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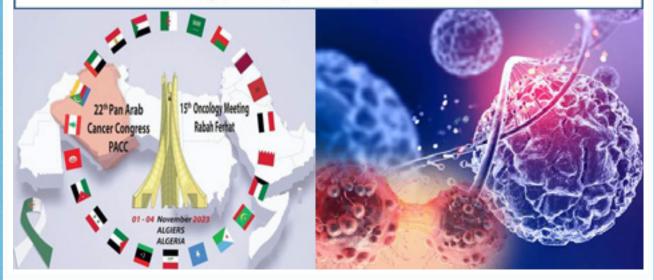
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The External Jugular Vein Cut–Down Method for Chemoport Insertion from a Tertiary Cancer Treatment Center in Central India: A Prospective Study

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Abstract

Introduction: In the realm of oncology, the development of TIVAD (chemoport) has been a blessing for cancer patients, freeing them from having to undergo numerous recurrent venepunctures throughout their treatment. The External Jugular Vein cut–down has been the standard procedure for administering chemotherapy to cancer patients at our institution. Here, we discuss our experience with the External Jugular Vein cut–down Chemoport Insertion Technique and the outcomes it produced.

Materials and Methods: We performed a prospective observational study and included all patients who underwent the open External Jugular Vein cut–down technique of Chemoport Insertion from January 2019 to January 2022 in the Department of Surgical Oncology at our hospital.

Results: Out of 136 patients, 3 (2.2%) had failed external jugular vein (EJV) cannulation, and alternative access (Internal Jugular Vein) was chosen for cannulation. The most common indication for chemoport insertion in our study was carcinoma of the breast, around 72.93% (97/133), and hence the majority of patients were

females, about 84.21% (112/133). Only 18.04% (24/133) were male patients. The age distribution ranged from 2 years to 84 years. Out of 133 patients, complications were observed in 14 patients (10.52%). Around 6 patients (4.5%) had problems with catheter blockage after one cycle of chemotherapy. 4 patients (3%) had port infections at the chamber region (pectoral region). 3 patients (2.2%) had catheter tip displacement into the brachiocephalic vein. 1 patient (0.75%) had extravasation of chemotherapy.

Conclusion: In conclusion, our study demonstrates that the External Jugular Vein cut-down technique offers several advantages in the realm of oncology, as it is a safe, efficient, and straightforward technique for chemoport insertion. With its minimal learning curve and simplicity, this technique represents a favorable initial option for successfully implanting chemoports in cancer patients. Further research and comparative studies are needed to validate and further explore the benefits of this technique in diverse patient populations and healthcare settings.

Keywords: Chemoport, TIVAD, External Jugular Vein, Chemotherapy access port, cut–down technique

Introduction:

Chemotherapy has been administered through central venous access devices since the 1970s. Central venous devices include external central catheters (such as Hickman's catheters), peripherally inserted central catheters (PICC), and subcutaneously implanted venous access devices. Compared to patients with fully implanted venous access devices, patients with external catheters require catheter irrigation and dressing changes more frequently ⁽¹⁾.

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Utilizing totally implantable venous access devices (TIVADs) has revolutionized cancer patients' treatment and

quality of life. The first TIVAD was implanted in 1982 at the MD Anderson Cancer Center in Houston by John Niederhuber using a surgical procedure involving the cephalic vein ⁽²⁾. Without the need for frequent venepuncture, these devices permit chemotherapy infusions, antibiotic delivery, and blood sampling. When long–term venous access is required, particularly for the long–term administration of cytotoxic medications or intravenous targeted therapies to cancer patients, TIVADs are a practical option ⁽³⁾.

There are multiple access sites (internal, external jugular, cephalic, and subclavian veins) and methods (open, percutaneous, and with ultrasound guidance) for insertion of the TIVAD (Chemoport). Chemoports are typically inserted percutaneously via the internal jugular vein or subclavian vein using the Seldinger technique ^(4,5). The External Jugular Vein cut–down technique is an alternate approach to chemoport implantation that is utilized infrequently. The External Jugular Vein cut–down has been the standard procedure for administering chemotherapy to cancer patients at our institution. Here, we discuss our experience with the External Jugular Vein cut–down Chemoport Insertion Technique and the outcomes it produced.

Materials And Methods:

Study Design:

Our prospective observational study included all patients who underwent the Open External Jugular Vein cut–down procedure for Chemoport Insertion in the Department of Surgical Oncology at our hospital between January 2019 and January 2022. All procedures in this study were conducted with institutional Ethical Committee approval and in accordance with the 2013 revision of the 1964 Helsinki Declaration of Ethical Principles.

Exclusion Criteria:

All patients with local skin infections, all patients with deranged coagulation parameters, and those unwilling to consent

Preoperative Preparation:

Chemoport insertion requires a comprehensive evaluation prior to surgery. Focus should be placed on any personal or familial history of bleeding tendencies. The history of central vein cannulation is crucial, as it may have led to thrombosis or stenosis of the central vein. It is essential to obtain a thorough drug history, including inquiries about antiplatelet and anticoagulant medications. Frequently, we search for indicators of enlarged upper thoracic veins, which may indicate a central venous thrombosis. Preoperative laboratory tests consist of a complete blood count, a platelet count, and a coagulation screen. In a highly sterile operating room, chemoport insertion is performed. For adults, local anesthesia with intravenous sedation (IV Promethazine and IV Pentazocine based on body weight) is administered; for children, general anesthesia is administered. We always administer one dose of IV antibiotic prophylaxis prior to procedures.

Surgical Anatomy of the External Jugular Vein:

The external jugular vein passes obliquely and superficially to the sternocleidomastoid muscle and deep to the platysma. The external jugular vein begins near the angle of the mandible, at the junction of the posterior division of the retromandibular vein with the posterior auricular vein. It usually ends by piercing the superficial investing layer of deep fascia and joining the subclavian vein, although it can also terminate in the internal jugular ⁽⁶⁾.

Our Open External Jugular Vein cut down Surgical Approach:

The patient is positioned supine with the neck extended (using a spongebag at the level of the scapula) and the head turned to the opposite side. In this External Jugular Vein cut–down method (Figure 1), a 1–2 cm supraclavicular transverse incision is made one finger above the clavicle at the external jugular vein (EJV) prominence seen by head tilt or Valsalva maneuver. The incision is carefully deepened, dividing the platysma until the EJV is identified; it is then dissected, hooked, and controlled with one proximal and one distal suture.

A second transverse incision is made in the anterior chest, two fingers below the collarbone, to establish a subcutaneous pocket. In order to prevent rotation, the chemoport chamber is affixed to the pectoral fascia in three places (Figure 2). The requisite catheter length is then



Figure 1. Marking of the neck incision (purple arrow) over EJV and the chest/pectoral region incision (black arrow) for the chemoport chamber

The External Jugular Vein Cut–Down Method for Chemoport Insertion, Sandeep Ghosh, et. al.

measured from the chamber to the EJV and down to the sternal angle. The excess catheter length is then trimmed.

The catheter enters the neck by creating a subcutaneous tunnel through the chest incision (Figure 3). The catheter is then secured to the chamber of the chemotherapy port. The chemoport chamber is pierced with a needle, and heparinized saline is infused into the catheter to evacuate air.

EJV is held with mosquito forceps on both sides during venous cut–down, the catheter is allowed to proceed freely through the lumen (Figure 4), and fluoroscopic guidance (C–arm machine) confirms catheter tip location at the

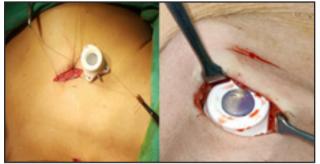


Figure 2. Chemoport chamber fixed to the pectoralis fascia (3–point fixation) in the subcutaneous pocket



Figure 3. Subcutaneous tunneling passing the catheter from the chest pocket to the neck wound next to the EJV before venotomy

intersection of the SVC and right atrium. To prevent a sharp kink at the EJV entrance, the catheter curve is maintained in a "gentle" shape. Prior to catheter closure, blood backflow is examined to ensure catheter patency. The neck and chest incisions are thoroughly rinsed with saline solution before being sutured (Figure 5).

Six hours after surgery, all patients underwent a standard chest radiograph to confirm and verify catheter tip placement at the SVC or its junction with the atrium (Figure 6) and to screen for complications such as pneumothorax. During catheter insertion, all patients underwent electrocardiographic monitoring to detect any arrhythmia induced by atrial irritation.



Figure 4. Venotomy wound and catheter inserted through the EJV venotomy site



Figure 5. Wound at the end of the procedure



Figure 6. Post–op Chest X–Ray of the right and Left EJV chemoports, respectively (blue arrow: chamber of the chemoport; black arrow: position of the tip of the catheter)

136 patient includ	led in the study
	3 Failed EN cannulation
133 Successful	LTV cannulation
64 Right E/V cannulated	49 Left E/V cannulated

Figure 7: Flow Diagram (EJV: External Jugular Vein)

Results:

Here, we discuss our institution's three–year experience inserting chemoports in 136 patients via the open External Jugular Vein cut–down technique (Figure 7). For chemoport

Diagnosis	Right EJV (number)	Left EJV (number)
Ca Breast	48	49
Bone Tumours a) Osteosarcoma b) Ewing's Sarcoma	3 8	NIL
Leukaemia	8	NIL
Hodgkins Lymphoma	2	NIL
Wilms tumour	3	NIL
Gastrointestinal Cancers a) Ca Colon b)Gastroesophageal Junction Ca	8 2	NIL
Ca Ovary	2	NIL
TOTAL	84	49

Table 1. Different Diagnosis for Chemoport

Complications	Number (%)	Corrective Measures
Catheter Blockage	6 (4.5%)	Removal of chemoport
Port Infection	4 (3.0%)	Removal of chemoport
Catheter Tip Displacement	3 (2.2%)	Tip Repositioning
Extravasation of chemotherapy	1 (0.75%)	Conservatively managed, and port was used in subsequent chemotherapy cycles
Pneumothorax	NIL	NIL
Hematoma	NIL	NIL
Arrhythmias	NIL	NIL

Table 2. Procedure–related complications

insertion, we typically select the right external jugular vein (EJV); however, left EJV access was utilized solely in patients with right breast cancer when access on the same side (right EJV) was avoided due to a higher risk of lymphedema.

In 3 (2.2%) of 136 patients, attempts to cannulate the external jugular vein were unsuccessful, necessitating the use of an auxiliary route (the internal jugular vein). Due to the narrow caliber of the vein, all three occurred in patients younger than 5 years old. The most common indication (Table 1) for chemoport insertion in our study was breast cancer, accounting for approximately 72.93% (97/133) of patients, with the majority of patients being females, accounting for approximately 84.21% (112/133). Only

18.04% (24/133) of the patients were male. The distribution of ages ranged from 2 to 84 years.

From incision to procedure completion, the average operating time for patients older than 15 years was less than 30 minutes, whereas it took longer for pediatric patients.

Complications:

14 out of 133 patients (10.52%) were found to have complications (Table 2). After one cycle of chemotherapy, the chemoport had to be removed from approximately six patients (4.5%) due to catheter blockage. The growth of Staphylococcus aureus in two cases and Pseudomonas aeruginosa in the other two was detected in the cultures of four patients with a port infection at the chamber region (pectoral region). All patients were treated with appropriate antibiotics, and the infected chemoport device was removed. Three patients (2.2%) experienced catheter tip displacement into the brachiocephalic vein, necessitating returning to the operating room for neck wound exploration and catheter tip repositioning under fluoroscopic guidance. 1 patient (0.75%) experienced extravasation of chemotherapy, which was managed conservatively with aspiration of the chemotherapeutic agent, prophylactic IV antibiotics, and alternative IV access for chemotherapy for that cycle; however, the chemoport chamber was utilized in subsequent cycles.

Discussion:

In the realm of oncology, the development of TIVAD (chemoport) has been a blessing for cancer patients, freeing them from having to undergo numerous recurrent venepunctures throughout their treatment. Chemoports are currently the most prevalent method for administering chemotherapy in oncology.

Traditional chemoport insertion involves using a closed technique to percutaneously puncture the vein using Seldinger's method while paying close attention to external landmarks, verifying the placement by aspirating blood with a pre–attached syringe, and inserting the guide wire. The tract is then widened with a blunt dilator while the guide wire remains in position, and the catheter is then placed over the guide wire. Due to the fact that this technique is blind, there is a chance of puncturing an artery instead of a vein, which could result in a hematoma, as well as a chance of laceration of the vessel wall and pleural puncture, which could result in a pneumothorax ⁽⁷⁾.

The majority of patients requiring chemoport insertion in our investigation were diagnosed with breast cancer. They

endure axillary lymph node dissection on the affected side; consequently, the ipsilateral arm is not used for peripheral venous access due to the risk of lymphedema and skin infections. In addition, they require six to eight cycles of chemotherapy (depending on the regimen), and central veins with higher patency rates are less affected by the irritant properties of chemotherapeutic drugs.

Silicone elastomer is the optimal material for venous access over the long term. Silicone has been found to have the lowest risk of infection when implanted peripherally ⁽⁸⁾. In all of our patients, silicone catheters and ports were utilized.

Although the External Jugular Vein cut–down strategy for central venous access is widely described in the medical literature, earlier studies described its application in patients for whom a percutaneous approach or a cephalic vein cut– down was technically impractical ^(9, 10). As the foundation for chemoport implantation, we have utilized and described our experience with the External Jugular Vein cut–down technique.

In our study, the rate of effective external jugular vein (EJV) cannulation was approximately 97.79% (133/136). According to research ⁽⁴⁾, the external jugular vein (EJV) offers inherent anatomical advantages for chemoport insertion. Its predominantly straight course and absence of crossing the costoclavicular space alleviate potential hindrances that can impede catheter advancement when accessing the subclavian vein ⁽⁴⁾. In this manner, the EJV eliminates concerns related to pinch–off syndrome, a condition characterized by catheter obstruction between the clavicle and the first rib. Radhakrishna V et al. ⁽¹¹⁾ reported a 99% success rate with EJV cutdown and a 94% success rate with the percutaneous technique.

The most common acute adverse effect following catheter insertion is pneumothorax. 2% of the 110 patients studied by J. Vardy et al. ⁽¹⁾ had pneumothorax. According to research by other authors ^(12, 13), the subclavian vein percutaneous procedure for placing central venous access devices poses a risk of pneumothorax in 1% to 4% of patients. In our study, however, no pneumothorax, which has been linked to venous puncture of the IJV or Subclavian vein, was observed. This appears to be the primary advantage of the open External Jugular Vein cut–down technique.

In the series by Memorial Sloan–Kettering Cancer Center ⁽¹⁴⁾, site infection was 4.4% and access failures such as thrombosis were around 5.7%, whereas in our study, port infection was 3% and thrombosis caused 4.5% of catheter obstruction. J. Vardy et al. ⁽¹⁾ reported a 6 % infection rate. Thus, the open venous cut–down technique appears to have a similar risk of surgical site infection as the closed percutaneous procedure.

In their retrospective study, Radhakrishna V et al. (11) compared the percutaneous and External Jugular Vein cut-down chemoport techniques in pediatric patients. Regarding the time required to insert the chemoport (40.9 \pm 7.6 min vs. 37.6 \pm 18.9 min; P = 0.14) and the number of failed cannulation attempts (one vs. six; P = 0.06), there were no significant differences between the EJV and percutaneous groups. Compared to the percutaneous group, the External Jugular Vein cut-down chemoport installation was associated with significantly fewer overall complications (4 vs. 14; P = 0.01). In our study, the External Jugular Vein cut-down technique did not result in severe complications such as pneumothorax or hematoma. No arrhythmias, which occur when the chemoport catheter is inserted into the right atrium, were observed during our investigation.

Similar to our study (82.35 % females), Pancholi M. et al. ⁽⁷⁾ performed the External Jugular Vein cut–down procedure on 23 patients, the majority of whom were female (65.21%). In our study, catheter tip displacement occurred in 2.2% of patients, compared to 4.34 % in the study by Pancholi et al. When transitioning from a recumbent to a standing position, catheter tips may migrate. For the majority of insertions, a supine or head–down position is used. In subsequent X–rays, the abdominal contents and diaphragm descend, and the catheter's location shifts in relation to the mediastinal contents ⁽¹⁵⁾. Similarly, there is scientific evidence that a pendulous breast may impart a drag on the extra–thoracic section of a tunneled catheter, causing lateral movement and the possibility of extravasation ⁽¹⁶⁾.

During chemoport insertion, the External Jugular Vein cut-down technique provides a safe and efficient method for entering the central venous system. This technique is simple, effective, and repeatable, with no significant learning curve. Importantly, the surgical External Jugular Vein cut-down approach for chemoport insertion helps avoid immediate and potentially fatal complications, such as pneumothorax and hemopneumothorax, that are associated with percutaneous techniques, particularly when performed without ultrasonography guidance. This technique was chosen with the primary objective of minimizing the distress and potential complications of cancer patients, whose quality of life is already compromised. The surgical cutdown technique is a time-tested and trustworthy method that has proven its efficacy over the course of four decades (17)

It is crucial to acknowledge the limitations of our study, which include a small sample size, the absence of comparative analysis, and a single-institution study. The small sample size may limit the statistical power of our findings. The lack of a comparative analysis prevents us from comparing this technique to other methods of chemoport insertion, which could provide valuable insights into the relative benefits and drawbacks of different approaches. In addition, the single–institution nature of the study may limit the generalizability of the findings to other healthcare settings, where variables such as institutional protocols and healthcare provider expertise may vary. These limitations emphasize the need for larger, multicenter studies with comparative analyses to validate and expand upon our findings.

Conclusion:

In conclusion, our study demonstrates that the External Jugular Vein cut–down technique offers several advantages in the realm of oncology, as it is a safe, efficient, and straightforward technique for chemoport insertion. With its minimal learning curve and simplicity, this technique represents a favorable initial option for successfully implanting chemoports in cancer patients. Further research and comparative studies are needed to validate and further explore the benefits of this technique in diverse patient populations and healthcare settings.

Conflict of Interest:

The authors declare that they have no conflict of interest and no external funding was received for the study.

Reference:

- Vardy J, Engelhardt K, Cox K, et al. Long–term outcome of radiological–guided insertion of implanted central venous access port devices (CVAPD) for the delivery of chemotherapy in cancer patients: institutional experience and review of the literature. *Br J Cancer*. 2004;91(6):1045– 1049. doi:10.1038/sj.bjc.6602082.
- 2. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. *Surgery*. 1982;92(4):706–712.
- 3. Zaghal A, Khalife M, Mukherji D, et al. Update on totally implantable venous access devices. *Surg Oncol.* 2012;21(3):207–215. doi:10.1016/j.suronc.2012.02.003.
- 4. lorio 0, Cavallaro G. External jugular vein approach for TIVAD implantation: first choice or only an alternative? A review of the literature. *J Vasc Access*. 2015;16(1):1–4. doi:10.5301/ jva.5000287.
- 5. Kock HJ, Pietsch M, Krause U, Wilke H, Eigler FW. Implantable vascular access systems: experience in 1500 patients with totally implanted central venous port systems. *World J Surg.* 1998;22(1):12–16. doi:10.1007/s002689900342.

- Bechmann S, Rahman S, Kashyap V. Anatomy, Head and Neck, External Jugular Veins. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. Available from: https://www.ncbi. nlm.nih.gov/books/NBK538222/
- 7. Pancholi M, Desai SM, Agrawal D, Mehta D, Pancholi A. External jugular venous cut down technique for placement of chemotherapy port and Hickman catheter: a study of 23 cases. Int Surg J.2016;3:565–9.
- 8. MacDonald AS, Master SK, Moffitt EA. A comparative study of peripherally inserted silicone catheters for parenteral nutrition. *Can Anaesth Soc J.* 1977;24(2):263–269. doi:10.1007/BF03006239
- Puig–la Calle J Jr, López Sánchez S, Piedrafita Serra E, Allende Honorato L, Artigas Raventós V, Puig la Calle J. Totally implanted device for long–term intravenous chemotherapy: experience in 123 adult patients with solid neoplasms. J Surg Oncol. 1996;62(4):273–278. doi:10.1002/(SICI)1096– 9098(199608)62:4<273::AID–JS09>3.0.C0;2–3.
- 10. Redo SF, Dinner MH. Placement of central venous catheters by cut–down with electrocardiogram positioning. *Surg Gynecol Obstet.* 1993;177(1):49–53.
- 11. Radhakrishna V, Radhakrishnan CN, Srinivasa Rao RC, Kireeti G. External Jugular Venous Cutdown versus Percutaneous Technique for Chemoport Insertion in Children: A Comparative Study. *J Indian Assoc Pediatr Surg.* 2022;27(2):140–146. doi:10.4103/jiaps.JIAPS_346_20.
- 12. Shukla NK, Das DK, Deo SV, Raina V. An analysis of longterm venous access catheters in cancer patients:experience from a tertiary care centre in India. *J Postgrad Med*. 2002;48(1):21–24.
- 13. D'Angelo FA, Ramacciato G, Aurello P, et al. Prospective randomised study of cephalic vein cut-down versus subclavian vein puncture technique in the implantation of subcutaneous venous access devices. Chir Ital. 2002;54(4):495–500.
- 14. Schwarz RE, Groeger JS, Coit DG. Subcutaneously implanted central venous access devices in cancer patients: a prospective analysis. *Cancer*. 1997;79(8):1635–1640.
- 15. Nazarian GK, Bjarnason H, Dietz CA Jr, Bernadas CA, Hunter DW. Changes in tunneled catheter tip position when a patient is upright. *J Vasc Interv Radiol*. 1997;8(3):437–441. doi:10.1016/s1051–0443(97)70585–2.
- 16. Moorman DW, Horattas MC, Wright D, Kaufman K, Ruf W. Hickman catheter dislodgement due to pendulous breasts. *JPEN J Parenter Enteral Nutr.* 1987;11(5):502–504. doi:10 .1177/0148607187011005502.
- 17. Toro A, Schembari E, Fontana EG, Di Saverio S, Di Carlo I. Forty years after the first totally implantable venous access device (TIVAD) implant: the pure surgical cut–down technique only avoids immediate complications that can be fatal. Langenbecks Arch Surg. 2021 Sep;406(6):1739–1749. doi: 10.1007/s00423–021–02225–6.