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EXPERT OPINION

Chinese Expert Consensus on Preventing and Managing Chyle Fistula in Cervical Lymph Node Dissection for Thyroid Cancer (2024)

Qingqing He[1], Wen Tian[2], Jingqiang Zhu[3], Ping Wang[4], Hao Zhang[5] On behalf of the Expert Working Group on Thyroid Surgery, Chinese Medical Doctor Association Division of Surgeons, Thyroid Disease Committee of Chinese Research Hospital, Association, General Surgery Branch of China International Exchange and Promotive Association for Medical and Health Care

[1]Department of Thyroid and Breast Surgery, the 960th Hospital of the PLA Joint Logistics Support Force, Jinan, Shandong Province, 250031, People's Republic of China; [2]Department of General Surgery, General Hospital of the People's Liberation Army (PLA), Beijing, 100853, People's Republic of China; [3]Center of Thyroid & ParaThyroid Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan Province, 610041, People's Republic of China; [4]Department of General Surgery, Second Affiliated Hospital of Medical College of Zhejiang University, Hangzhou, Zhejiang Province, 310009, People's Republic of China; [5]Department of Thyroid Surgery, The First Hospital of China Medical University, Shenyang, Liaoning Province, 110001, People's Republic of China

Correspondence: Qingqing He, Email heqingqing@yeah.net; Wen Tian, Email tianwen301_cta01@163.com

Background: The prevalence of thyroid carcinoma is on the rise, with cervical lymph node metastasis being a frequent occurrence necessitating surgical intervention. Chyle fistula, a significant postoperative complication, can have a substantial impact on recovery.

Objective: To reduce the incidence of chyle fistula, enhance the effectiveness of postoperative treatment, and assist thyroid surgeons in performing cervical lymph node dissection, the consensus was compiled in a standardized and secure manner.

Methods: Drawing from the expertise of Chinese specialists in managing chyle fistula and the latest international advancements in this field following cervical lymph node dissection, the thyroid tumor experts group of Chinese Thyroid Association, Chinese College of Surgeons, Chinese Medical Doctor Association and Thyroid Disease Professional Committee of Chinese Research Association have developed innovative approaches to address this issue. An evidence-based approach was employed, integrating the knowledge and practical experience of the panelists.

Results: We developed twelve expert consensus recommendations, addressing the prevention, diagnosis, and treatment of post-operative chyle fistula. These recommendations included the dietary management and nutritional support, continuous negative pressure suction, local adhesive treatment, application of local compression methods, the use of somatostatin and its analogs, and surgery treatment.

Conclusion: This evidence-based consensus would be valuable to assist front-line surgeons and medical specialists in the management of chyle fistula.

Keywords: thyroid carcinoma, Chyle fistula, expert consensus, cervical lymph node dissection, thoracic duct

Introduction

Thyroid cancer is the predominant malignancy within the endocrine system, with a prevalence that places it as the seventh most frequently diagnosed cancer in women in the United States and the fourth most common in women in China.[1] This disease frequently manifests with cervical lymph node metastasis, necessitating cervical lymph node dissection as the primary therapeutic intervention. Chyle fistula is a serious complication after cervical lymph node dissection, with an incidence of approximately 1%~3%.[2,3] The impact of chyle fistula on patients' quality of life is substantial, resulting in prolonged hospital stays and significant healthcare costs. Large amounts of chyle in severe cases can induce metabolic/electrolyte disturbances, hypoproteinemia, bleeding, chylothorax or chyloperitoneum, respiratory

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distress, chest and/or abdominal infections.[3] Given the rarity and complex clinical presentation of chyle fistula, a standardized perioperative operating guidelines for preventing and treating chyle fistula is warranted.

This consensus was achieved by pertinent domestic expert panels to offer guidance and reference for clinical practice. It is an improvement on the basis of the 2022 edition,[4] which has been registered in Practice guideline Registration for transparency (PREPARE-2023CN034). It aims to reduce the occurrence of chyle leakage, improve the efficacy of postoperative treatment, and assist thyroid surgeons in performing cervical lymph node dissection in a standardized and safe manner.[5]

Materials and Methods

The Literature Retrieval Strategy

A panel of 43 experts from China with a declared interest was established. This consensus is formed through structured discussions of experts in different fields. After discussion by the expert group, the main literature retrieval strategy is as follows: Publication between 2000 and 2024 were searched in electronic databases including Medline EMBASE, Web of Science China Biomedical Literature Database CNKI, Wanfang Database Guideline Clearing House Cochrane Library, Sum Search. The main search keywords are chyle fistula and thyroidectomy, including but not limited to the following keywords: thyroid neoplasms, postoperative complications, lymph node excision, lymphatic vessels, and thoracic duct.

Level of Evidence and Recommended Strength

In accordance with established principles for the grading of evidence in guidelines,[6] the GRADE Working Group's system for evaluating evidence levels and recommendation strength was employed. Each issue addressed in this consensus is structured using the "Question-Evidence-Recommendation" framework, which includes both the evidence level and the recommendation level. A "strong recommendation" is issued when the benefits of an intervention significantly outweigh its risks and are economically feasible. Conversely, when the benefits are reduced or the risks are heightened, the recommendation is downgraded to a "weak recommendation". In cases of divergent recommendations, the consensus-forming conference method will be employed. Through this method, an evidence-based consensus will be achieved via discussions between the support group and experts from various professional fields to resolve any discrepancies. The evidence level is shown in Table 1, and the consensus recommendation level is shown in Table 2.

Results

Key question 1:What is the anatomy of the cervical lymphatic vessels?

The cervical portion of the thoracic duct extends from the thorax to reach the base of the neck, draining lymph from the left cervical trunk, the left subclavian trunk, and the left bronchomediastinal trunk. The thoracic duct follows a curved anterior path before posteriorly passing the left common carotid artery, vagus nerve, and internal jugular vein, ultimately terminating at the junction of the left subclavian vein and internal jugular vein. Valves are present at the entrance to prevent the backflow of lymphatic fluid. (Figure 1).

Table 1 The Evidence Level

Evidence Level	Description of Supporting Evidence
A	High quality. Consistent RCT[a], cohort studies, all-or-none conclusive studies, and clinical decision rules that have been validated in diverse populations.
B	Moderate quality. Consistent retrospective cohort studies, prospective cohort studies, ecological studies, outcome studies, case-control studies, or conclusions derived from extrapolation of A-level evidence.
C	Low quality. Conclusions derived from case series studies or B-level evidence extrapolation.
D	Insufficient. Evidence is conflicting, of poor quality, or lacking.

Abbreviation: [a]RCT, randomized controlled trial.

Table 2 The Recommendation Level

Recommendation Level	Clarity of Recommended Strength
A	Strongly recommended. Evidence-based medicine evidence is positive and improves prognosis. Benefits clearly outweigh harms.
B	Recommended. Evidence-based medicine evidence is good and improves prognosis. Benefits outweigh harms.
C	Conditionally recommended. Benefits are closely balanced with harms.
D	Not recommended. The pros and cons cannot be determined.

The location of the termination point within the cervical region exhibits significant variability, typically falling within the left venous angle triangle defined by the lower portion of the internal jugular vein, the inferior border of lower belly scapular hyoid muscle, and the superior border of the clavicle. In addition to termination at the left venous angle, It can also terminate at internal jugular, subclavian, external jugular, and innominate veins, as well as variants at the right venous angle. The right lymphatic duct is a short trunk, measuring 1.0~1.5 cm in length and approximately 0.2 cm in diameter, which drains lymph from the right jugular trunk, the right subclavian trunk, and the right bronchial-mediastinal trunk into the right venous angle. Both the thoracic duct and the right lymphatic duct exhibit significant anatomical variation, characterized by numerous interconnected branches.

The thoracic duct is characterized by a well-developed basement membrane and a ductal wall composed of three distinct layers: the inner, middle, and outer membranes. The stroma of the duct is comprised of smooth muscle fibers surrounded by connective tissue containing elastic fibers, which contract periodically to facilitate lymph flow. Unlike capillary lymphatics, the thoracic duct and all other lymphatic vessels are equipped with valves, which are more densely distributed and closely spaced compared to venous valves. Capillary lymphatic vessels are thin-walled structures composed of only one layer of hyaline epithelial cells, lacking basement membrane and elastic fiber layer, with large cell gaps, easy to tear, poor self-healing ability, and negative pressure in lymphatic vessels, which is difficult to detect after injury.[7]

Recommendation 1: Surgeons should possess a thorough understanding of the anatomy of the cervical lymphatics to minimize the risk of intraoperative injury to the thoracic duct and lymphatic trunk and mitigate the occurrence of chyle fistula. (Grade of evidence: C; Grade of recommendation: B)

Key question 2: How to perform preoperative evaluation and preparation to prevent chylous fistula?

Extensive and advanced thyroid cancer typically necessitate neck dissection, underscoring the importance of precise preoperative evaluation of cervical lymph node metastasis in determining the need for concurrent lymphadenectomy. High-resolution ultrasonography is the preferred imaging modality for preoperative identification of thyroid cancer and cervical lymph node metastases. Additionally, in select cases, magnetic resonance imaging (MRI) or medical 3D printing

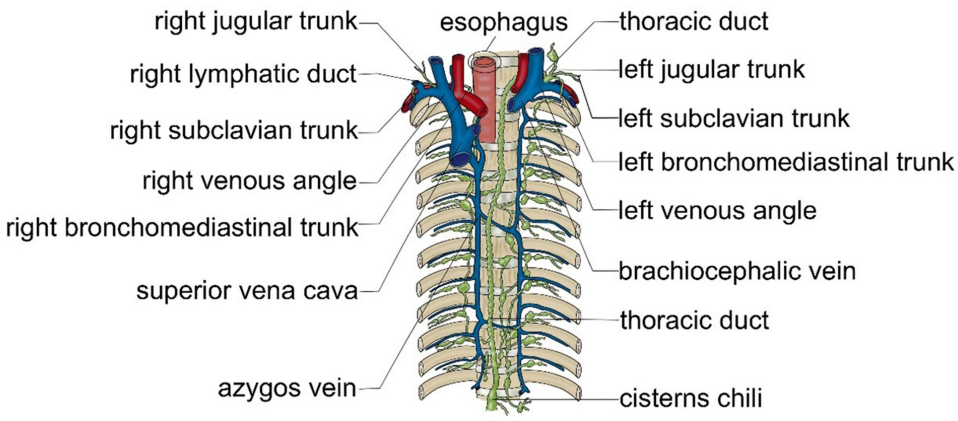

Figure 1 Thoracic duct and right lymphatic duct.

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digital simulation may be required to more accurately delineate the spatial relationship between lymph nodes and adjacent tissues.

Preoperative fine-needle aspiration cytology (FNAC) is a highly efficacious method for assessing lymph node metastasis, necessitating lymphadenectomy in confirmed cases. Region IV lymph nodes are particularly susceptible to chylous leakage, particularly in instances where metastatic nodes are extensively adherent or fused to adjacent tissue.[8]

Precautions: (1) Preoperative ultrasound-guided dye injection (eg nanocarbon or mitoxantrone) serves to safeguard parathyroid glands and enhance lymph node visualization during surgical procedures; (2) FNAC and washout of thyroglobulin and calcitonin from the punctured tissue can aid in the identification of lymph node metastases; (3) Healthcare providers should educate patients and their families about the potential occurrence of chyle fistula and its treatment, as well as provide guidance on maintaining a controlled diet and engaging in postoperative functional training to ensure a smooth recovery period.[9] Additionally, healthcare providers should offer support to alleviate patient anxiety and stress.

Recommendation 2: Surgeons should conduct thorough preoperative evaluations and enhance perioperative care to minimize the likelihood of chyle fistula. (Grade of evidence: C; Grade of recommendation: A)

Key question 3: How to prevent intraoperative chyle fistula?

Key points of operation: (1) Due to the histological features of lymphatic vessels, lymphatic ligation is considered a dependable method for the excision of venous angle lymph nodes. The judicious and efficient utilization of energy devices is advised, with caution against sole reliance on monopolar electric energy instruments in open surgical procedures. In endoscopic and robotic surgeries, the use of an ultrasonic knife for the coagulation of adjacent tissues is recommended; (2) When lymphatic vessel injury happened, meticulous examination for leaks is essential, followed by the ligation of both ends or the fractured segments of the leak. If a significant break is not identified, the adjacent muscle flap or fibrofatty tissue can be approximated using 4–0 or finer noninvasive sutures; (3) In the event of lymphatic vessel injury during endoscopic or robotic surgery, the ligation or suturing of the leak may prove challenging, prompting the utilization of tissue closure clips to address the compromised lymphatic vessels; (4) Prior to irrigating the injury site, maintaining cleanliness is essential, and anesthesiologists should collaborate to facilitate lung expansion for 10~15 seconds to elevate the intrathoracic pressure, while vigilantly monitoring for potential chyle fluid leakage from the operative site.[10]

Precautions: (1) During intraoperative procedures, it is advisable to avoid focusing solely on the identification and ligation of lymphatic vessels, as this may heighten the likelihood of causing injury to these vessels; (2) Narrowing the scope of the operation out of concern for potential chyle fistula may inadvertently result in the omission of metastatic lymph nodes, necessitating subsequent reoperation; (3) In cases where numerous metastatic lymph nodes in the neck are closely adhered to surrounding tissues, it is imperative to ligate not only the primary lymphatic vessels but also the adjacent small and medium-sized lymphatic vessels; (4) The thoracic duct's variability may result in chyle fistula during central lymph node dissection, necessitating careful identification and protection of lymphatic vessels; (5) Damage to the thoracic duct during cervical root lymph node dissection may manifest as chylothorax, marked by a sudden decrease in drainage and symptoms such as shortness of breath, chest tightness, and dyspnea. In such cases, ultrasound or chest CT imaging should be conducted to confirm the presence of chylothorax; (6) The diameter of the drainage tube in the surgical area should not be of adequate size to prevent bending and twisting.

Recommendation 3: It is essential to accurately identify and protect the lymphatic trunk and its major branches during surgery, promptly addressing any injuries by suturing or stapling them. (Grade of evidence: C; Grade of recommendation: B)

Key question 4: How to diagnose postoperative chylous fistula?

Clinical diagnosis: Postoperatively, an increase in neck drainage should be observed, with a change in the color of the fluid from serous to milky white cloudy fluid, often worsening during feeding.

Laboratory diagnosis: A postoperative drainage fluid triglyceride concentration greater than 100 mg/dL or exceeding serum levels may have diagnostic significance.[11,12]

Recommendation 4: The diagnosis of chyle fistula includes an abnormal amount of milky white cloudy drainage fluid and high serum triglyceride levels. (Grade of evidence: A; Grade of recommendation: A)

Nonsurgical Treatment

Treatment of postoperative chyle fistula includes nonsurgical and surgical treatments. In addition to surgical interventions, several nonsurgical modalities such as dietary modifications, continuous negative pressure suctioning, local compression dressings, adhesive injections, and pharmacological agents are available for the management of postoperative chyle fistula. These nonsurgical interventions can be utilized in combination for enhanced therapeutic outcomes.

Key question 5: What dietary management and nutritional support should be followed for postoperative chylous fistula?

Dietary interventions for managing chyle fistula focus on reducing chyle production and preventing water-electrolyte imbalances. In cases of postoperative chyle fistula, a low-fat or fat-free diet, in combination with fasting and parenteral nutrition, is recommended.[13] It is advisable to create a personalized nutrition management plan in conjunction with a registered dietitian, diligently observe the patient's clinical progress, thoroughly evaluate their nutritional status, monitor hepatic and renal function, and assess electrolyte levels to prevent potential deficiencies, electrolyte imbalances, or other adverse outcomes.

Recommendation 5: A low-fat or fat-free diet combined with fasting and parenteral nutrition can help reduce chylous production and prevent water and electrolyte imbalances. (Grade of evidence: C; Grade of recommendation: B)

Key question 6: How to apply continuous negative pressure suction and drainage tubes to postoperative chylous fistula patients?

In cases of chyle fistula, it is recommended to connect the neck drainage device to continuous negative pressure suction, typically set at negative 50~80kPa.[13] Patients should be advised to remain in bed with their head elevated at a 30~40° angle.[14] Continuous negative pressure suction can prevent fluid buildup, reduce the risk of infection, facilitate granulation tissue growth, and promote healing of the leak. Precautions for continuous negative pressure suction: (1) Chyle fistula typically occurs in the vicinity of the internal jugular vein, and persistent negative pressure suction may result in vascular rupture. Consequently, it is imperative to closely monitor and promptly adjust negative pressure levels; (2) To safeguard against negative pressure interference with lymphatic vessel healing, the negative pressure drainage tube should be positioned approximately 1~2cm away from the vein's junction; (3) If the drainage flow fails to meet extubation criteria (< 10 mL/24h) despite continuous negative pressure suction, a gradual withdrawal of the tube is recommended, approximately 1~2 cm each time, with careful observation of any ensuing changes in drainage flow. Ultrasound imaging is recommended for monitoring lymph fluid accumulation in the surgical site during extubation.

Recommendation 6: Drainage of the neck under negative pressure can prevent chylous fluid buildup, reduce the risk of infection, and promote healing of leakage. (Grade of evidence: B; Grade of recommendation: B)

Key question 7: What should be noted in the application of local pressure dressing in postoperative chylous fistula?

Proper positioning of the compression bandage, specifically placing 1~2 gauze blocks to create a loose mass of 3~5cm in diameter at the vein angle projection of the supraclavicular fossa, is crucial for effective drainage. Accurate compression placement can lead to a rapid reduction in drainage flow.[15]

Precautions for pressure dressing: (1) Obese patients may present challenges due to the presence of a thick subcutaneous fat layer, which can obscure surface anatomical landmarks. Hence, the challenge of securing the gauze mass and the tendency for the pressure position to shift and deviate are evident; (2) This is particularly pronounced in male patients due to the developed sternocleidomastoid muscle, which hinders the effective guidance of external pressure to the venous angle, resulting in suboptimal pressure distribution; (3) Conversely, emaciated female patients with thick subcutaneous fat and weak sternocleidomastoid muscle are susceptible to cervical plexus or brachial plexus nerve function damage, upper arm numbness, pain, and movement disorders from excessive pressure; (4) Excessive pressure may lead to skin tension blisters or flap necrosis; (5) The refractory low-flow chylous leak is predominantly attributed to a minor lymphatic vessel injury, with the precise site of the leak remaining unidentified.[8]

Recommendation 7: Local compression at the vein angular projection of the supraclavicular fossa on the affected side can rapidly reduce the drainage of chylous fistula. (Grade of evidence: B; Grade of recommendation: B)

Key question 8: How to perform local adhesive treatment?

The primary mechanism of action of local adhesives involves inducing localized aseptic inflammation to promote the proliferation and adhesion of granulation tissue surrounding the leak, ultimately leading to its closure. Among the various mucoadhesive agents available, Pseudomonas aeruginosa injection stands out as a prominent example.[16] The recommended dosage for this agent is 2mL per administration. In cases where the drainage flow fails to decrease by at least half of the original flow rate within 3 days following the initial injection, a repeat administration of 2mL is advised, but the administration of injections should be limited to a maximum of three times. If drainage does not show signs of reduction or persists following three injections, surgical intervention should be contemplated. In instances of significant lymphatic vessel injury, continuous chyle fluid leakage may be observed even in ultrasound-guided aspiration. The medication should be administered in close proximity to the leak under ultrasound guidance. If the leak cannot be identified under ultrasound guidance, the drug may be injected in the vicinity of the venous angle.

Following injection, gentle pressure should be applied for 30 minutes to help the drug take effect. Following the administration of the injection, the patient may exhibit symptoms such as fever, nausea, pain, and other potential side effects, typically of a transient and manageable nature.[17] The efficacy parameters post application of local adhesive involve a notable decrease in drainage output (less than 30 mL per day for two consecutive days) and absence of fluid accumulation on imaging studies.[12] Prior to the removal of the drainage tube, a "fat meal" test is necessary. The presence of non-degradable adhesions can result in the obliteration of normal anatomical spaces and formation of scar tissue. However, reoperation carries the risk of injuring vital structures such as the internal jugular vein and phrenic nerve. Hence, the utilization of degradable adhesives is advised.[18] Currently, adhesives are frequently employed in case studies, necessitating additional research on their effectiveness and safety.

Recommendation 8: Local adhesives induce localized aseptic inflammation to promote adhesion of granulation tissue surrounding the leak, in which the role of Pseudomonas aeruginosa injection is outstanding. (Grade of evidence: B; Grade of recommendation: B)

Key question 9: Is the application of somatostatin and its analogs recommended for postoperative chylous fistula?

The precise mechanism by which somatostatin and its analogs, such as octreopeptide, diminish chylous secretion remains unclear.[18] It is possible that they achieve this by inhibiting pancreatic and gastrointestinal secretions through endocrine and paracrine pathways, decreasing hepatic venous pressure and visceral blood flow, or directly impacting angiosomatostatin receptors to decrease lymphatic fluid production The optimal therapeutic dosage of octreotide for the management of chyle fistula following cervical lymph node dissection exhibits considerable variability. The recommended initial subcutaneous injection dosage is 100 μg (Every 8 hours), with a potential escalation to 200 μg if the desired therapeutic effect is not achieved. Discontinuation of octreotide treatment is advised within 2 days of meeting the established treatment criteria for chyle fistula to ensure treatment efficacy.[19]

Recommendation 9: Application of somatostatin and its analogs contribute to diminish chylous secretion. (Grade of evidence: C; Grade of recommendation: C)

Key question 10: How to surgically treat chyle fistula?

Surgical intervention may be warranted in cases where non-surgical interventions have proven ineffective. The criteria for surgical exploration of chylous leaks are not universally agreed upon, but generally include persistent drainage volumes exceeding 1000mL per day despite non-surgical interventions. In cases of continuous drainage exceeding 2000mL per day and inadequate response to non-surgical treatments or refractory low-flow chyle fistula (less than 1000 mL per day), prompt surgical intervention is recommended. Severe malnutrition and water-electrolyte disorders, along with other serious complications such as infection, valve necrosis, or bleeding, may need surgical intervention.

Precautions: (1) Consumption of high-fat liquid food (such as milk or olive oil) 6~8 hours prior to the procedure can lead to increased chyle production, resulting in a significant amount of chylous fluid leakage from the leak site, facilitating intraoperative identification of the leak; (2) Adjusting the patient to a head-low, foot-high position during surgery can further enhance chyle fistula, aiding in the localization of the leak; (3) Once the leak is clearly identified, it can be sutured using "4–0" or finer non-invasive sutures. However, a significant presence of fibrinous exudate, localized edema, and proliferation of granulation tissue typically surrounds the site of lymphatic leakage. Additionally, the thin and fragile nature of the lymphatic vessel walls often complicates attempts to suture them individually. In such cases, it may

be necessary to suture the lymphatic vessel trunk along with the surrounding tissue; (4) If the leakage site is not readily apparent, suturing the area in conjunction with nearby muscle or fibrous tissue may be necessary; (5) Following suturing and ligation, medical professionals should conduct a 10~15 minute observation period, during which the anesthesiologist may be asked to briefly expand the lung for 10~15 seconds, and then suture the incision after confirming that there is no chyle fistula; (6) Chyle fistula recurrence following lymphatic trunk suturing may necessitate further intervention, with non-surgical treatment being the preferred option if drainage volume is reduced compared to pre-surgical levels. In cases where drainage volume remains high, repeat surgical exploration and ligation of the lymphatic stem or thoracoscopic thoracic duct may be required.

Recommendation 10: Surgical intervention may be warranted in cases where non-surgical interventions have been proven ineffective.

Key question 11: How to deal with chyle fistula after endoscopic cervical lymph node dissection?

Postoperative chyle fistula management in patients with chyle fistula following endoscopic or robotic neck dissection should initially involve non-surgical approaches, with thoracoscopic thoracic catheter ligation considered if non-surgical treatment is ineffective or a neck incision is not accepted by the patient.[20] One potential benefit of thoracic duct ligation is the prevention of lymphatic fluid leakage, while another advantage is the favorable cosmetic outcome that helps to avoid neck scarring.[21] There is ongoing debate among experts regarding the short-term effects of thoracoscopic thoracic duct ligation on immunity and gastrointestinal absorption function, with some suggesting potential impacts and others noting the establishment of collateral circulation due to the extensive lymphatic system. Thoracoscopic thoracic catheter ligation may be considered in the following conditions: (1) Secondary exploration failure in open neck surgery; (2) Chyle fistula is encountered during initial surgery despite standard management; (3) Thoracic duct variation that difficult to explore by imaging; (4) Chyle fistula caused by endoscopic and robotic thyroid surgery.[18] Following thoracic catheter ligation, there is a potential increase in lymphatic fluid reflux pressure, leading to the possibility of chylous fluid leakage from the thoracic duct into the chest due to the thin wall of the catheter and negative pressure in the pleural cavity, resulting in the formation of chylothorax. In the presence of symptoms such as dyspnea and shortness of breath, diagnostic imaging such as ultrasound or chest CT should be conducted.[22] Upon confirmation of chylothorax, initial management should focus on symptomatic relief through fluid and nutrition support, with consideration of surgical intervention if conservative treatment proves ineffective.

Recommendation 11: Thoracoscopic thoracic catheter ligation is an appropriate surgical approach to treat chyle fistula following endoscopic or robotic neck dissection. (Grade of evidence: B; Grade of recommendation: B)

Discussion

As rare but significant complication of thyroid surgeries, serious chyle extravasation can result in electrolyte abnormalities from fluid loss, nutritional deficiencies from dietary adjustments, chylothorax and increased length of hospital stay. The thoracic duct is at risk of injury during any thyroid surgeries due to the high variability in its anatomy. Prompt identification and management of it are essential to ensure optimal outcomes after surgeries. Given the adherent and diffuse nature of nodal metastasis in PTC, there are many uncertainties in perioperative management. Hence, the combination of treatment options should be tailored to the individual patient's presentation. In addition to conventional surgical and non-surgical treatments, we have innovatively added Pseudomonas aeruginosa injections therapy to this consensus. We believe that combined application is beneficial for rapid recovery because each method has its limitations. Clinicians should select the best treatment plan based on the duration of the leak and the amount of chyle that is leaking.

Conclusion

Intraoperative prevention is the key to preventing chyle leakage. Low daily drainage may damage the branches of lymphatic vessels rather than the main trunk. Non-surgical treatment methods such as continuous strong negative pressure suction, local compression, low-fat diet, and nutritional support can usually cure chyle leakage. For patients with refractory high flow (peak drainage volume $\geq$ 1000 mL) chyle leakage and unsatisfactory curative effect for more than 2 weeks of treatment, timely surgical treatment is necessary. This consensus attempts to provide the optimal therapeutic methods for surgeons to achieve optimal outcomes.

Consent for Publication

All the experts involved in this study agree to the use of their opinions in this submission.

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Members of expert group/Writing Group (Listed in alphabetical order by last name in mandarin): Guang Chen, Wenjie Dai, Youben Fan, Ziyi Fan, Rongzhan Fu, Zhuming Guo, Qingqing He, Tao Huang, Kewei Jiang, Qinghai Ji, Hua Kang, Bin Luo, Xingrui Li, Zhihui Li, Shanting Liu, Shaoyan Liu, Xiubo Lu, Huadong Qin, Tiefeng Shi, Zijie Su, Hui Sun, Wen Tian, Xingsong Tian, Ping Wang, Xudong Wang, Yu Wang, Wei Wei, Zhixin Wei, Gaosong Wu, Yijun Wu, Bo Xu, Qing Xu, Zhengang Xu, Jing Yao, Shijian Yi, Qingdong Zeng, Hao Zhang, Yanjun Zhang, Wenxin Zhao, Yongfu Zhao, Luming Zheng, Jingqiang Zhu, Dayong Zhuang.

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Disclosure

The authors report no conflicts of interest in this work.

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