scar tissue in the muscularis layer. Original magnification: a,b x 100; c,d x 400.

Table 1: Comparison of preoperative, intraoperative and postoperative values for blood pressure, heart rate, hemoglobin and oxygen saturation in anesthetized pigs undergoing CT-guided anterior vena cava puncture

Index	Preoperative	Intraoperative	Postoperative	*P* value
SBP (mmHg)	162.92 ± 5.71*	163.50 ± 16.07	161.67 ± 8.98	0.919
NBP (mmHg)	104.58 ± 6.39	105.50 ± 15.44	105.33 ± 5.30	0.972
HR (beats/min)	73.67 ± 10.08	80.42 ± 16.24	79.92 ± 9.42	0.338
HGB (g/L)	135.83 ± 7.58	135.42 ± 7.46	134.83 ± 7.35	0.947
SO2 (%)	97.00 ± 2.00	96.42 ± 2.11	97.00 ± 1.60	0.693

*Values are expressed as mean SEM. SBP: Systolic blood pressure; NBP: Diastolic blood pressure; HR: Heart rate; HGB: Hemoglobin; SO2: Oxygen saturation

applicator, intraoperative, interstitial and more recently by irradiated seed expandable stents in esophageal cancer and biliary malignancy.[12,13]

In interstitial brachytherapy, radioactive sources are introduced permanently into the tissue with the use of needles and catheters of small diameter, ^{125}I seeds being the commonest sources. ^{125}I seeds emit gamma-rays and X-rays with energy below 0.035 MeV, a half-life of 59.7 days and are readily shielded by a few tenth of a millimeter of lead. Gamma-rays have the ability to penetrate 17 mm, effective kill radius of about 10–15 mm. The short effectiveness area with precise location increases the target effect, prevents damage to normal tissue and reduces radiation exposure of personnel. Percutaneous ^{125}I seeds implantation has been widely used for treatment of lung cancer, lung metastasis, liver cancer, pancreatic cancer, and soft tissue malignancy.[14-16] Several studies also confirm the value of CT guided ^{125}I seed implantation for patients with metastatic lymph nodes of the mediastinum integrating the advantages of CT intervention and radiotherapy.[17,18]

Puncture of the great vessels (aorta and IVC) is well-documented. Translumbar aortography was extensively used as a diagnostic procedure until the 80's.[19] CT performed after angiography documented only a small retroperitoneal hematoma.[20] The rate of complications after the translumbar aortography was low, and the procedure was considered safe. Biopsy procedure involving puncture of the IVC wall using a 19G needle resulted in no bleeding.[21] Moreover, a case report described CT-guided puncture through the portal vein for radiofrequency ablation of tumor thrombus without significant side-effects.[22] In favor of these procedures is the fact that both human and pigs venous pressures are relatively low. For instance, in a healthy human the venous pressure ranges from −10 to −3 mmHg resulting in a pressure gradient of only 6–16 mmHg. With similar values in pigs, bleeding following venous puncture is unlikely. Further supporting the safety were the normal vital sign recordings prior, during and after the procedure.

The lack of changes in Hgb concentration or oxygen saturation suggested an absence of significant intraoperative bleeding or pneumothorax. Conversely, the slight increase in BP or HR detected may have been due to puncture-related pain leading to increased sympathetic activity because the values returned to baseline following the procedure. Postprocedure CT and the histopathology report confirmed the absence of hematomas. Furthermore, effective tissue repair is important to guarantee the prevention of postoperative bleeding. Accordingly, histological examination showed complete repair of the vascular endothelial and muscular layers within 72 h following the procedure, supporting the lack of postoperative bleeding complications.

An additional risk of puncture of AVC has been the development of embolism. In healthy animals, the pleural cavity pressure is negative which minimizes this risk. Monitoring of vital signs as well as postprocedure enhanced CT showed no evidence of this complication.

The main complication of the procedure was pneumothorax in 2 animals. Pneumothorax is a well-recognized complication of intrathoracic placement of needles and catheters. The percentage of pneumothorax after lung biopsy depends on the size of the needle, the number of needle passes and lung disease like emphysema. Cooperative patient and early explanation of the procedure always diminishes the risk. We use a relatively large bore 18G needle (TRUSCO Ltd., Tokyo, Japan) similar to needles used in percutaneous transthoracic brachytherapy. In our experiment, in brachytherapy of the thorax (lung cancer and mediastinal lymph nodes), small pneumothoraxes are common in procedures that require multiple needle insertion due to the size of lesions. However, the necessity of chest tube insertion is quite rare. The absence of mediastinal hemorrhage confirms the safety of AVC puncture and brachytherapy with approach through SVC in cases where middle mediastinal lymph nodes are surrounded by anatomical structures that limit direct insertion of the needle into lymph nodes.

Encouraged by this study, we started brachytherapy needle insertion through and through SVC (both walls) in middle mediastinal lymph nodes metastasis which we previously were not able to treat by brachytherapy (unpublished data). However, it must be stated clearly that brachytherapy via trans-SVC approach is only an alternative treatment for a small group of metastatic middle mediastinal lymph nodes, not for most mediastinal metastasis. Moreover, due to lack of enlarged lymph nodes in experimental pigs, no seeds were implanted after the puncture of AVC, which remains one shortcoming of this study.

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