CLINICAL ARTICLE

Transnasal Endoscopic and Transoral Approaches in the Biopsies of Ventral Atlas and Axis Vertebrae: A Comprehensive Retrospective Study for Preprocedural Scheme, Biopsy Procedure, Core Technique Analysis, Diagnostic Yield and Clinical Outcome

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Objective: This study aims to describe and analyze the transoral and transnasal approaches for pathologies of the ventral atlas and axis vertebrae, which are considered technically challenging regions for diagnostic biopsy.

Methods: A series of transnasal endoscopic approach (TNA) and transoral approach (TOA) biopsies for the pathologies of the first and second cervical vertebrae were conducted and retrospectively analyzed from July 2014 to May 2021. The depth of the biopsy trajectory was measured on computed tomography images for all nine patients (eight males and one female with an average age of 58.11 ± 11.60 years), as were the coronal, sagittal, and vertical biopsy safe ranges. The characteristics of each lesion, including radiographic features, blood supply, and destruction of anterior or posterior vertebral body edges, were evaluated to guide the biopsy. Four biopsy core techniques (BCTs), including "lesion perforating", "aspiration", "cutting-and-scraping" and "biopsy forceps utilization" were elaborated in this study. The biopsy procedures and periprocedural precautions were demonstrated. Patient demographics, clinical data, lesion characteristics, diagnostic yield, and complications were recorded for each case.

Results: Eight TOA biopsies for the axis vertebral body and one TNA biopsy for the atlas anterior arch were successfully performed and yielded adequate pathologies. All biopsies were organized based on the preprocedural radiographic measurements, which showed that the average length of biopsy trajectory and coronal, sagittal, and vertical safe biopsy ranges were 85.00 ± 5.88, 20.63 ± 4.75, 16.25 ± 1.49, and 24.63 ± 2.26 mm, respectively, and these corresponding data were 95, 36, 9, and 26 mm in the TNA patient. Six osteolytic lesions (66.7%), one osteoblastic lesion (11.1%), and two mixed lesions (22.2%) were observed, among which seven lesions had a rich blood supply. Biopsy forceps and core needles were utilized to obtain samples in six and three patients, respectively. All the TNA and TOA biopsies were performed with cooperative application of multiple BCTs under compound anatomic and stereotactic navigations. Intraprocedural or postprocedural complications occurred in no patients who underwent the biopsy in the follow-up period (1–39 months). No significant differences were found between the preprocedural and postprocedural blood indexes and visual analogue scale scores.

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Conclusion: With a sophisticated preprocedural arrangement, cooperative application of BCTs, and careful periprocedural precautions, transnasal endoscopic and transoral biopsies are two feasible, efficient, and well-tolerated procedures that achieve satisfactory diagnostic yield, complication rate, and clinical outcome.

Key words: Atlas vertebra; Axis vertebra; Biopsy; Diagnostic yield; Transnasal approach; Transoral approach

Introduction

Biopsy, the gold standard for preoperative diagnosis,[1] is extensively conducted *via* the percutaneous approach to obtain samples for the histopathological characterization of osseous oncologic and infectious lesions in most situations,[2,3] but if this approach becomes arduous after numerous attempts to yield adequate pathological tissue in technically challenging anatomic regions, it might be time to consider biopsy *via* other approaches. Atlas and axis are regarded as two surgically challenging vertebrae[4,5] because they are unique in comparison with the rest of the cervical vertebrae in that they have bony anatomy, joint configuration, and lateral neurovascular structures.[6,7] The biopsy for C1 and C2 in the ventral regions was thereby omitted before therapeutic surgical interventions in several previous studies.[8–10] However, the precise diagnosis based on preoperative biopsy may benefit patients.[11,12] Our team discovered the following phenomena in routine needle biopsies: (i) compared with the other vertebrae, tumorous or infectious lesions that invade C1 and C2 seem to possess a lower diagnostic yield and higher complication rate in percutaneous biopsy; and (ii) for pathologies involving the ventral atlantoaxial region, it may be difficult to obtain adequate biopsies for histopathological examinations *via* a percutaneous approach.

The transnasal endoscopic approach (TNA) and transoral approach (TOA) have recently become two vital options for otolaryngological and neurosurgical interventions.[13–15] Biopsy through a transoral or transnasal route has been utilized to obtain pathological tissues of the pituitary, oral cavity, nasopharynx, oropharynx, esophagus, parapharyngeal space, retropharyngeal lymph node, and clivus[16–21] and may therefore elevate the diagnostic accuracy.[21–23] The transoral approach is widely applied and offers direct access to the pathology without neurovascular tissue retraction in craniovertebral junction (CVJ) surgery.[24] In the past 30 years, the TNA has also been extensively utilized in surgery to treat diseases involving the clivus, C1, and C2.[25,26] Therefore, the transoral and transnasal approaches to the CVJ are currently well-established routes of access to the atlantoaxial region.[26–28] Biopsy for ventral atlas and axis vertebral pathologies in which chordomas, metastatic tumors, and infectious lesions are common[29–31] has rarely been investigated as an independent topic in previous studies[32,33] and is undertaken as just one step in therapeutic tumor resection in most cases.[34,35] Currently, although TNA and TOA techniques are widely utilized in myelopathy, rheumatism and trauma in C1 and C2;[34–36] however, to the best of our knowledge, there are no specific reports that comprehensively investigate the biopsy for atlas and axis vertebral lesions *via* TNA and TOA, which contain more than four clinical cases.[36–38] Also, compared to the other vertebrae, the tumor occurrence in atlas is quite low, in which the lesion involving the anterior arch of the atlas is quite rare (<1% in all vertebral lesion).[39] Therefore, there exists limited specific description for the TNA biopsy of the anterior arch of the atlas in previous investigations.[32–34]

Transoral and transnasal approaches have been developed extensively in the surgical treatment of the head and neck,[16–18] and the surgical field is generally limited cranially in a transoral approach and caudally in a transnasal approach.[40,41] The inferior limit of craniocervical lesions that can be reached *via* an endoscopic endonasal approach is therefore well investigated and expressed as the nasopalatine line, naso-axial line, or rhinopalatine line.[41–43] A recent study also indicated that the sphenoid-occipital junction represents the cranial limit of TOA surgery to the CVJ region.[44] However, transoral and transnasal biopsies in which there are more limited longitudinal retropharyngeal incisions may require a less minimally invasive operative region in the vertical direction compared to surgeries *via* the same approach. Moreover, the coronal and sagittal safe ranges for cervical vertebrae biopsy *via* TNA and TOA have seldom been investigated.[45,46] The surgeons who perform the vertebral biopsy for intraosseous oncological and infectious pathologies usually formulate their strategy only after referring to multiple factors, including the radiographic features, vascularization of the lesion and the structural integrity of vertebral body edges on preprocedural computerized tomography (CT) and magnetic resonance imaging (MRI),[3,47,48] and the diagnostic yield can be higher than 90%.[32,33] However, these factors have rarely been investigated to indicate the technical application and tool selection in particular ventral approaches to C1 and C2 for diagnostic biopsy. Currently, extensive investigations have been conducted to elaborate the biopsy steps and application of novel auxiliary equipment.[47–49] In contrast, less attention has been given to the systemic summary and analysis of biopsy core techniques (BCTs), which may elevate the biopsy histopathologic yield and decrease the complication rate in routine biopsy (as was the applicable situation and the collaborative utilization of these BCTs[37,38]). To the best of our knowledge, demonstration of the application of the core biopsy technique, measurement of the three-dimensional secure biopsy range, characterization of individual lesions, assessment of histopathological yield and analysis

of clinical data have never been integratively investigated in biopsies of upper cervical vertebrae *via* TNA and TOA.

Based on the clinical background above, our study aims to systemically investigate the biopsy for ventral atlantoaxial pathologies *via* TNA and TOA, describe the details of relevant biopsy techniques, analyze the periprocedural precautions and assess the postprocedural outcomes. The specific purposes of this study are stated as follows: (i) to preliminarily determine the measurements of the surgical corridor and coronal, sagittal and vertical biopsy safe ranges in TNA and TOA biopsies for the atlantoaxial region: (ii) to introduce four original biopsy core techniques as well as their scope of application based on the lesion characteristics; and (iii) to document the diagnostic histopathologic yield and complication rates of TNA and TOA biopsies for C1 and C2 pathologies.

Methods

Patient Information, Inclusion and Exclusion Criteria

This study was conducted in Qilu Hospital of Shandong University with the approval of the Institutional Ethics Committee (No. LL-2013-1-029). All of the patients signed relevant informed consent forms. Correlating data from our institution on nine patients (eight males and one female with an average age of 58.11 ± 11.60 years) from July 2014 to May 2021 were gathered and included in this study according to the inclusion and exclusion criteria displayed below.

The inclusion criteria included: (i) patients with lesions in the ventral atlas and/or axis vertebrae; (ii) patients whose pathologies required biopsy for definitive diagnosis; and (iii) patients with lesions that were more suitable for selecting transoral or transnasal approaches compared to percutaneous approaches. The exclusion criteria included: (i) patients who were unable to tolerate the biopsy due to coagulopathy, severe cardiovascular diseases, or other surgical contraindications; (ii) patients who have undergone diagnostic or therapeutic surgery in other hospital medical institutions; and (iii) patients who did not consent to the inclusion of their private clinical information in this study.

Localization and Characterization of Lesions

The vertebrae were divided into 12 radiating zones based on the Weinstein–Boriani–Biagini surgical staging system.[50] In this study, all the TNA and TOA biopsy procedures were performed for the lesions located in the anterior arch of the atlas and the vertebral body of the axis, which means the region of zones 4–9 and layers A to C according to WBB Surgical Staging System described by Boriani *et al.*[50] An isolated pathology involving only the odontoid process was not observed in this study.

The radiographic appearances of the lesions were recorded, as were their blood supplies. Therefore, the pathologies were divided into osteolytic lesions, sclerotic/osteoblastic lesions and mixed lesions judged by CT. Lesions with rich blood supply were estimated by contrast-enhanced MRI and especially recorded. We also assessed whether the anterior or posterior vertebral body edge was partly or totally damaged, and the path of the prebuilt biopsy corridor should be maximum avoided from the damaged posterior vertebral body edge.

Biopsy Core Techniques

Four BCTs in TNA and TOA biopsy, the application of which may promote the surgeons to yield adequate pathological tissue and to avoid intraprocedural risks, are specifically elaborated based on our original research.

BCT 1: Lesion Perforating

Lesion perforation was conducted by trocar penetration to traverse the pathological tissues, reach the lesion margin on the opposite side, and attempt to acquire samples (Fig. 1A). This BCT enlarged the effective range to contact the lesion and facilitated the tissue extractions at multiple points and the implementation of cutting-and-scraping if necessary. The performance of lesion perforation should be confined to the safe range for biopsy.

BCT 2: Aspiration

Aspiration refers to the process of an empty syringe containing an appropriate amount of normal saline being attached to the biopsy trajectory to give 3–5 ml negative pressure after the biopsy trajectory had accessed the lesion region (Fig. 1B). The lesion was then irrigated with saline. Bleeding must be closely supervised during this BCT. If excessive bleeding should occur, the interruption of aspiration and thorough surgical hemostasis should be performed immediately. In this situation, we would obtain the typical samples gently by biopsy forceps and finish the whole biopsy procedure as soon as possible.

BCT 3: Cutting-and-Scraping

Cutting-and-scraping was performed by the serrated edge of the trephine at the tip of the trocar to separate and curette the pathological samples within the lesion or on the internal lesion rim. The performance of this BCT should be strictly confined to the biopsy trajectory and forbidden in normal tissues.

BCT 4: Biopsy Forceps Utilization

According to our research, the biopsy forceps or bone biopsy core needle (Gallini or PARAGON 09G15Cm/14G20Cm) was chosen to obtain samples, in which the biopsy forceps were utilized on appropriate occasions (Fig. 1C,D). For pathologies with rich blood supply, the biopsy forceps were preferentially recommended due to their less invasive nature; however, the biopsy forceps were not suitable for sclerotic or osteoblastic lesions compared to the core needle. Both biopsy forceps and core needles were suitable for lesions with osteolytic appearance.

Cooperative Application of BCTs

In considerable circumstances, the four BCTs should be proficiently and cooperatively rather than separately utilized

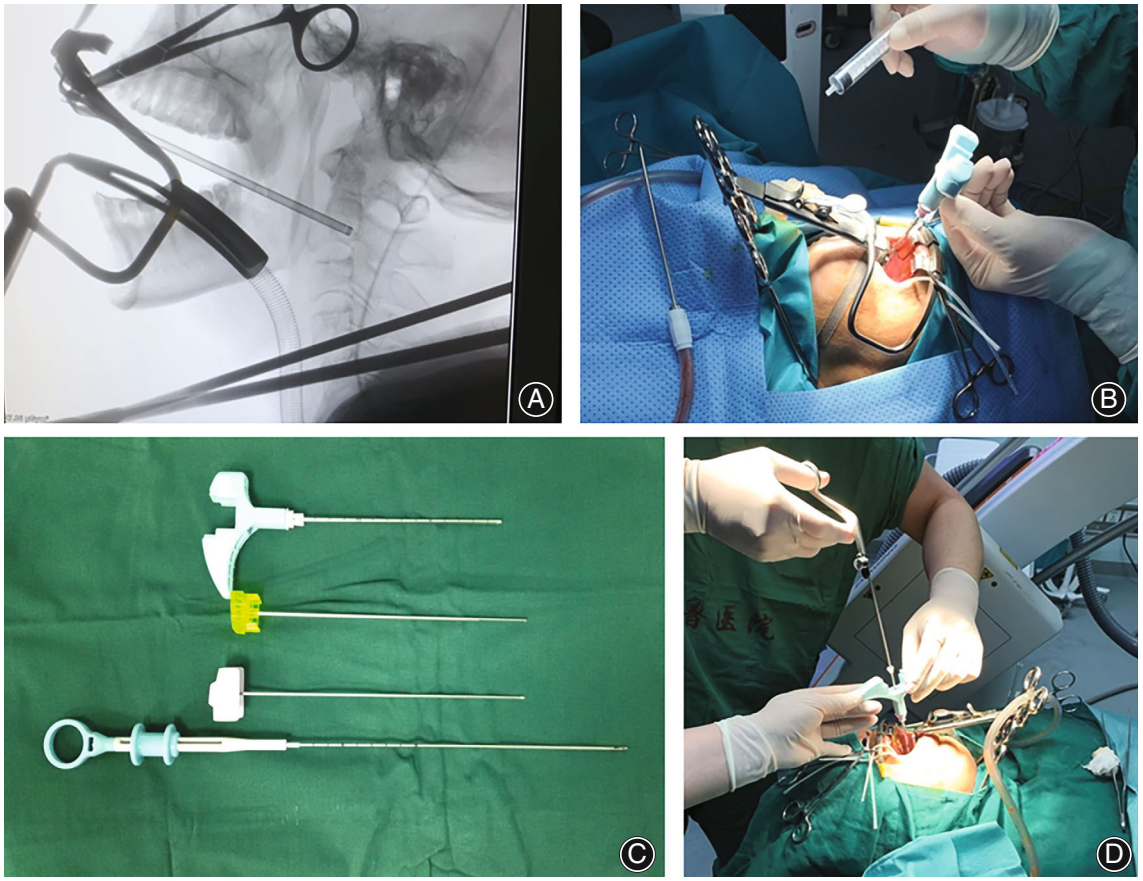

Fig. 1 The application of biopsy core techniques. (A) Lesion perforation under C-arm fluoroscopy. (B) The aspiration performed after the establishment of the biopsy corridor. (C) The bone biopsy core needle and biopsy forceps. (D) Biopsy forceps utilization in the pertinent case

after a coaxial biopsy trajectory reaching the pathology was established. For example, we often performed cutting-and-scraping when lesion perforation occurred and selected biopsy forceps for intraosseous fibrous tumors. Osteolytic or cystic samples were extracted by either biopsy core needle or forceps after the combined applications of lesion perforation, aspiration, and cutting-and-scraping. For lesions with sclerotic/osteoblastic features, it was vital to implement cutting-and-scraping and to choose a core needle for biopsy procedures.

Biopsy Procedure

The performance of TNA biopsies required endoscopic assistance, while all TOA biopsies were conducted under direct scope. TOA biopsy is described below, and TNA biopsy was performed as described previously.[51]

Preprocedural Intervention

After general anesthesia and orotracheal intubation, the patient was placed in a supine position, and the oral cavity and retropharyngeal mucosa were sterilized. A mouth gag was positioned to expose the oral cavity (Fig. 2A), and then the uvula was dragged out of the original position through the nasogastric tubes that were sutured to the uvula and pulled through the nasal cavity (Fig. 2B), thereby clearly revealing the oral and oropharyngeal scope (Fig. 2C).

The anatomic and stereotactic navigations were synergically utilized for the guidance of the biopsy. Anatomical navigation relies heavily on the surgeon's clinical experience for bony and soft tissue. This navigation showed more accuracy in distinguishing the bilateral parts of the vertebrae and roughly orientated the sagittal directions. Stereotactic navigation was performed under C-arm fluoroscopy or CT. In most situations, we preferred C-arm fluoroscopy in the operating room rather than CT scanning if the lesion was able to be identified due to its convenience and cost effectiveness for the patient. The caudal retropharyngeal space below the operative area was tamped with cotton to avoid contamination and clots that could obstruct the trachea.

Intraprocedural Steps

With reference to the collaboration of anatomical and stereotactic navigations, the hub of a radiopaque needle was inserted into the retropharyngeal space to locate the

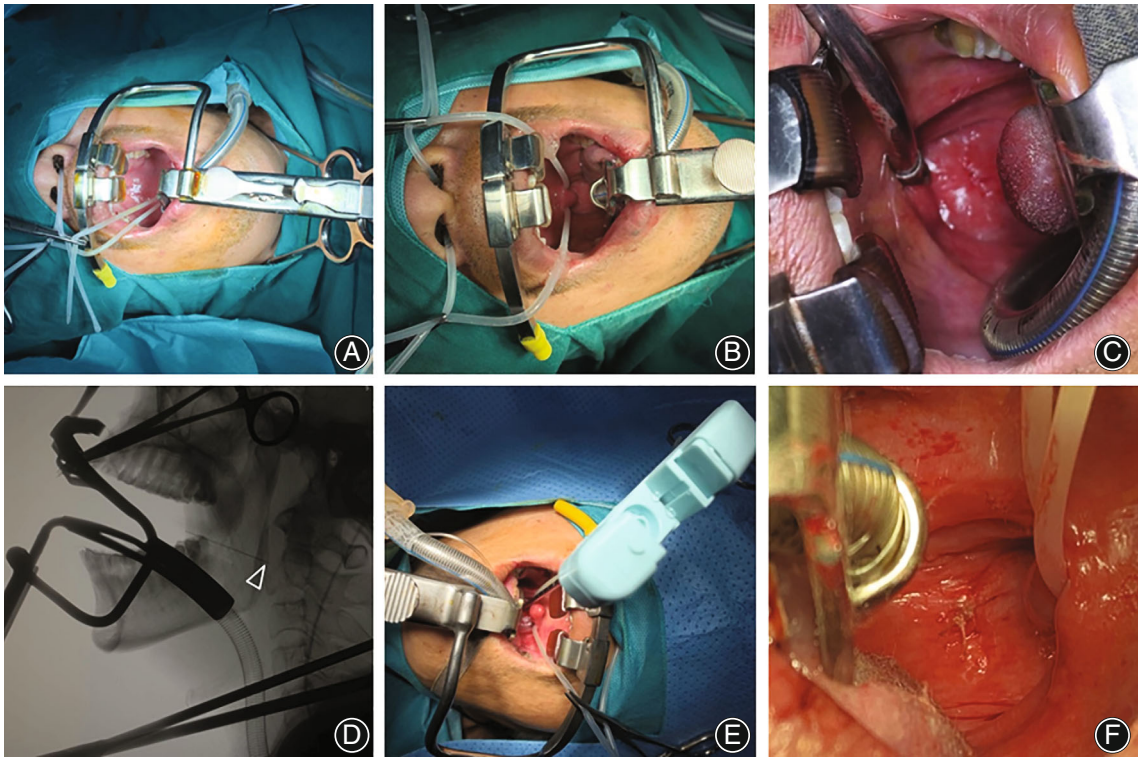

Fig. 2 The manipulation of the biopsy procedure. (A) The disposal of the oral cavity by the self-retaining transoral system. (B) The retracted uvula attached to the silicone tubes. (C) The oral and oropharyngeal soft tissues were exposed. (D) Preprocedural localization by a radiopaque needle (arrowhead). (E) The complete establishment of the biopsy trajectory. (F) Posterior pharyngeal wall sutured with absorbable sutures

trajectory for biopsy (Fig. 2D). After fluoroscopic determination, the radiopaque needle was withdrawn, and a sharp stylet pierced the posterior wall of the pharynx with a 3 mm incision allowing the bone biopsy trocar system to access the anterior border of the vertebra through the mucosal incision. The coaxial technique, which contributed to establishing the biopsy trajectory through the trocar, guaranteed that the whole biopsy procedure was confined to a fixed corridor and thus allowed the reusable and multipoint obtainment of samples (Fig. 2E). With appropriate application of the BCTs, samples were extracted through the biopsy corridor. To guarantee the abundant samples obtained, multiple punctures were performed. In all patients, at least two puncture points were selected, with multiple biopsy directions and sufficient biopsy depth. After harvesting the pathologies, the surgeons primarily identified whether each sample was well-defined tumor tissue. In osteolytic and mixed lesions, heparinized saline can be used to soak the pathologies in vertebral blood, avoiding coagulation. After that, the obtained pathological tissues were presented on sterile gauze for macroscopic selection. The trocar system was retracted after adequate biopsies were obtained, and the pharyngeal mucosal incision was sutured with absorbable sutures and pressurized for 10 min (Fig. 2F). To avoid intraoperative bleeding for vertebral tumors with abundant blood, aspiration, as a BCT, should be minimally conducted, so intraprocedural extensive destruction of tumor tissue should be avoided. Meanwhile, biopsy forceps were preferentially utilized to obtain the samples. All samples were delivered to the pathology department for routine histopathological examinations.

Periprocedural Precautions

Each patient was given daily oral or nasal cleansing and received the prophylactic application of cefuroxime 30 min before the biopsy (0.5 mg atropine was also given 30 min before the biopsy to negatively regulate the secretion of pharyngeal glands). To avoid postoperative hematoma for pathologies with rich blood supply, gelatin sponges were applied to tamp the operation region, and sterile cottons were utilized for local compression to avoid postoperative hematoma when the biopsy procedures were finished. After the biopsy, each patient was given total parenteral nutrition for 1–5 days, and the nurse in charge gave each patient daily oral or nasal care and disinfection.

Intra- and Periprocedural Data/Complications

The preoperative and postoperative hematological tests included routine blood, blood biochemistry, erythrocyte

sedimentation rate and C-reactive protein tests. All data collected were recorded. All patients were requested to fill out a visual analogue scale (VAS) to assess pain.[52]

The electronic medical record of each patient was reviewed for evidence of intraprocedural and postprocedural complications within 30 days of the biopsy. The threshold definition for intraprocedural complications in our study included excessive bleeding, hematoma, intraoperative hypertension or hypotension, arrhythmia, cerebrospinal fluid leakage and the related symptoms. Postprocedural complication thresholds included hematoma, infection, anemia, dysphagia, pharyngeal edema or swelling, dyspnea, velopharyngeal insufficiency, dysphonia, myelopathy and lower cranial nerve symptoms.

Radiographic Measures

In this study, several parameters were measured on preprocedural CT images and MRI to indicate the biopsy trajectory and biopsy safe range. Each parameter is separately illustrated below.

Depth of the Biopsy Trajectory

The depth of the biopsy trajectory was defined as the distance from the nasal or oral entry points to the penetrating point of the anterior pathological margin.

Coronal Distance of Biopsy Safe Range

The coronal distance of the biopsy safe range referred to the length of the posterior pharyngeal wall or retropharyngeal space on the targeted biopsy coronal plane.

Sagittal Distance of Biopsy Safe Range

The sagittal biopsy safe range was determined as the distance between the anterior and posterior nonpathological vertebral areas (between the anterior and posterior vertebral body edges if the lesion traversed the whole vertebral body) and was measured in a collinear manner to the biopsy trajectory.

Vertical Distance of Biopsy Safe Range

In this study, the superior and inferior safe margins of TNA biopsy were the middle third of the clivus[53] and rhinopalatine line,[43] respectively, as previously described. The inferior border of the C1 anterior arch and anteroinferior aspect of the C2 vertebral body were chosen as the cranial and caudal margins for TOA biopsy, respectively. This distance was believed to be within the vertical limitation of TOA in recent researches.[44,54]

Evaluation for Selecting Different Approaches

To evaluate the rationality for selecting TNA to C1 anterior arch and TOA to C2 vertebral body biopsy, we also measured the depths and angles of the biopsy trajectories to ventral C1 and C2 when selecting different approaches. The virtual biopsy trajectories for C2 biopsy *via* TNA and C1 anterior arch *via* TOA were thereby established, and the angles of different biopsy trajectories were measured based on a previous description.[45] For further assessments, we also analyzed the relationship between different approaches and the involvement of the hard palate, maxillary bone and soft palate in all patients.

Statistical Analysis

Data were analyzed using SPSS 21.0 (IBM, Armonk, NY, USA). Student's *t*-test was used to quantitatively analyze the significant differences between the preprocedural and postprocedural VAS scores and hematological indexes, including hemoglobin, white blood cells, erythrocyte sedimentation rate, and C-reactive protein. A paired *t*-test was used to quantitatively analyze the significant differences between the different approaches. Statistical significance was set at $P < 0.05$. $P < 0.01$ was considered highly statistically significant.

Results

Demographic Data and Lesion Characteristics

Nine patients harboring different lesions involving C1 or C2 were enrolled in this study. Minimally invasive biopsy procedures were successfully performed in nine patients, in which eight patients and one patient underwent TOA biopsy for axial pathology and TNA biopsy for atlas pathology, respectively.

Before each biopsy, the depth of the biopsy trajectories and biopsy safe ranges were measured on CT images. The mean biopsy trajectory depth and coronal, sagittal and vertical distances of biopsy safety ranges were 85.00 ± 5.88, 20.63 ± 4.75, 16.25 ± 1.49 and 24.63 ± 2.26 mm in all TOA patients, respectively, and these corresponding data were 95, 33, 10 and 26 mm in the TNA patient (Fig. 3A,B; Table 1). These parameters were mainly measured on CT images; however, MRIs may also be referenced (Fig. 3C). After all parameters were measured, the biopsy safe ranges were visualized on 3D reconstructed models (Fig. 3D).

The virtual biopsy trajectories for C2 lesions *via* TNA and C1 lesions *via* TOA were successfully created in all patients. For the pathology in the C1 anterior arch, the depth of the biopsy trajectory in TNA was shorter than that in TOA (95 mm in TNA *vs.* 102 mm in TOA), as was the straighter angle of the biopsy trajectory (95° in TNA *vs.* 76° in TOA) (Fig. 3E). For the lesions in the C2 vertebral body, the average depths of the biopsy trajectories were 85.00 ± 5.50 and 96.88 ± 7.91 mm in the TOA and TNA, respectively, showing a highly statistically significant difference ($P < 0.01$) (Fig. 3F). Moreover, the mean angles of the biopsy trajectories were $90.13° \pm 3.69°$ and $107.75° \pm 4.41°$ in the TOA and TNA, respectively, also leading to a highly statistically significant difference ($p < 0.01$) (Fig. 3F). In all patients with C2 lesions, the inferior margin of the lesion could not be completely reached *via* TNA due to the interruption of the hard palate and maxillary bone, and the soft palate was involved in biopsy if TOA was chosen for C1 (Fig. 3E,F).

Six osteolytic lesions, one osteoblastic lesion, and two mixed lesions were present on the CT images for all patients

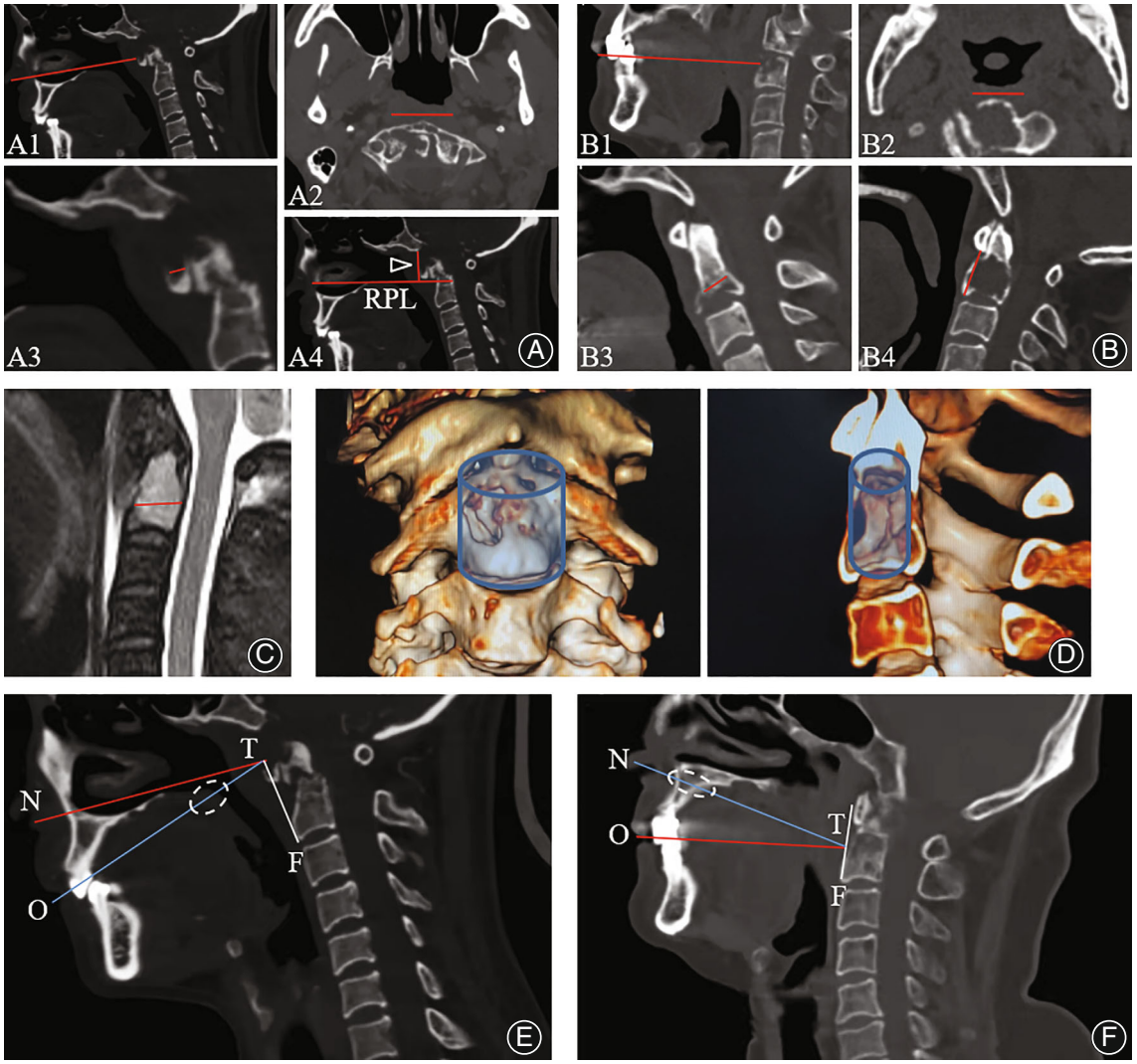

Fig. 3 Radiographic measurements for biopsy trajectory and biopsy safe range and prebuilt stereotactic biopsy model. (A) The measurements for transnasal endoscopic approach (TNA) biopsy on CT images showing depth of biopsy trajectory (A1), coronal distance (A2), sagittal distance (A3) and vertical distance (A4) of biopsy safe range. The vertical biopsy safe range (arrowhead) and rhinopalatine line (RPL) are displayed in A4. (B) The measurements for transoral approach (TOA) biopsy on CT images showing depth of biopsy trajectory (B1), coronal distance (B2), sagittal distance (B3) and vertical distance (B4) of biopsy safe range. (C) The measurement of the sagittal biopsy safety range for TOA biopsy on MRI. (D) The preplanned safe biopsy ranges (blue areas) on reconstructed stereotactic 3D models. (E) The evaluation of different biopsy trajectories for lesions in the C1 anterior arch *via* TNA (red line) and virtual TOA (blue line). ∠NTF and ∠OTF represent the angles of the biopsy trajectories *via* TNA and TOA, respectively. The involvement of the soft palate is shown (dashed lines). Point T, the target biopsy point of the lesion; point F, intersection of the anterior and inferior borders of the axis; point N, the entry point *via* TNA; point O, the entry point *via* TOA. (F) The evaluation of different biopsy trajectories for lesions in the C2 body *via* TOA (red line) and virtual TNA (blue line). ∠NTF and ∠OTF represent the angles of the biopsy trajectories *via* TNA and TOA, respectively. The involvement of the hard palate and maxillary bone is shown (dashed lines). Point T, the target biopsy point of the lesion; point F, intersection of the anterior and inferior borders of the axis; point N, the entry point *via* TNA; point O, the entry point *via* TOA

(Fig. 4A-C). Seven of these pathologies showed rich blood supply (Fig. 4D). The anterior and posterior vertebral body edges were partly damaged in eight (88.9%) and six (66.7%) patients, respectively, and total destruction of the vertebral body border was not observed in any patients (Fig. 4E). Sequentially, the potential preferential selection of biopsy core needle or biopsy forceps was determined by the radiographic findings (Table 2).

Biopsy Procedure and Clinical Outcomes

In this study, all of the pathologies invaded zones 5 to 8; therefore, all the puncture points on the anterior vertebral

TABLE 1 Demographics and radiographic measurements of patients

ID/ sex/age	Vertebra	Approach	Depth of biopsy trajectory (mm)	Coronal distance of BSR (mm)	Sagittal distance of BSR (mm)	Vertical distance of BSR (mm)
1/M/34	C1	TNA	95	33	10	26
2/F/59	C2	TOA	77	16	15	22
3/M/52	C2	TOA	81	17	16	25
4/M/69	C2	TOA	81	21	16	25
5/M/61	C2	TOA	90	29	15	26
6/M/66	C2	TOA	89	26	18	28
7/M/48	C2	TOA	93	16	15	26
8/M/65	C2	TOA	89	21	16	21
9/M/69	C2	TOA	80	19	19	24

Abbreviations: TNA, transnasal endoscopic approach; TOA, transoral approach; BSR, biopsy safety range.

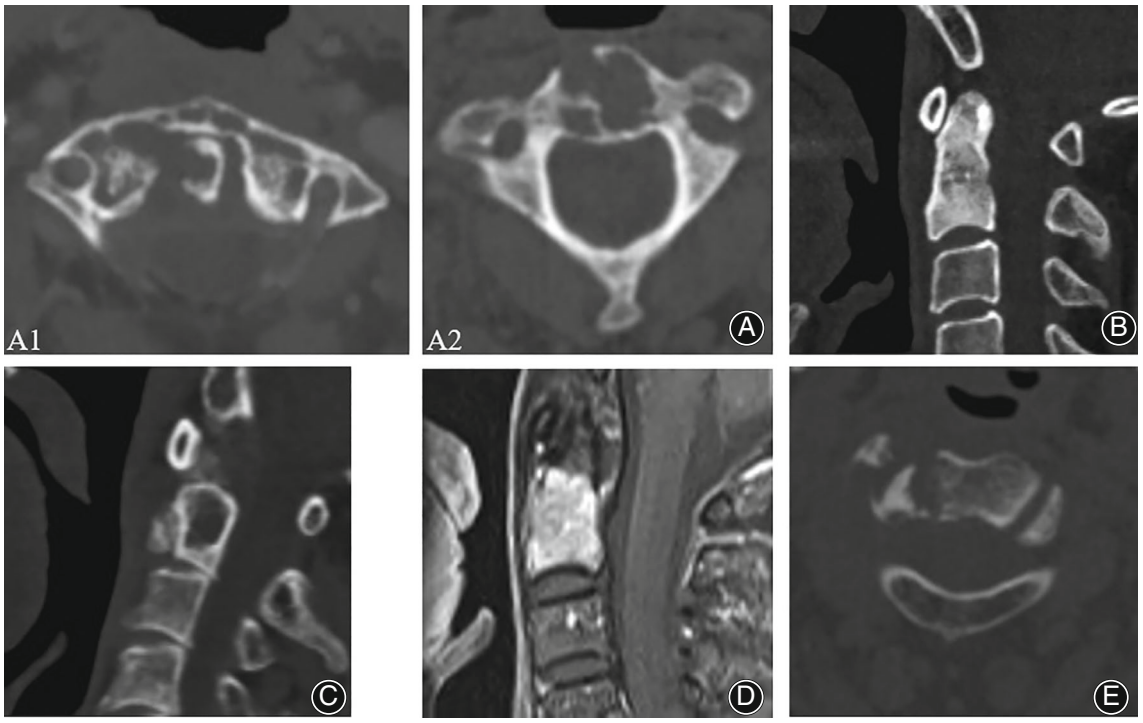

Fig. 4 Radiographic characteristics of lesions. (A) The osteolytic appearance of lesions in atlas vertebrae from patient 1 (A1) and axis vertebrae from patient 4 (A2) shown on CT images. (B) The osteoblastic appearance of the lesion from patient 6 shown on reconstructed sagittal CT images. (C) The mixed lesion with osteolytic and sclerotic appearance from patient8 shown on reconstructed sagittal CT images. (D) Lesion with rich blood supply from patient 4 judged by MRI. (E) Partially damaged anterior and posterior vertebral body edges of axis vertebra from patient 2

edge of the C1 anterior arch or C2 vertebral body were confined to zones 6 and 7. Based on the radiographic features and intraprocedural findings, appropriate BCTs were utilized, and the cooperation of multiple BCTs was conducted in all patients to facilitate the multiple-point extraction, negative pressure suction and splitting of typical samples. Bone biopsy core needle and biopsy forceps were chosen in three and six cases, respectively, and the selection of biopsy implement for each patient was consistent with preprocedural evaluation. In five patients with osteolytic rich blood supply lesions, a portion of pathologies were obtained through vertebral blood. Fortunately, no lesions with excessive bleeding were found in any of our patients; therefore, no core technique was interrupted. All biopsies were undertaken within their individual biopsy safe ranges. Repeat biopsies (open surgical biopsies) were not performed in any of our cases.

Sufficient tissue for histopathologic analysis was obtained in all cases, for a diagnostic yield of 100%. The

TABLE 2 The radiographic features of pathologies and preferential biopsy instruments

ID	Lesion characteristic	Blood supply	Anterior vertebral body edge	Posterior vertebral body edge	Preferential biopsy instrument
1	Osteolytic	Rich	Partly damaged	Partly damaged	Forceps
2	Osteolytic	Rich	Partly damaged	Partly damaged	Forceps
3	Mixed	/	Partly damaged	Intact	Needle
4	Osteolytic	Rich	Intact	Intact	Forceps
5	Osteolytic	/	Partly damaged	Intact	Forceps/needle
6	Osteoblastic	Rich	Partly damaged	Partly damaged	Needle
7	Osteolytic	Rich	Partly damaged	Partly damaged	Forceps
8	Mixed	Rich	Partly damaged	Partly damaged	Needle
9	Osteolytic	Rich	Partly damaged	Partly damaged	Forceps

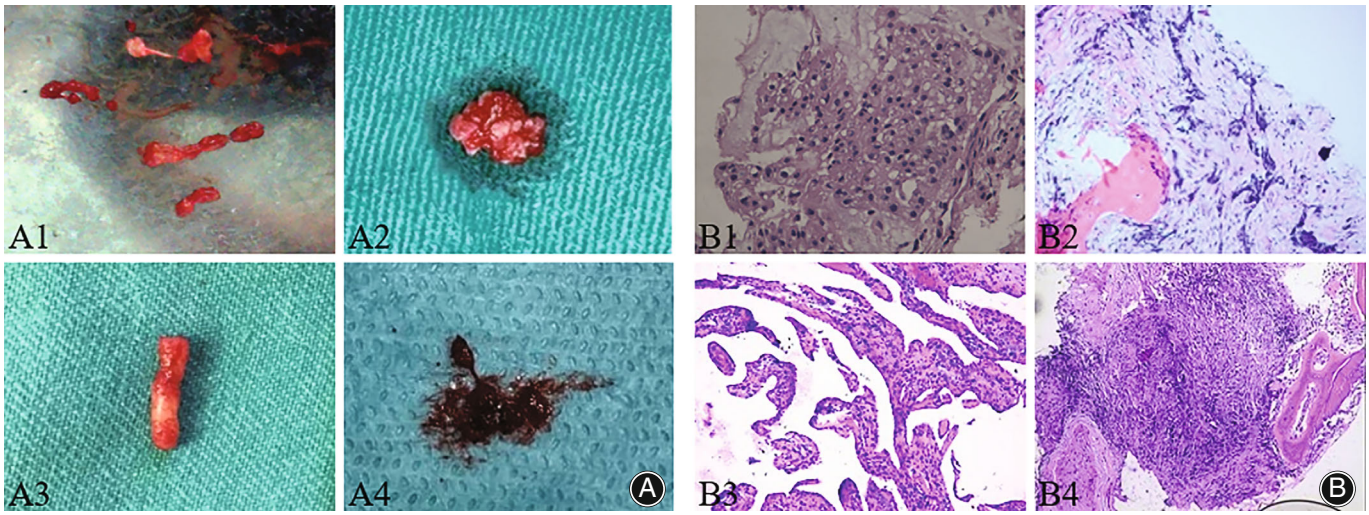

Fig. 5 Macroscopic and microscopic characteristics of the obtained biopsies. (A) The gross appearance of biopsies. (A1) Yellowish, gelatinous mass from patient 1.[51] (A2) Gray-white and gray-red hard mass from patient 6. (A3) Gray-red solid mass from patient 8. (A4) Gray-red soft mass from patient 7. (B) The histopathological characteristics of biopsies. (B1) Chordoma (after immunohistochemical identification) from patient 1.[51] (B2) Metastatic tumor cells infiltrated by inflammatory cells (after immunohistochemical identification) from patient 6. (B3) Vertebral hemangioma (after immunohistochemical identification) from patient 8. (B4) Acute and chronic inflammatory cells and normal osseous tissues from patient 3

gross appearances (including matter state, shape, color, etc.) of the intraprocedural obtained biopsies were described and recorded to macroscopically judge whether the samples belonged to pathological or normal osseous tissues (Fig. 5A). The longest axis of each sample showed an average length of 5.44 ± 1.51 mm, ranging between 3 and 8 mm (Table 3). The final pathologic confirmation of these biopsies revealed three metastatic tumors, two chordomas, two vertebral hemangiomas, one plasma cell myeloma and one inflammatory lesion (Fig. 5B; Table 3). Surgical treatment was performed in five patients, and all the postoperative pathological results were consistent with the biopsies showing 100% sensitivity and specificity. As in three typical cases, the radiographical and pathological characteristics of one osteolytic lesion (from patient 1), one osteoblastic lesion (from patient 6) and one mixed lesion (from patient 8) are illustrated in a series of images (Figs 4 and 5).

Intraprocedural and Periprocedural Data/Complications

All patients underwent the biopsy procedures for an average of 42.78 ± 9.72 min. There was no intraprocedural visual evidence of hematoma, and the measurements of intraprocedural blood loss were 0–5 ml. All patients showed normal blood pressure during their biopsies. No statistically significant differences were found between preprocedural and postprocedural blood indexes or in VAS scores (Table 4). Electrolyte disorder, hyperproteinemia and hypoproteinemia were nonexistent in this study. The mean duration of postprocedural total parenteral nutrition for all patients was 2.67 ± 1.12 days, and none of our patients exhibited feeding difficulties after oral fluid and food intake. One patient (Patient 5) experienced pharyngitis that was assessed by a respiratory physician before biopsy and recovered after receiving aerosol inhalation of expectorant and levofloxacin.

TABLE 3 Intraprocedural findings and pathological results of the biopsies

ID	Maximum length of obtained biopsies (mm)	Number of obtained biopsies	Gross appearance	Result of histopathological examination
1	5	3	Yellowish, gelatinous mass	Chordoma
2	5	1	Reddish, gelatinous mass	Chordoma
3	3	1	Gray-white and gray-red mixed mass	Inflammation
4	5	3	Sarcoid strip-like tissue	Metastatic tumor (renal cancer)
5	6	1	Gray-white and gray-black solid mass	Vertebral hemangioma (infiltrate by inflammatory cells)
6	8	1	Gray-white and gray-red hard mass	Metastatic tumor (lung cancer or thyroid cancer)
7	4	3	Gray-red soft mass	Plasma cell myeloma
8	6	2	Gray-red solid mass	Vertebral hemangioma
9	7	1	Sarcoid strip-like tissue	Metastatic tumor (carcinoma of the ureter)

We did not observe any intraprocedural complications requiring surgical revision, nor did we observe postprocedural complications in the follow-up period (1–39 months). All patients showed good incision healing on the posterior pharyngeal mucosa with no swelling or infection. No signs of abscess, acute pharyngitis, or hematoma were observed during the postprocedural period. The mean duration of hospital stay was 7.67 ± 1.32 days (range: 6–10 days). All nine patients were discharged uneventfully (Table 4).

Discussion

The Necessity of TNA and TOA Biopsies for Ventral C1 and C2

Currently, the surgeon has a large armamentarium of surgical approaches available to safely treat lesions in CVJ, which include TNA and TOA techniques;[55–59] however, the application of TNA or TOA for diagnostic biopsy is rare.[38] Compared to a traditional lateral percutaneous approach with potential risks for neurovascular injury,[8,60–62] biopsies *via* transnasal and transoral approaches to ventral C1 and C2 may elevate the diagnostic yield, reduce the intraprocedural risk and decrease the complication rates; however, the related technical application and periprocedural precaution have not been comprehensively investigated in previous studies.[36,37]

In this study, we elaborated the biopsy procedure for ventral atlas and axis vertebral pathologies and our results reveal that: (i) both transnasal and transoral approaches to C1 and C2 are appropriate and secure biopsy pathways for pathologies located in the anterior vertebral body; (ii) high diagnostic yield and low complication rates in TNA and TOA biopsy for the anterior atlas and axis vertebrae are verified; and (iii) it is vital to conduct in-depth preprocedural planning, select appropriate core technique application, outline scientific surgical steps and be aware of periprocedural precautions in each biopsy to achieve an optimistic prognosis. To the best of our knowledge, this is the first systematic analysis of the TNA and TOA biopsy for ventral vertebral pathologies of the atlas and axis.

The Advantages of TNA and TOA Biopsies for Ventral C1 and C2

In previous studies, the predictors of vertical limits in TNA and TOA surgeries have been widely investigated.[44,45] The inferior limit of the endoscopic endonasal approach is expressed as various created lines,[41–43] while the cranial and caudal limits of TOA have also been subjected to extensive research;[41,44] however, little research has been done to determine the coronal and sagittal safe range of TNA and TOA. In this study, the three-dimensional biopsy safe range was estimated, which indicates the more suitable vertical TOA safe borders for diagnostic biopsy compared to previous studies focusing on TOA surgeries.[44,53] Meanwhile, the coronal and sagittal safe ranges were two relatively novel concepts to circumscribe the biopsy field. Thus, the 3D biopsy safe range may not only help to guide the secure manipulation of the biopsy procedure but also provide a stereoscopic "safe region" to the biopsy for upper cervical vertebrae *via* the transnasal or transoral approach. Previous studies on the diagnostic yield and safety of transoral biopsies for upper cervical vertebrae have been limited to four or fewer patients.[36,37] In comparison to TOA, TNA is rarely selected for vertebral biopsy, and most are simultaneously performed with therapeutic surgery.[34,35] Based on the original and successful clinical attempt in this study, we provided an effective alternative method for needle biopsy for anterior arch of the atlas. Although previous attention to the relevant studies is limited,[37,51] we recommend selecting TNA to the C1 anterior arch and TOA to the C2 vertebral body for pathological biopsies because our findings demonstrate that the TNA and TOA within reliable biopsy safe ranges attain 100% diagnostic yield for the biopsies of ventral C1 and C2 lesions, respectively. In this investigation, the shorter depth and straighter angle degree of the biopsy trajectory were shown when selecting TNA to C1 anterior arch and TOA to C2 vertebral body biopsy. Moreover, we found that the hard palate

TABLE 4 Intra- and periprocedural data and complications for biopsy

ID	Biopsy duration	Intraprocedural bleeding	Pre/postprocedural Hb	VAS score	WBC	ESR	CRP	Postprocedural temperature	Duration of parenteral nutrition	hospital stay	Intraprocedural complications	Postprocedural complications
1	60	<5 ml	143/139	1/1	9.38/9.15	2/4	6.85/7.36	37	1	6	No	No
2	55	<5 ml	147/151	2/1	5.99/6.42	16/13	7.24/5.87	35.4	2	8	No	No
3	35	NOB	151/142	1/1	8.16/9.14	15/17	1.43/3.67	36.9	2	8	No	No
4	30	<5 ml	168/163	0/1	6.76/7.04	13/12	4.75/6.12	36.4	3	6	No	No
5	45	NOB	162/141	3/3	10.80/10.16	33/24	15.04/12.39	36.3	5	10	No	No
6	35	NOB	123/130	0/1	4.51/4.97	8/10	0.54/1.23	37	3	7	No	No
7	40	<5 ml	153/140	1/2	5.88/5.62	9/6	1.46/0.91	36.5	3	7	No	No
8	45	<5 ml	142/146	0/1	5.41/5.24	5/11	0.21/1.45	36.8	3	9	No	No
9	40	NOB	146/152	2/1	8.17/7.89	11/9	2.83/3.39	36.2	2	8	No	No
t value			1.073	−0.8	−0.377	0.465	−0.451					
p value			0.315	0.447	0.716	0.654	0.664					

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; NOB, no overt bleeding; VAS, visual analog scale; WBC, white blood cell.; *P* value <0.05 was set for data to be statistically significant.

notably confines the C2 biopsy region *via* TNA; meanwhile, there are potential risks for the injury of the soft palate due to this structure located on the biopsy corridor when selecting TOA for the biopsy of ventral C1 lesions. Based on the above analysis, the rationality for selecting TNA to C1 anterior arch and TOA to C2 vertebral body biopsy was proven, revealing that such alternative choices were more direct, effective and rational.

Percutaneous biopsy is a mainstay for pathologies in vertebrae;[32,47] however, the percutaneous approach may not be the preferential alternative to TOA and TNA for the biopsy route to ventral C1 and C2 due to the following points. First, several percutaneous approaches are regarded as "oblique" approaches, in which the biopsy target is often concealed by a delicate tangle of neurovascular structures.[46] Its application appears more suitable and safer in "straight" approaches such as TNA and TOA in which there are no nerves or vessels interposed.[44,46] Second, the location of the vertebral lesion indicates which approach should be used. Some scholars hold the opinion that the transoral approach affords a reasonably wide runway to C1 and C2, while alternative approaches may be more suitable for lower cervical and upper thoracic vertebrae.[63] Last, TOA and TNA allow the shortest, widest, and most direct access to the ventral C1 and C2 when compared to the other approaches in the anterior atlantoaxial region.[26,64] Cox *et al.* reported that 43 patients who underwent percutaneous biopsies for cervical spine showed a diagnostic yield of 95%, in which there were five C2 lesions, and Wiesner *et al.*[33] also evaluated the histopathologic and microbiologic yield for percutaneous cervical bone biopsies in 73 patients, including six oncological lesions in the vertebral body of C1 and C2, their diagnostic yield was 96% and two intraprocedural complications occurred. However, neither of the above studies specifically divided the C1 and C2 into anterior and posterior regions, nor did they mentioned the TOA or TNA biopsies. Compared to previous investigations, the TNA biopsy for the C1 anterior arch and the TOA biopsy for ventral C2 body are applied in our study, acquiring 100% diagnostic yield and 0% complication rate. Therefore, the TOA and TNA biopsy for ventral atlantoaxial regions may guarantee accurate biopsy rates and decrease the risks for biopsy-related complications when comparing to traditional percutaneous approaches.[32,33,46] Moreover, preventing tumor contamination of the surrounding tissue is important in biopsy procedures.[2] Compared to other approaches that may cause tumor contamination for pivotal neurovascular structures, there are several unique superiorities in TNA to the C1 anterior arch and TOA to the C2 vertebral body according to the biopsy procedures in this study. First, the shortest and most rational biopsy corridors would maximally diminish the risk of potential tumor contamination. Second, core needle biopsy possesses fewer opportunities for tumor contamination than open biopsy. Finally, tamping the operation region with gelatin sponges not only decreased the incidence of hematoma but also diminished the occurrence of puncture tract tumor contamination.

Rational and Collaborative Application of BCTs

In this study, we summarize some experiences for the rational and collaborative implementation of BCTs to facilitate their wider applications. Generally, lesion perforation provides a more extensive biopsy range and potential multiple points for obtaining samples, and cutting-and-scraping facilitates the surgeon's acquisition of more typical pathologies, especially for sclerotic or osteoblastic lesions. However, careful attention must be paid not to transgress the posterior safe border and puncture the spinal canal when either lesion perforation or cutting-and-scraping is conducted, especially for lesions with an osteolytic appearance and fragile rim, as well as pathologies causing partial or even total destruction of posterior vertebral body edges. Aspiration, as a widely accepted BCT,[38,47] is conducted to assist the sample acquisition, particularly in cases where samples may be insufficiently obtained even if lesion perforation or cutting-and-scraping has been performed. The negative pressure generated by aspiration may increase the risk of intraprocedural hematoma and postprocedural hidden blood loss; therefore, immoderate negative pressure should be strictly prohibited in this BCT. In our opinion, aspiration may be recommended in lesions with fluid or fibrous tissue and should be conducted with caution in lesions with a rich blood supply. Biopsy forceps were seldom utilized for the upper cervical vertebrae previously[51] and we recommend that once the biopsy forceps are maneuvered, the depth and angle for advancing this biopsy instrument within the coaxial biopsy corridor must be well planned. Reddy *et al.*[37] reported four transoral biopsies on C2 lesions under CT guidance showing a biopsy yield of 50%; however, with utilizing proper BCTs, a higher diagnostic yield (100%) was acquired in this study. Based on our successful attempts, we summarized some rules as follows. First, for general osteolytic lesions, lesion perforation is encouraged, as is the cooperative utilization of aspiration and biopsy forceps. Second, once the pathology shows a sclerotic or osteoblastic appearance, we prefer core bone needles to biopsy forceps due to their strong strength, and cutting-and-scraping is also recommended in this situation. Last, aspiration should be prudently manipulated, and biopsy forceps should be given priority for lesions with abundant blood supply.

The Critical Points in TNA and TOA Biopsies

In addition to the appropriate application of multiple BCTs, the appropriate implementation of biopsy procedures is also pivotal. Therefore, the following critical items that may contribute to the smooth implementation of TOA and TNA biopsy are proposed based on our experiences: (i) compared to tapping the core biopsy needle with a mallet to penetrate tumorous walls which present more resistance,[38] it was determined that a more accurate and less invasive access technique is to spin the core biopsy needle that penetrated the lesion rim with an 100% success rate in this study; (ii) for each TOA patient, a 3 mm mucosal incision was made to avoid mucosal injury caused by direct invasion of the trocar, which further reduced the biopsy-related complication rates; (iii) the cooperation of anatomic and stereotactic navigations, which was seldom discussed in previous studies, should be emphasized in TNA and TOA biopsies. Furthermore, both the TNA and TOA biopsies were not fraught with any complications in this study; therefore, the strict implementation of periprocedural precautions may decrease the risk of infection caused by contamination of the surgical field from oral flora or nasal cavity;[57,60] And (iv) to avoid intraoperative bleeding and postoperative hematoma, we conducted both intraoperative procedures, including averting aspiration or extensive destruction of tumor tissue, and postoperative procedures, including applying gelatin sponges and sterile cotton. As a result, no severe intraoperative bleeding or postoperative hematoma was observed in this study.

Limitations

The main limitations in our study are as follows: first, it must be acknowledged that the TNA and TOA biopsies for the C1 anterior arch and C2 vertebral body, which are associated with rare oncological and infectious morbidities, were undertaken in a relatively modest number of cases.[5,60,65] The universality of our results would be more validated in multicenter and long-term collaborative studies that incorporate larger and prospective series of patients. Second, creating and maintaining experienced multidisciplinary teams may prove to be another limitation of TNA and TOA biopsies for atlas and axis vertebrae. Last, investigations on the compound application of TNA and TOA biopsies for the atlantoaxial region and the latest evolved surgical techniques (e.g., robotic surgery and mixed reality visualization techniques) remain in the preliminary stage.

In conclusion, our study demonstrates that both transnasal endoscopic biopsy for C1 anterior arch and transoral biopsy for ventral C2 vertebral body are safe procedures, with a high diagnostic yield when appropriate biopsy techniques are applied. This research may contribute to increase the opportunity of preoperative diagnostic biopsies for ventral atlantoaxial region in the future.

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Author Contribution

Jianmin Li and Zhenfeng Li designed the study and supervised the investigation. Xianhao Shao conducted the majority of this study and analyzed data. Xianhao Shao prepared the manuscript. Qiang Yang, Ka Li and Zhenfeng Li helped with correlative surgery. Yuan Yao helped with radiographic observations and measurements. Feifei Sun helped with histological and pathological examinations. All authors contributed to the article and approved the submitted version.

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