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Contents

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REVIEW

MINIREVIEWS

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Contents

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REVIEW

Central neck compartment dissection in papillary thyroid carcinoma: An update

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Abstract

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximatley 90% of thyroid malignancies in areas of the world without deficit of Iodine. It's universally accepted that total thyroidectomy is the minimal surgical treatment for patients with PTC higher than 1 cm. When a quality surgery is performed, the prognosis for PTC is excellent with 10 and 20-year overall survival rates around 90% and 85%, respectively. Lymph node metastases are very frequent in PTC, occurring in 50%-80% of PTC patients, the most of them being located in the central compartment of the neck (CCN) and with a high rate of occult or clinically undetectable disease. A lot of controversy exists regarding how to treat the central nodal compartment disease of PTC. The first problem is the lack of standardization of the terminology and concepts related to the CCN, which are clearly established and defined in this paper according to the most recent consensus documents of endocrine societies. This uniformity will provide a more consistent and clear communicaction between all the specialist involved in the treatment of PTC. CCN can be performed to treat patients with clinically detectable, radiologically suspected of intraoperative visualized nodal disease (this is defined as therapeutic) or when these findings are absent (also called prophylactic). Indicactions, advantages and disadvantages of both therapeutic and prophylactic CCN dissection are widely discussed and clear recommendations provided.

Key words: Thyroid; Cancer; Papillary; Central; Node; Compartment; Dissection; Prophylactic; Therapeutic

Core tip: When papillary thyroid cancer is discussed anywhere, there are two main matters of controversial which centralize the debates. The first one is the need of having an uniform standardization of the concepts related to the dissection of the central compartment: limits and terminology. The second point is about the concept of prophylactic dissection of the central compartment if patients with neither clinical nor radiological nodal disease related to papillary thryroid carcinoma. Both of the points are clearly defined in this paper and the readers will have clear ideas about what to when facing a papillary thyroid carcinoma.

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INTRODUCTION

During the period from 1973 to 2002, the incidence of thyroid cancer (TC) increased from 3.6 to 8.7 per 10^5[1]. This is almost entirely related to an increase in papillary thyroid cancer (PTC) likely influenced by detection of smaller cancers, accounting for 80% of TC and ranking as the sixth most common cancer in females[2,3]. Nowadays the most part of PTC are nonpalpable lesions incidentally diagnosed because of the proliferation and widespread of multiple different radiographic evaluations, specially neck ultrasound (US) and its increasing sensitivity in screening of small thyroid nodules. Papillary thyroid microcarcinoma, which is defined as a PTC measuring equal or less than 10 mm in diameter according to the World Health Organization classification, accounts for 38.5% of PTC in the United States, 35.7% in Shangai and 48.8% in France[4,5]. The therapeutic mainstay for PTC is resection consisting of total thyroidectomy (TT) with or without lymphadenectomy.

PTC tends to exhibit intra- and extraglandular lymphatic spread, being lymph nodes (LN) involvement and dissemination common; unlike other malignancies, and this is a very important detail, presence of LN metastases generally does not adversely influence prognosis, especially in patients under the age of 45 years. Up to 40% of patients with PTC have clinically detectable macroscopic LN metastases at initial diagnosis and up to 85% have occult or microscopic LN metastases, being clinically apparent LN more common at the extremes of age[6]. The yield of metastatic LN in every compartment of the neck is significantly related to the number of LN retrieved in the neck dissection and to the extent of pathologic examination[7,8]. At this point, it is important to know that all LN metastases are not the same in terms of their implications for locoregional recurrence and mortality, which are the main endopoints to be evaluated in the surgery of PTC. Clinical LN metastases, specially if macroscopic at the time of surgery, are associated with higher recurrence rates and poorer prognosis than are similar cases in which LN metastases are preoperatively undetectable[9-13]. In addition, an increased mortality rate has also been observed in patients with LN metastases who are 45 years or older[13,14]. By contrast, microscopic LN metastases are associated with much lower rates of recurrence and do not affect patient survival, suggesting that they remain dormant and rarely become clinically significant[15,16].

The purpose of this paper is to review and update the concepts and surgical options related to the central neck compartment (CNC) dissection in PTC, the most common well-differentiated thyroid carcinoma, according to the best evidence recently published. At this point, it is important to emphasize that no level of evidence 1 information is available in the literature with the highest reported being level 4 (http://www.cebm.net/?O=125). Papillary thyroid cancers are poorly suited for prospective studies as they tend to be clinically indolent and highly responsive to radioactive iodine (RAI) therapy, with extremely high percentage of long-term survival.

CNC: THE ANATOMICAL CONCEPT

The CNC includes LN levels Ⅵ and Ⅶ. It is bounded superiorly by the hyoid bone, laterally by the sheath of the carotid arteries, anteriorly by the superficial layer of the deep cervical fascia (undersurface of the sternothyroid muscles) and posteriorly by the deep layer of the deep cervical fascia (prevertebral fascia). Initially, the CNC was considered only as LN level Ⅵ and inferiorly bounded by the sternal notch. As the thyroid gland is located low in the neck, its lymphatic drainage is contiguous with the anterior superior mediastinum that can be accessed by a cervical approach. Then, LN level Ⅶ was added to the concept of CNC and its inferior border is actually defined approximately at the level of the innominate artery crossing the trachea on the right and the corresponding axial plane on the left (Figure 1). Anyway, this inferior boundary is more theoretical than practical and somehow arbitrary because the innominate arterial trunk does not exist in the left side and its relation with the sternal notch is variable with the artery rising above the notch in 25% of cadaveric dissections[17].

The CNC contains critical anatomical structures as the trachea, esophagus, parathyroid glands and recurrent laryngeal nerves (RLNs) (Figure 2). Other structures are the larynx, the hipopharynx, cervical thymus, superior laryngeal nerves and vessels (superior and inferior thyroid arteries and superior, middle and inferior thyroid veins).

LN IN CNC: SURGICAL ANATOMY AND TERMINOLOGY

The most commonly involved LN in the CNC in thyroid carcinoma are the prelaryngeal (also known as Delphian), pretracheal and both right and left paratracheal. Paratracheal LN have been also described as *"the nodes of the recurrent laryngeal nodes"* and typically start cranially at the lower margin of the cricoid cartilage and extend caudally to the level of the innominate artery crossing the trachea. The right sided paratracheal LN may be found posterior to the common carotid artery because of its more ventral and medial location compared with the left (Figure 3). LN related to superior pole PTC may sometimes be located in the paralaryngopharyngeal space along the course of the superior thyroid vasculature. Other nodal basins included in the CNC are retroesophageal, retropharyngeal and superior mediastinal

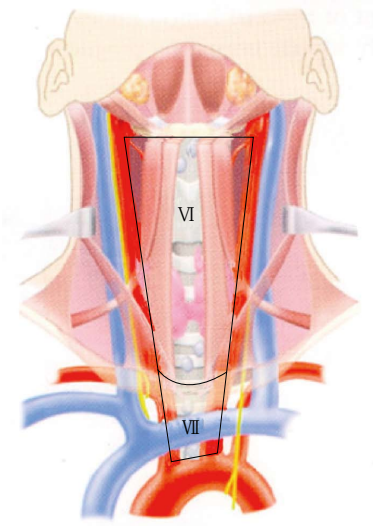

Figure 1 Lymph nodes groups of central neck compartment and their anatomic boundaries.

(inferior to the innominate artery). The mean number of LN in the paratracheal region has found to be an average of 2 to 15 in each side. Weber *et al*[18] reported a mean number of 3.9 paratracheal LN removed (range, 1 to 30) in the analysis the medical records of 645 patients who underwent total laryngectomy for squamous cell carcinoma of the larynx, hypoparynx and cervical esophagus. Pereira *et al*[19] published a mean of 8.4 ± 6.6 nodes resected in the series of 43 patients who had a TT and CNC dissection (CNCD) for PTC.

Generally, cervical LN metastases tend to spread in a stepwise fashion from the thyroid to the ipsi-lateral central LN, then to lateral compartment and/or contra-lateral central compartment. Therefore, the CNC is considered to be the first echelon of LN metastasis in PTC and its removal may theoretically alter the prognosis of this neoplasm. The surgical literature has classically lacked of standardization to define a consistent terminology relevant to the CNCD and this lacking is the main responsible of the great variability and bias in the published series. In 2009, the American Thyroid Association (ATA) published a consensus manuscript with the purpose of establishing the standard definitions to be used in future publications in order to obtain a more effective and safe CNC surgery for TC. This document was supported by the American Association of Endocrine Surgeons, American Academy of Otolaryngology - Head and Neck Surgery and the American Head and Neck Society[20]. The following definitons were suggested (and are still actually accepted) regarding a CNC.

A therapeutic CNCD (*tCNCD*) implies resection of LN metastases that are clinically apparent (cN1) in an attempt to decrease recurrence and theoretically improve survival. Clinical appearance means that there is macroscopic nodal disease grossly apparent preoperatively by physical exam (5%-10%), imaging studies (up to 30% of patients with PTC, biopsy-proven or not) or intraoperatively by visual inspection (LN larger than 1 cm and dark blue or dark appearance).

The most frequently imaging study performed is US of the neck. Preoperative US is recommended for all patients undergoing thyroidectomy for malignancy and may reduce rates of recurrent/persistent disease by allowing an adequate initial surgical treatment[21]. Some sonographic features raising suspicion for LN metastasis have been described: a diameter > 1 cm; loss of the normal fatty hilum; an irregular rounded contour with a long-access to short-access ratio < 1.5; heterogeneous echogenicity; microcalcifications; hypervascularity; and cystic changes. Anyway, US is much more sensitive for detection of metastatic LN in the lateral neck (82%-94%) than in the CNC (30%-60%)[6,22,23]. Detection of LN metastasis in the CNC using US remains difficult even in expert hands beacuse of the abnormal LN are often small in size or microscopic and frequently located deep inside the neck or just posterior to the sternum, where the overlying thyroid gland often hinders adequate visualization[21,23,24]. Kouvaraki *et al*[25] demonstrated that physical examination will miss macroscopic LN metastases in 39% of patients with PTC when a complementary neck US was performed. Although it is well accepted that intraoperative inspection underestimates the presence of pathologically detected nodal metastases, specially microscopic, a recent study documented the reliability of the surgeon to accurately determine the need for tCNCD based on a combination of preoperative US and intraoperative node inspection[26]. Neck computed tomography or magnetic resonance imaging may be appropriate for the assessment of cervical nodal status in centers where experience with neck US is lacking.

A prophylactic, elective or routine CNCD (*pCNCD*) implies resection of LN that are neither apparent clinically nor by imaging methods (cN0) with the theoretical goal of removing undetected metastatic disease and then decreasing persistent local disease. The actual role of pCNCD in PTC remains a major topic of debate and will be widely discussed in this paper.

At a minimum, CNCD should include the prealryngeal, pretracheal and at least one paratracheal LN basin (usually the ipsilateral). LN "plucking" or "berry picking" implies removal only of the clinically involved LN rather than a complete nodal group within the compartment. This LN "plucking" is not recommended because violates the nodal compartment entered without adequately addressing its disease and may be associated with higher recurrence rates.

Finally, every operative record of CNCD should indicate if it has been uni- or bilateral. When bilateral, prelaryngeal, pretracheal and paratracheal right and left nodal groups are removed; for the unilateral CNCD, the difference is that only one paratracheal (right or left) nodal basin is resected.

Thymectomy (uni or bilateral) is usually performed during the CNCD to provide a good clearance of LN level Ⅶ and has been a matter of debate. Huang *et al*[27] recently published a comparative analysis of the incidence of

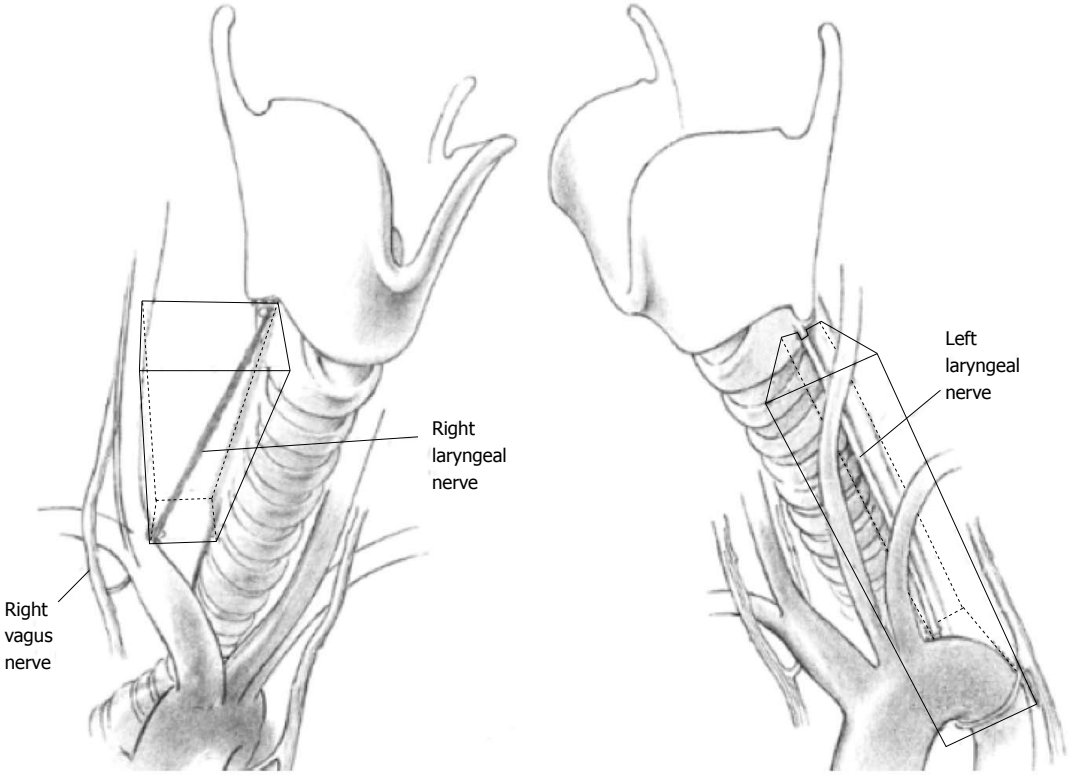

Figure 2 The way of recurrent laryngeal nerves in the central neck compartment.

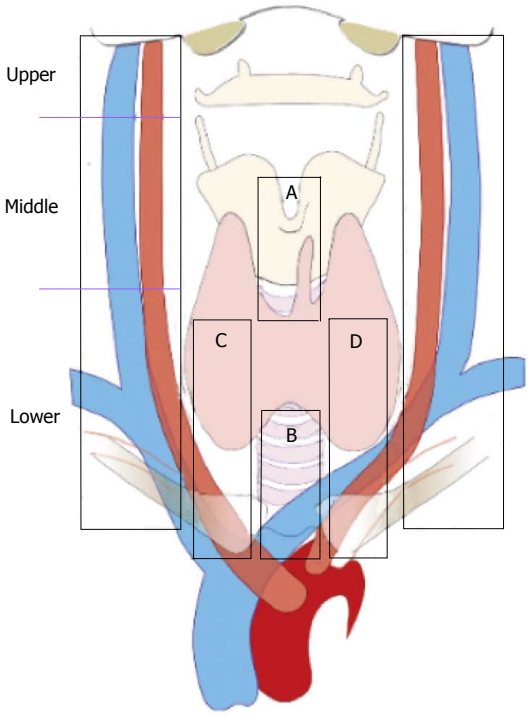

Figure 3 Boxes A, B, C and D representing lymph nodes in the central neck compartment (prelaryngeal, pretracheal and left/right paratracheal).

LN metastases in the thymus in two groups of patients undergoing CNCD with unilateral (n = 73) and bilateral (n = 82) thymectomy for PTC. A very low rate of LN micrometastasis was found in both groups (2.7% *vs* 3.6%, and always ipsilateral to the tumor) and the bilateral group presented a higher rate of transient (but not permanent) hypoparathyroidism (HP) (13.7% *vs* 52.4%). With this results, it seems clear that bilateral thymectomy during the CNCD does not provide a better carcinologic resection as no contralateral thymic metastases were found. The unilateral thymectomy with TT during the CNCD may represent an effective strategy for reducing the rate of postoperative hipocalcemia[27].

THERAPEUTIC CENTRAL NODAL COMPARTMENT DISSECTION

A general consensus exists among the different endocrine/thyroid scientific societies about TT + Therapeutic central neck compartment dissection (tCNCD) being the "gold standard" for the treatment of patients with cN1 PTC. Multiple historical and retrospective series have demonstrated that positive nodal metastases of PTC correlates with increased rates of persistent/recurrent disease and lower overall survival. Then, the rationale of removing grossly evident nodal disease along with any adjacent subclinical disease includes reducing the risk of recurrence and potentially increasing survival.

The first important reference in the medical literature defining the negative impact of age and LN involvement in local recurrence of differentiated thyroid cancer was reported in the classical paper of Harwood *et al*[9]. Globally, tumor recurrence and mortality rates were in 32%/24% and 14%/8% for LN(+) and LN(-) patients, respectively. In patients with more than 40 years old, mortality related

to the tumor was 41% and 15%, respectively, for LN(+) and LN(-) cases[9]. These results were confirmed by Tubiana *et al*[10] (*n* = 546) and Sellers *et al*[11] (*n* = 76), who published both of them series with more than 34 years of follow-up in which age older than 45-50 years old and the presence of cervical LN metastases (specially if palpable) were negative prognostic factors for poorer survival and higher locoregional recurrence[10,11]. Wada *et al*[28], in a retrospective study of 259 patients with PT microcarcinoma and routine CNCD found that recurrence was 16.7% for cN1 (*n* = 24) and only 0.43% (*n* = 235) for cN0 (this latter did not differ with a control group of non-performed CNCD, 0.65%).

Lundgren *et al*[12], in a large popullation-based control-case study, reported a 2.5-fold higher disease-related mortality in patients with differentiated thyroid cancer and LN metastases. Zaydfudim *et al*[13], in a review of the Surveillance, Epidemiology and End Results (SEER) registry found an increased risk of death in patients with PTC aging 45 years or older and having nodal metastasis, with no difference in survival in patients younger than 45 years with or without nodal metastasis. The review of the SEER by Podnos *et al*[29] described a survival at 14 years of 82% for node-negative patients and 79% for node-positive ($P < 0.0001$) being this difference also remarkable in the group with age 45 years or younger (96% N0 *vs* 90% N1). Ito *et al*[30] reviewed retrospectively 759 patients with PTC and found a 63% of central LN metastases which independently predicted worse disease free survival.

National Cancer Comprehensive Network, version 2.2014, establishes that "clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level Ⅵ dissection"[31]. The British Thyroid Association and the Royal College of Physicians, in the third edition of their guidelines in the management of thyroid cancer (2014), recommended that "overt disease in the central compartment discovered prior to/at surgery should be treated by a therapeutic level Ⅵ/Ⅶ node dissection"[32]. The ATA, in the 2009 revised Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer says in recommendation number 27 that "therapeutic central-compartment neck dissection for patients with clinically involved central or lateral neck LN should accompany TT to provide clearance of disease from the central neck"[33]. The Société Française d'Oto Rhino Laryngologie clearly defines the role of tCNCD, with recommendation number 7 being as follows: "when facing cN1 LN disease in the central compartment, it is recommended to avoid performing a berry picking and it is always preferred a compartment oriented central dissection when technically feasible"[34]. Finally, recommendation number 18 of the German Association of Endocrine Surgeons Guidelines is very convincing treating the role of tCNCD: "for clinically node-positive PTC, whatever the size of the thyroid primary, central compartment dissection should be combined with TT *to* diminish the risk of locoregional recurrence and improve survival"[35].

As it can be observed, there is a lot of surgical literature of low evidence level confirming the negative association between LN metastases and recurrence or survival in PTC. Nonetheless, it is also important to remark that data demonstrating improved survival and/or long-term recurrence risk among differentiated thyroid cancer patients treated with tCNCD are also lacking.

PROPHYLACTIC CENTRAL NODAL COMPARTMENT DISSECTION

Although it was longly abandoned at the end of the last century, the debate over the usefulness of prophylactic central neck compartment dissection (pCNCD) has been renewed over the past 10-15 years. During this period, the most important endocrine/thyroid medical and surgical societies have treated this topic in their published guidelines and, curiously, have been changing and swinging their recommendations about the indication of performing pCNCD in PTC. It must be considered that no level of evidence 1 information from prospective randomized trials is available in the literature and that the highest evidence reported is level 4 from retrospective studies comparing contemporaneous cohorts of patients treated with TT with or without pCNCD associated.

The main points for discussion about performing pCNCD are: rates of recurrence free survival and mortality; postoperative thyroglobulin (Tg) levels; importance of accurate staging; and, safety.

It is unknown what the natural history is in patients with PTC with microscopic LN involvement or subclinical nodal metastases (cN0). It is doubtful that they would eventually develop into clinically significant recurrences in the future as the studies of Wada *et al*[28] and Gemsenjäger *et al*[36] reported, the latter with only 17% of LN involved in pCNCD dissection and only 3.44% of nodal recurrence with no deaths related.

An example of how this issue is controversial can be appreciated in the different conclusions of recently reported meta-analysis. The good prognosis of PTC and its natural evolution has resulted in the inability of several studies to demonstrate a difference between TT+pCNCD compared with TT alone because of the short term follow-up. The one published by Lang *et al*[37] included 3331 patients and reported a 35% reduction in the risk of locoregional recurrence for patients with pCNCD (4.7% *vs* 8.6%) but it is not posible to know how much of this reduction is related to an increased rate of patients who underwent postoperative RAI-131 ablation (71.7% *vs* 53.1%). A previous meta-analysis published by Zetoune *et al*[38]. found no difference in recurrence rates favouring pCNCD, and Wang *et al*[16] also failed to evidence a significant difference between TT+pCNCD and TT, but they observed a trend toward a lower local recurrence (4.7% *vs* 7.9%). In Table 1 it can be seen that recent guidelines of the most important endocrine scientific societies about

Table 1 Recommendations of the different international endocrine and thyroid societies about prophylactic central nodal compartment dissection

Scientific Thyroid Society	Year	Recommendations about prophylactic central neck compartment dissection
European Society of Endocrine Surgeons[36]	2014	Recommended in T3 or T4 tumors; age > 45-yr or < 15-yr; male sex; bilateral or multifocal tumors; and, evidence of involved lateral LN
British Thyroid Association[32]	2014	Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of lymph node involvement. May be considered for patients: PTC non-classical type; > 45-yr; multifocal tumors; > 4 cm; and extra-thyroidal extension on US, but benefit is unclear
National Comprehensive Cancer Network (NCCN version 2.2014)[31]	2014	Consider prophylactic CNC dissection in patients with known distant metastases; bilateral nodularity; extrathyroidal extension; tumor > 4 cm; poorly differentiated histology (although the level of evidence is low, NCCN considers the intervention as appropriate)
Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons[40]	2014	Previous 2010 JSTS/JAES guidelines recommended routine bilateral central node dissection in patients who underwent total thyroidectomy. At present guidelines, it is not routinely considered and the indication may depend on institutional policy and surgeons' skill levels, joining ATA phylosophy
Société Française d'Oto Rhino Laryngologie et de Chirurgie de la Face et du Cou[34]	2012	In patients cN0, the diagnostic value of surgical exploration of the CNC is weak. Two different strategies are recommended: a compartment oriented CNC or not performing any surgical tecnique. Nonetheless, in patients with T3/T4 tumors prophylactic CNC dissection is strongly recommended
European Society of Medical Oncology Clinical Practice Guidelines[38]	2012	The benefit of prophylactic central node dissection in the absence of evidence of nodal disease is controversial. There is no evidence that it improves recurrence or mortality rate, but it permits an accurate staging of the disease that may guide subsequent treatment and follow-up
American Thyroid Association[33]	2009	Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)
German Association of Endocrine Surgeons[35]	2013	The clinical benefit regarding locoregional recurrence and survival after prophylactic compartment dissection for clinically node-negative PTC > 10 mm is unproven although occult lymph node metastases are common in this setting. To prevent the risk of surgical complications from outweighing a conceivable oncological benefit, prophylactic lymph node dissection is not advised unless the requisite surgical expertise is available

PTC: Papillary thyroid carcinoma; CNC: Central neck compartment; NCCN: National Comprehensive Cancer Network; ATA: American Thyroid Association; JSTS: Japanese Society of Thyroid Surgeons; JAES: Japanese Association of Endocrine Surgeons; LN: Lymph nodes.

pCNCD are dim and use very vague expressions[31-35,39-41]. A global analysis of this table led us to consider pCNCD only in selected group of patients with recognized factors of higher locoregional recurrence (specially T3/T4 tumors, bilateral or multifocal tumors and age older than 45 years). Some reports agree that the mutation of BRAF V600E is associated with tumor aggressiveness, a poor prognosis, resistance to postoperative RAI therapy and the need for a more extended surgery. However, the potential role of the preoperative assessment of BRAF V600E mutation status in decisions regarding whether to perform pCNCD remains controversial. When the necessity of pCNCD in patients with PTC is preoperatively determined, we should recommend to perform pCNCD if BRAF V600E mutation and other conventional clinical risk factors are coexistent[42]. All these data suggest that the benefit provided by a pCNCD in cN0 patients may only be limited in terms of recurrence and that a prospective study with a very long follow-up, homogenous population and rigurous inclusion criteria is needeed. Nonetheless, a randomized controlled trial will hardly be performed because it has been estimated to cost $20000000 and would need 5840 patients to achieve statistical power[43].

As it would be expected, pCNCD has not shown any cancer-specific survival benefit. Costa *et al*[44], in a study on a group of 244 PTC who underwent TT+pCNCD or TT alone, did not find any difference in recurrence rates (6.3% *vs* 7.7%) or survival even when 47% of pCNCD showed LN involvement. Zuniga *et al*[45] also had a rate of 82.3% patients with LN involved after pCNCD but similar 5-year disease-free survival (88.2% *vs* 85.6%) was obtained for this cohort when compared to that having only TT. The most recent controversy has been provided by Barczyński *et al*[46], who has published the first paper in the literature showing a benefit not only for local recurrence (5.5% *vs* 12.4%) but also for specific disease survival (98% *vs* 92.5%) for patients with PTC having TT + pCNCD (n = 358) in comparison with those who had only TT (n = 282). Major bias in this study are its retrospective nature and that patients considered at risk in any group had RAI treatment.

Complete remission of PTC is defined by normal US and negative Tg levels in blood in the follow-up. Theoretically, pCNCD will result in higher rate of undetectable levels of Tg, facilitating follow-up and cancer surveillance and being a good surrogate for recurrence. Nonetheless, this difference may be overlaped by administration of postoperative RAI.

Lang *et al*[47] examined the results of surgical treatment of 185 patients PTC having TT + pCNCD (n = 82) or only TT (n = 103). The first group had lower median postoperative Tg levels (0.5 μg/L *vs* 6 μg/L) and higher rate of athyroglobulinemia (51.2% *vs* 22.3%) both of the differences with $P < 0.05$. When RAI was indicated by clinical or histological risk criteria, similar values with no significative differences were achieved six mo later. The only explanation posible is that residual microscopic disease not treated by pCNCD surgery in the TT-alone group was ablated by radioiodine administration. So *et al*[48], in a similar study comparing 113 patients having

TT alone with 119 undergoing TT+pCNCD found that the latter had significative lower levels of Tg (1.07 ng/mL *vs* 2.24 ng/mL), but this difference disappeared when low-dose RAI ablation was given and 3 years locoregional control was similar in both groups (96.5% *vs* 98.3%). Sywak *et al*[49] used Tg levels in an attempt to support pCNCD in his study of 447 PTC patients cN0 undergoing TT alone (n = 391) or TT+pCNCD (n = 56) and having RAI ablation following a similar algorithm. Mean postablation Tg levels were lower in the pCNCD (0.4 mg/L *vs* 9.3 mg/L, $P < 0.02$) and also was the rate of undetectable Tg levels (72% *vs* 43%, $P < 0.001$). However, no significant differences were found in locoregional recurrence rates (3.2% *vs* 5.6%) or cancer-specific mortality rates (0% *vs* 0%) despite a shorter median follow-up duration (25 mo *vs* 70 mo) in the pCNCD group. It can be thought that the impact of performing pCNCD to obtain an analytical control of the disease is more theoretical than really useful[49].

Performing a pCNCD provides the most real and adequate TNM staging for PTC and upstages 30%-50% of patients from cN0 to pN1. Then, patients aging 45 yr or older and having tumors staged as TNM Ⅰ (T1N0) or Ⅱ (T2N0) become TNM Ⅲ (T1 or T2 with N1a/b). The immediate consequence of stage migration is a different rate of overall cancer-specific survival (85%-90% for stage Ⅲ, 95% for stage Ⅰ). In addition, pN1 patients will be included in the ATA group of intermediate risk of recurrence and will receive RAI ablation at higher dosis, while T1 or T2 with cN0 patients are usually included in the low risk of recurrence group and receive lower dosis of RAI ablation. A recent systematic review published by Sawka *et al*[50] showed, however, that there is no benefit from RAI in reducing disease-specific mortality or recurrence in early stages (T1/T2). Bonnet *et al*[51] reviewed the records of 115 patients with PTC < 2 cm (T1) and cN0 undergoing pCNCD, considering the ATA guidelines and indicating RAI ablation for T1 PTC only if LN involvement existed. LN metastases were found in 42% and, globally, 58% of patients received RAI treatment (age < 18 years, aggressive cell types on pathology and vascular or capsular invasion were the other indications diferent than LN+ for RAI ablation). LN status modified the indication of RAI treatment in 30.5% of patients (14.65% were T1a tumors, < 1 cm, which resulted in pN0 and 15.85% were T1b tumors, between 1-2 cm, which resulted in pN1). Morbidity was limited to a 0.9% of permanent HP and the same percentage of RLN palsy. One year follow-up revealed 97.4% of patients with normal neck US and undetectable Tg levels, concluding the authors that, for T1 PTC, a pCNCD may change the need for RAI ablation without increasing the standard rate of complication or the risk of local recurrence[51].

Hughes *et al*[52] observed that patients with TT + pCNCD had higher dose of RAI than those with only TT (150 *vs* 30 mCi, P = 0.01), and Moo *et al*[53] found similar results (102.7 *vs* 66.3 mCi, P = 0.002). In both series, there was no difference in the rates of central neck recurrence or survival between both groups. Then, pCNCD allows better staging and stratification with more patients in early stage recieving higher dose of RAI ablation. Nevertheless, neither local recurrence rates nor survival are affected, some patients who will have no oncological benefit are exposed to potential side effects of RAI and, finally, health care costs are increased.

Safety can not be used nowadays to justify not performing a pCNCD in patients with PTC. CNC resection means wide dissection and sometimes gentle manipulation of the RLNs (which may result in temporary or permanent dysphonia up to 1%-3%) and clearance of all the fatty and lymphatic tissue aorund the parathyroid glands (which may be unintentionally removed o devascularised causing permanent or transient HP in, respectively, 2%-5% and 10%-50% respectively).

Lang *et al*[37] found that patients with pCNCD were 2.5 times more likely to have temporary HP than those undergoing TT alone in a systematic review reporting short-term results of patients operated for PTC. A recent meta-analysis about adverse effects of TT compared with TT + pCNCD included 1132 patients from 5 retrospective studies and found that there was one extra case of transient HP for every 8 (most exactly, 7.7) pCNCD performed. However, there was no increased risk of permanent HP and RLN injury[54]. Although some isolated series have reported higher rates of temporary RLN lesions with pCNCD (always with non-significant values of "*P*"), to date no studies have shown an increased risk of permanent RLN injury[55-57].

If pCNCD is not performed, the patient is at risk for central recurrence and may require a second operation in order to remove persistent or recurrent nodal disease. Because of the presence of fibrosis and scar tissue, re-operation may be associated with higher morbidity than pCNCD done at the first surgery. Segal *et al*[58] reviewed 503 patients retrospectively operated on for PTC, and the 48 requiring reoperation had higher complication rates of permanent RLN injury (25% *vs* 8%) and permanent HP (8.3% *vs* 5%). Simon *et al*[59] reported 77 patients undergoing a second surgery for recurrence out of a total of 252 primarily operated PTC, also being rates of permanent RLN palsy (6.8% *vs* 2.6%) and HP (3.9% *vs* 1.7%) higher for the re-operative group. On the other hand, Shen *et al*[60] found similar results in all the parameters analysed related to morbidity between first time performed pCNCD (n = 189) and re-operated patients (n = 106) with PTC (permanent HP, 0.5% *vs* 0.9%; permanent hoarseness, 2.6% *vs* 1.9%; and, transient hoarseness, 4.8% *vs* 4.7%).

As a conclusion, when an extensive review of the literature is done there seems to be no arguments favouring routine or pCNCD as an universal rule for patients with PTC. The guidelines and consensus documents of the most important medical and surgical societies are in the direction of selecting subgroups of patients with high risk of recurrence for pCNCD, specially T3 or T4 tumors, multifocal/bilateral tumors and patients with BRAF V600E mutation detected in the preoperative setting. In the rest

of PTC, which are the majority, TT must be considered an oncological proper treatment providing the best overall survival.

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REVIEW

Comprehensive treatment for the peritoneal metastasis from gastric cancer

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Abstract

Recently, a novel comprehensive treatment consisting of cytoreductive surgery (CRS) and perioperative chemotherapy (POC) was developed for the treatment of peritoneal metastasis (PM) with a curative intent. In the treatment, the macroscopic disease is completely removed by the peritonectomy techniques in combination with POC. This article reviews the results of the comprehensive treatment for PM from gastric cancer, and verifies the effects of CRS and POC, including neoadjuvant chemotherapy (NAC) and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Completeness of cytoreduction, peritoneal carcinomatosis index (PCI) less than the threshold levels after NAC,

absence of ascites, cytologic status, pathologic response after NAC are the independent prognostic factors. Among these prognostic factors, PCI threshold level is the most valuable independent prognostic factor. After staging laparoscopy, patients with PM from gastric cancer are recommended to treat with NAC before CRS. After NAC, indication for CRS is determined by laparoscopy. The indications of the comprehensive treatment are patients with PCI less than the threshold levels, negative cytology, and responders after NAC. Patients satisfy these factors are the candidates for the CRS and HIPEC.

Key words: Gastric cancer; Hyperthermic intraoperative intraperitoneal chemotherapy; Peritoneal metastasis; Peritonectomy

Core tip: This article reviews the results of the comprehensive treatment for peritoneal metastasis from gastric cancer, and verifies the effects of cytoreductive surgery and perioperative chemotherapy, including neoadjuvant chemotherapy (NAC), and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Multivariate analyses revealed that the completeness of cytoreduction, peritoneal cancer index less than the threshold levels after NAC, cytologic status, pathologic response after NAC are the independent prognostic factors. Patients satisfying these factors are recommended to undergo D2-gastrectomy combined with complete removal of PC and HIPEC.

Yonemura Y, Canbay E, Endou Y, Ishibashi H, Mizumoto A, Li Y, Liu Y, Takeshita K, Ichinose M, Takao N, Saitou T, Noguchi K, Hirano M, Glehen O, Brűcher B, Sugarbaker PH. Comprehensive treatment for the peritoneal metastasis from gastric cancer. *World J Surg Proced* 2015; 5(2): 187-197 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i2/187.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i2.187

INTRODUCTION

Peritoneal metastasis (PM) was considered as a terminal stage with very poor prognosis. In the late 1990s, Peritoneal Surface Malignancy Oncology Group International proposed a novel comprehensive treatment consisting of cytoreductive surgery (CRS) and perioperative chemotherapy (POC). In the comprehensive treatment, the macroscopic disease is completely removed by the peritonectomy techniques in combination with POC. POC includes neoadjuvant intraperitoneal/systemic chemotherapy (NIPS), bidirectional intraperitoneal and systemic induction chemotherapy (BISIC), laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC), hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC), extensive intraoperative peritoneal lavage (EIPL), early postoperative intraperitoneal chemotherapy and late postoperative systemic chemotherapy[1-3].

This article reviews the rationale of the comprehensive treatment for PM from gastric cancer.

Quantitative evaluation of PM

Preoperative and intraoperative diagnosis for PM should provide reliable information about the tumor burden and distribution of PM[4,5]. At present, the peritoneal carcinomatosis index (PCI) is used worldwide[5]. The abdominal compartments were divided into 13 sectors. The tumor involvement in each compartment is macroscopically evaluated by the lesion size scores from 0 to 3. PCI described the tumor load in the abdominal cavity from 0 to 39. PCI score is considered an important prognostic indicator after CRS. Threshold levels of PCI for favorable *vs* poor prognosis were reported from several high volume centers. Glehen *et al*[6,7] reported that all patients died within 3 years after CRS when the PCI score was higher than 12. Even if complete cytoreduction appears to be possible, patients with PCI of higher than 12 should be contraindicated for the aggressive CRS[7]. Yonemura *et al*[8] reported patients with PCI of lower than 6 survived significantly better than those with PCI of higher than 7. Yang *et al*[9] proposed the best candidates for the CRS could be patients with PCI < 20. To select patients for CRS, PCI assessed by preoperative computed tomography (CT) may have an important role. However, the accuracy of CT for the preoperative evaluation of PM from gastric cancer is limited, because the size of PM from gastric cancer is usually small[10].

In the preoperative evaluation for PM, Hong *et al*[11] proposed a new classification consisting of three grades. Grade 0 was defined as PM detected during operation with no evidence of PC in the preoperative evaluation, and grade 1 was defined as PM or ascites detected by CT scan, however, no bowel involvement or need for paracentesis was recorded. Grade 2 was defined as bowel wall involvement or a large amount of ascites requiring paracentesis[11]. When the grade 0 and grade 1 were summed as low-grade and grade 2 was defined as high-grade, survival of patients with low-grade PM was significantly longer than the patients with high-grade PM. Among the patients with low-grade PC, patients who received a gastrectomy had longer survival than those who did not receive a gastrectomy[11]. This staging system is useful to determine the indication of gastrectomy or systemic chemotherapy.

In the Japanese general rules of gastric cancer treatment, status of PM is grouped into three categories: P0/Cy0, Po/Cy1, and P1[12]. P0/Cy0 status is no macroscopic PM and a negative peritoneal wash cytology. P0/Cy1 status shows no macroscopic PM but positive peritoneal wash cytology, and P1 status means the macroscopic PM with or without a positive peritoneal cytology. The survival of patients with P0/Cy1 is similar to that of patients with P1[13,14]. The proliferative activities of peritoneal free cancer cells (PFCCs) is considered

high[14]. Accordingly P0/Cy1 status is classified into stage Ⅳ disease even in patients with no macroscopic PM. Bando *et al*[13] reported that 114 (11%) of 1039 potentially curable patients showed positive cytology (P0/Cy1).

However, there is no universal consensus on the most appropriate treatment regimen for this particular group of patients. Cabalag *et al*[15] performed a meta-analysis of treatment results in patients with P0Cy1 status. The use of S1 monotherapy was associated with a significant survival benefit[16]. A recent randomized controlled trial examining EIPL with intraperitoneal chemotherapy (IPC) showed a significant improvement on overall survival (5-year overall survival, 43.8% for EIPL plus IPC group compared with 4.6% for IPC group)[17]. In addition, the role of gastrectomy remains unclear in patients with P0/Cy1[18]. Furthermore, Kang *et al*[19] reported that peritoneal washing cytology was not able to predict peritoneal recurrence or survival in gastric cancer patients[19]. These results indicate that more clinical trials should be done to define the best treatment option for patients in P0/Cy1 status.

Score of the completeness of cytoreduction

Score of the completeness of cytoreduction score (CC score) is an assessment grade after CRS[4]. The residual disease after CRS is classified into four grades of CC-0 to CC-3. CC-0 indicates a status of no macroscopic residual tumors after CRS. CC-1 means residual tumor burden of less than 2.5 mm in diameter. CC-2 shows that the total tumors between 2.5 mm and 25 mm in diameter are left. CC-3 means the residual tumor of greater than 25 mm in diameter. The CC-1, CC-2 and CC-3 are evaluated as the incomplete cytoreduction. Histological positive margin is classified CC-1[2].

The role of CRS in the comprehensive treatment

CRS or chemotherapy alone can not confer the cure for patients with PM. In contrast, CRS combined with intraperitoneal chemotherapy applications improves a long-term survival, because invisible metastasis left after CRS can be eradicated by intraperitoneal chemotherapy[3]. Accordingly, the comprehensive treatment is now justified a state-of-the-art treatment for patients with PM.

Among the treatment options using in the comprehensive treatment, the completeness of CRS is the important prognostic factor[8,20]. Survival of patients underwent incomplete cytoreduction was not improved, as compared with that of patients treated with chemotherapy alone[2]. In contrast, patients underwent complete cytoreduction survived significantly longer than those treated with incomplete cytoreduction or chemotherapy alone. PCI score correlates with the completeness of cytoreduction. CC0 was achieved in 91% of the patients when the PCI score was lower than 6, but in only 42% of the patients with a PCI $\geqslant$ 7[8]. Even in patients with complete cytoreduction, all patients with PCI higher than the threshold value died of the recurrence[7,8]. Accordingly, surgeons should decide to perform CRS for CC-0 after counting PCI score.

Peritonectomy techniques to achieve CC-0 CRS for PC from gastric cancer

The final goal of CRS is to remove all macroscopic PM, including primary tumor, the regional lymph nodes and PM, using peritonectomy technique[1,8,14]. Peritonectomy procedures include parietal and visceral peritonectomy. In parietal peritonectomy right and left subdiaphragmatic peritonectomy, pelvic peritonectomy, peritonectomy of right and left para-colic gutter and Morrison's pouch are removed. In visceral peritonectomy, multivisceral resection of small bowel, colon, rectum, spleen, gall bladder, uterus, vagina, lesser omentum, and omental bursa, are performed when they are involved. To remove primary tumor, total gastrectomy in combination with D2 lymph node dissection is usually done. Piso *et al*[21] reported that the incidences of postoperative morbidity and mortality after gastric resection and peritonectomy were acceptable even when combined with HIPEC.

For the skin incision, a generous midline skin incision starting at the xiphi-sternal junction above to symphysis pubis below is designed. If there is a scar of previous operation, it should be included in the skin incision. Ascites is then aspirated through a small window made on the peritoneum, and the ascites is studied for cytological examination. Before starting CRS, EIPL is done[17]. The peritoneal cavity is extensively shaken and washed after injection of 1 L of saline, and then the saline is completely aspirated. This procedure is repeated 10 times[17]. The rationale of EIPL is the removal of PFCCs from the peritoneal cavity by 10 times wash with 1 L of saline according to the "limiting dilution theory".

Parietal peritoneum is dissected off from the posterior sheath of rectus muscle (Figure 1). Then the dissection between diaphragm and peritoneum is done by ball-tip electrosurgery[14]. On the left upper quadrant, spleen and right subdiaphragmatic peritoneum are dissected from the anterior renal fascia, and the dissection plane reaches to the left side of celiac axis (Figures 2 and 3). Stomach is isolated from the attachment of lesser onentum to the Arantius' duct, and hepatoduodenal ligament by ligation of right gastric artery (Figure 4). On the right upper quadrant, complete stripping of the peritoneum covering subdiaphragmatic muscle, and the retroperitoneum covering on Morrison's pouch is dissected. Second portion of duodenum is identified and the anterior leaf of transverse mesocolon is removed with greater omentum (Figures 5 and 6). Then, 1st portion of the duodenum is cut at 1cm from pyloric ring. The proper hepatic artery and common hepatic artery are skeletonized by electro-surgical techniques. The left gastric artery and left coronary vein are cut at the roots. Esophagus is transected above the esophago-gastric junction, and the proximal margin of esophagus is sent to pathologic department to confirm the negative proximal surgical margin. Next, lymph nodes along splenic artery and splenic hilum are dissected and then splenic artery and

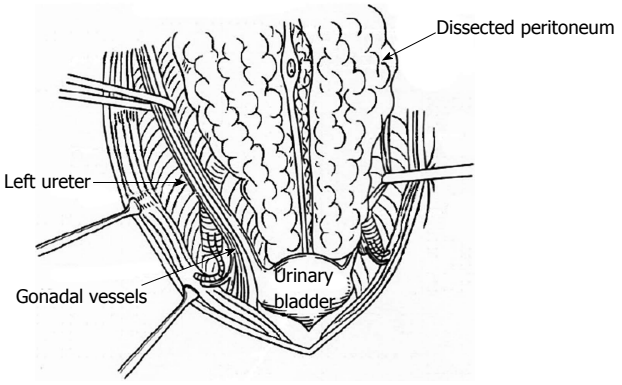

Figure 1 Dissection of the lower parietal peritoneum.

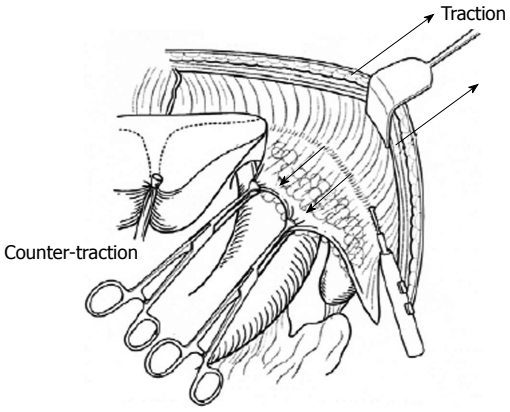

Figure 2 Dissection of the upper right parietal peritoneum.

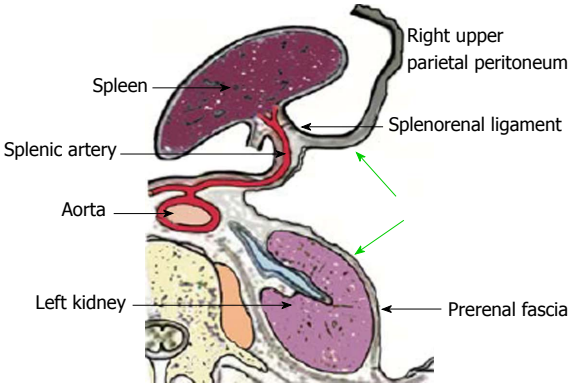

Figure 3 Mobilization of spleen and pancreas tail. The prerenal fascia is cut and the anterior surface of the left adrenal gland is visualized.

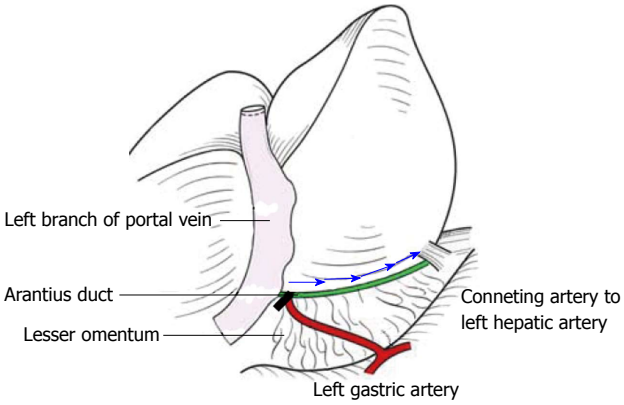

Figure 4 Detachment of lesser omentum from Arantius' duct.

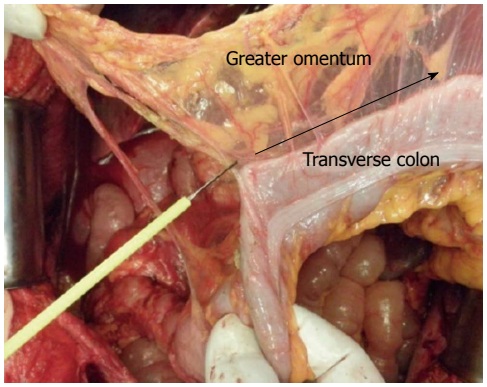

Figure 5 Detachment of greater omentum from transverse colon.

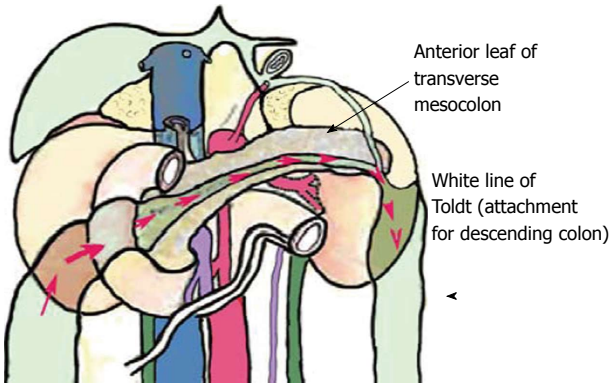

Figure 6 Dissection plane between posterior and anterior transverse mosocolon.

vein are cut at proximal part of their divergence.

Pelvic peritonectomy is started by stripping the peritoneum covering the urinary bladder. In male, anterior dissection plane reaches to the rectovesical pouch. In female, vagina is cut below the uterine cervix (Figure 7). After cutting and ligating the uterine vessels, vagina is transected with electric knife. Then, the posterior wall of vagina is dissected from the rectum. Rectum is freed from the pelvic structure. The posterior dissection reaches to the S4 presacral space by the preservation of pelvic nerve plexus and hypogastric nerve.

If the rectum is not involved, rectum-preserving pelvic peritonectomy is done (Figure 8).

When the rectum is involved, rectum is transected at 2 cm below cul-de-sac (Figure 9).

In terms of the treatment of ovarian metastasis from appendiceal mucinous neoplasm, Elias *et al*[22] proposed the preservation of ovaries in young women with appendiceal mucinous neoplasm for the childbearing, when the ovaries are macroscopically normal. Recurrence in the preserved ovary was found in 14% (3/21), and two women became pregnant after ovary-preserving peritonectomy. In patients with PM from gastric cancer,

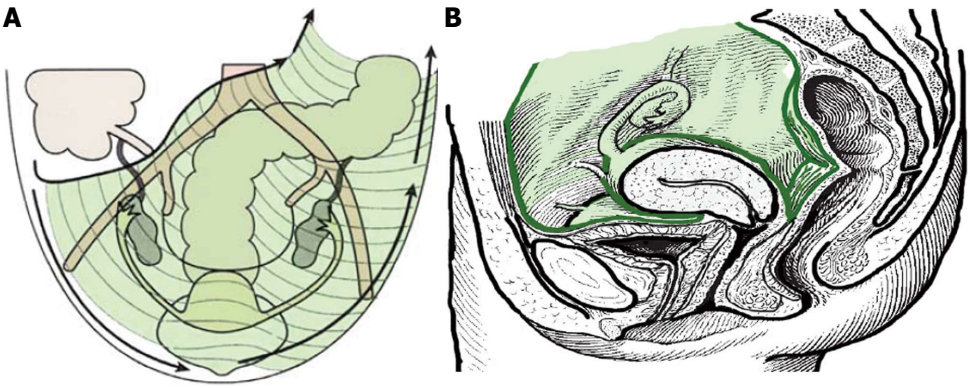

Figure 7 Stripping of the pelvic peritoneum. A: Stripping of the pelvic peritoneum from the urinary bladder and side walls of the pelvis in male; B: Stripping of the pelvic peritoneum with uterus and ovaries in female.

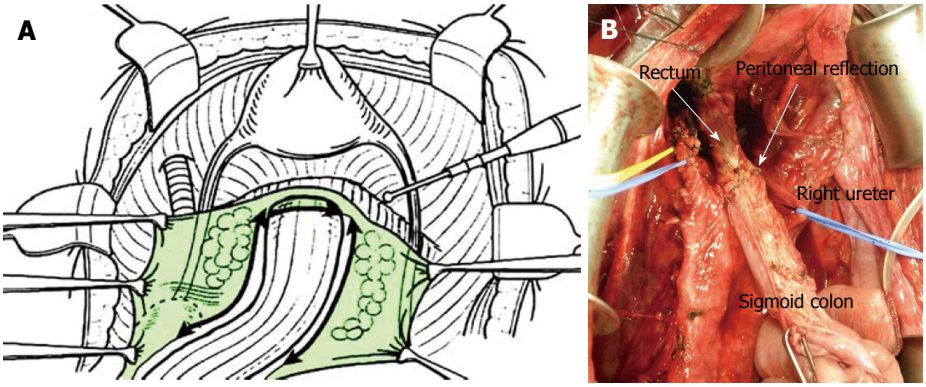

Figure 8 Rectum-preserving peritonectomy. A: The pelvic peritonectomy is started by stripping the peritoneum covering urinary bladder and recto-vesical pouch in male.and the dissection plane reaches the anterior wall of the rectum; B: Photograph after removal of pelvic peritoneum. Rectum is preserved completely.

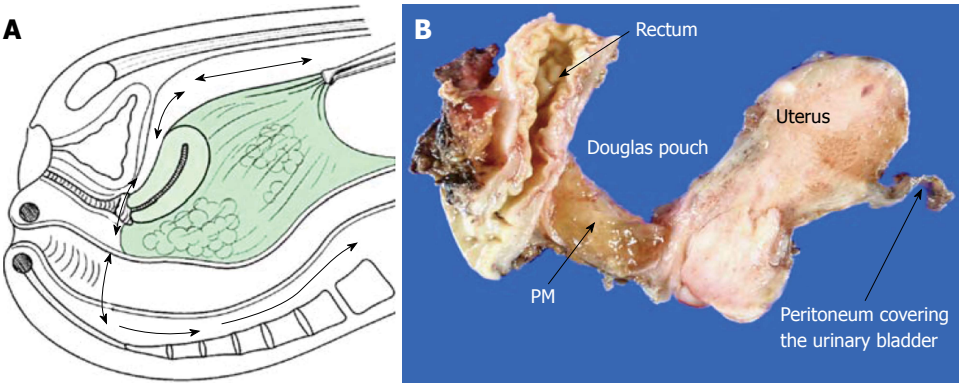

Figure 9 Pelvic peritonectomy combined with the resection of rectum, uterus and vagina (A) and cut-section in a specimen of low anterior resection of rectum/hysterectomy/bilateral salphyngo-oophorectomy shows peritoneal metastasis on Douglas pouch (B).

however, ovaries should be removed, because the incidences of ovarian and uterine involvement are higher than those from appendiceal mucinous neoplasms. In addition, the biological behavior of gastric cancer is more malignant than that of appendiceal mucinous neoplasms.

NEOADJUVANT CHEMOTHERAPY

Complete cytoreduction is the strongest independent prognosticator[2-4]. However, survival of patients with PCI higher than the threshold value is poor, even if they received complete cytoreduction.

By the preoperative laparoscopic examination, Yonemura *et al*[23] reported that 21 (60%) of 35 patients without NAC showed the PCI score higher than the threshold level. Valle also reported that CC-0 can be achieved only in fewer than 30% of the cases who had not been treated with neoadjuvant chemotherapy (NAC)[24]. These results indicate that the patients with PCI higher than the threshold value diagnosed by

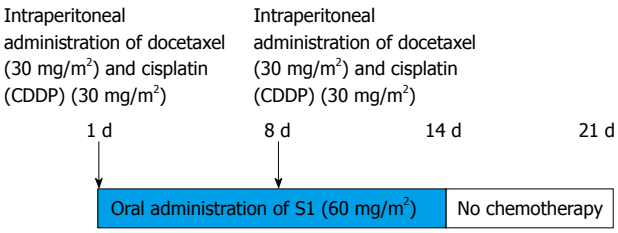

Figure 10 Neoadjuvant intraperitoneal/systemic chemotherapy. Oral S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is administered for 14 d at a dose of 60 mg/m^2, following 7 d rest. Docetaxel (30 mg/m^2) and cisplatin (CDDP) (30 mg/m^2) are administered by intraperitoneal infusion on day 1 and days 8. Therapy is repeated three times, and laparptomy is done 3 to 4 wk after the last cycle.

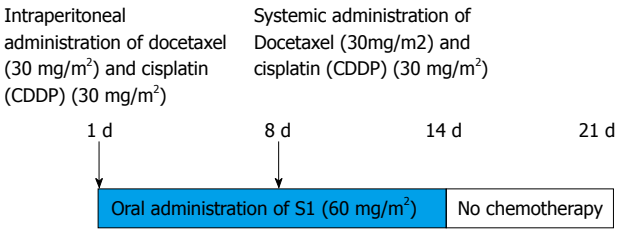

Figure 11 Bidirectional intraperitoneal and systemic induction chemotherapy. Oral S-1 is administered for 14 d at a dose of 60 mg/m^2, followed 7 d rest. Docetaxel (30 mg/m^2) and cisplatin (CDDP) (30 mg/m^2) are administered by intraperitoneal infusion on day 1, and the same dose of docetaxel and CDDP are systemically administered on days 8. Therapy is repeated three times, and laparotomy is done 3 to 4 wk after the last cycle.

Table 1 Peritoneal wash cytology before and after bidirectional intraperitoneal and systemic induction chemotherapy

Cytology	Cytology after BIPSC		
Before BIPSC	Negative	Positive	Total
Negative	15	0	15
Positive	26 (79%)	7	33
	41	7	48

Peritoneal wash cytology was done through a peritoneal port system after intraperitoneal administration of 500 mL of saline. BIPSC: Bidirectional intraperitoneal and systemic induction chemotherapy.

Table 2 Peritoneal wash cytology before and after neoadjuvant intraperitoneal/systemic chemotherapy

Cytology	Cytology after NIPS		
Before NIPS	Negative	Positive	Total
Negative	47	1	48
Positive	69 (70%)	30	99
	116	31	147

NIPS: Neoadjuvant intraperitoneal/systemic chemotherapy.

preoperative laparoscopy should be treated by NAC to reduce PCI less than the threshold level for good prognosis before CRS.

The aims of NAC are to achieve stage reduction to eradicate micrometastasis and PFCCs in the peritoneal cavity, and to improve the incidence of complete cytoreductiom.

Although systemic chemotherapy is still the standard treatment option for NAC[23,25,26], the response rates for PM after systemic chemotherapy were reported to be very low[23,26]. After systemic chemotherapy, treatment failure as a result of toxicity was also reported[26-29]. The reason why systemic chemotherapy does not work on PM is considered the existence of a blood-peritoneal barrier (BPB). BPB is a barrier consisting of stromal tissue between mesothelial cells and submesothelial blood capillaries[30]. BPB hinders the penetrating of drugs from systemic circulation into the peritoneal cavity. Accordingly, significantly larger amount of the drugs administered by systemic chemotherapy moves to the vital organs other than the peritoneum, resulting in the development of adverse effects.

In contrast, intraperitoneal (IP) chemotherapy generates a higher locoregional intensity of drugs in the peritoneal cavity than systemic chemotherapy[31,32]. During IP chemotherapy, the area under the curve (AUC) ratios of IP *vs* plasma exposure (PE) become high. Significant high AUC IP/PE ratios were found after the IP administration of paclitaxel, docetaxel, gemcitabine, 5-fluorouracil and doxorubicin[32]. The intraperitoneal concentrations of these drugs maintain long time because the molecular weights of these drugs are high.

In IP chemotherapy, penetration distance varies from drug to drug and drugs with a high penetration activity into the PM nodules should be selected. In the experimental PM, cisplatin penetrate approximate 2 mm from the surface of PM[31,32].

Recently, a combination chemotherapy of IP administration of cisplatin and docetaxel in combination with the oral administration of S-1 was developed and this method is designated NIPS (Figure 10)[28]. Yonemura *et al*[33] reported that PFCCs were eradicated by NIPS in 69% of patients with positive cytology before NIPS. Histologic examination of the resected specimens of PM after NIPS showed a complete histologic response rate of 37%. In addition, down staging was experienced in 15% of patients[33], and the survival of histological responder after CRS was significantly better than that of non responders. Accordingly, NIPS improves the complete cytoreduction rates, resulting in the long term survival after NIPS plus CRS.

More recently, a new regimen consisting of alternate administration of systemic and intraperitoneal chemotherapy was proposed. This method is called BISIC. By the alternate administration of systemic and IP chemotherapy, a wider treatment area can be treated than IP administration alone. Yonemura *et al*[34] reported a new method of BISIC. Oral S-1 is administered for 14 d at a dose of 60 mg/m^2 per day, followed by 7 d rest. Docetaxel (30 mg/m^2) and cisplatin (CDDP, 30 mg/m^2) are administered by IP infusion on day 1, and the same dose of docetaxel and CDDP are administered intravenously on day 8 (Figure 11). Therapy is repeated three times, and laparotomy is done two weeks after the last administration of S-1 (Figure 10). As shown in Table 1, 79% of patients with positive cytology before BISIC

Table 3 Histoloogic effects of primary tumor and peritoneal carcinomatosis in 41 patients after bidirectional intraperitoneal and systemic induction chemotherapy

	EF-0	EF-1	EF-2	EF-3	Total
Primary tumors	3 (12%)	15 (58%)	7 (27%)	1 (4%)	26 (100%)
Peritoneal metastasis	7 (17%)	18 (44%)	7 (17%)	9 (22%)	41 (100%)

EF-0: No histological change or histologic change is found in less than one-third of the tumor tissue; EF-1: Degeneration of cancer cells is detected in the tumor tissue ranging from one-third to less than two thirds; EF-2: The degeneration of cancer cells is found in more than two-thirds of the tumor tissue; EF-3: Complete disappearance of cancer cells.

Table 4 Histoloogic effects of primary tumor and peritoneal carcinomatosis in 147 patients with PC treated with neoadjuvant intraperitoneal/systemic chemotherapy

	EF-0	EF-1	EF-2	EF-3	Total
Primary tumors	13 (18%)	38 (54%)	20 (28%)	0	71 (100%)
Peritoneal metastasis	59 (40%)	35 (24%)	14 (10%)	39 (25%)	147 (100%)

Table 5 Side effects during bidirectional intraperitoneal and systemic induction chemotherapy

Grade 0	Grade 1-2	Grade 3	Grade 4	Grade 5	Total
44 (76%)	8 (14%)	4 (7%)	2 (3%)	0 (0%)	58

Experienced grade 3 side effects were meningitis in 1, ileus in 1 and bone marrow suppression in 2 patients. Grade 4 side effects of diarrhea and port infection were experienced in two patients.

became negative cytology after 3 cycles of BISIC (Table 1). Table 2 shows the changes of the cytologic status before and after NIPS. After NIPS, 70% of patients with positive cytology before NIPS became negative cytology. Histologic response rates in PC after BISIC and NIPS were 83% (34/41) and 60% (88/147), respectively (Tables 3 and 4). There was a statistical significance in histologic response rate between BISIC and NIPS. Complete pathologic response on primary tumor and PM were found in 4%, (1/26), and 22% (9/41) of patients treated with BISIC (Table 3).

Ishigami *et al*[35] reported a new BISIC method using systemic and IP paclitaxel (PTX) combined with S-1. The overall response rate was 56%, and one-year overall survival rate was 78%.

A systemic review and meta-analysis, IP chemotherapy combined with CRS is associated with significant improved overall survival[36].

From these results, NIPS and BISIC are effective treatments to eradicate PFCCs and to reduce PCI before CRS.

Yonemura *et al*[34] reported that the incidences of major complications (grade 3, 4, and 5) during NIPS and BISIC were 10.4% and 9.9%[35-37] (Table 5). These values are similar to the major complication rates after systemic chemotherapies[28,38], and are considered to be acceptable.

Although NIPS/BIPSC may improve the incidence of complete cytoreduction at CRS, NIPS might increase the morbidity and mortality after CRS. Yonemura *et al*[38] reported that the hospital death occurred in 3.7% of patients after NIPS plus CRS, and postoperative major complications occurred in 24.4% of patients. Reoperation was done in 7.6% (6/79) of patients. Glehen *et al*[7] reported a mortality rate of 4%, and a major complication rate of 27%. The magnitude of surgery, number of resected organs and anastomoses, and the operation time contribute to the development of complication after CRS plus HIPEC. To avoid futile CRS, the patients for the candidate of CRS should be strictly selected. For the selection of patients, preoperative PCI assessment by laparoscopy is important.

ROLES OF LAPAROSCOPY

There are limitations to estimate the precise PCI by CT, magnetic resonance imaging and positron emission tomography[10]. The sensitivity of the diagnosis for the PM smaller than 10 mm in diameter by CT is reported to be only 8%[10].

To improve the preoperative correct diagnosis of PCI and to select the patients for CRS, staging laparoscopy was introduced[39]. Laparoscopy enables to know the histological and cytological diagnosis and to evaluate the effects of NAC. In addition, LHIPEC just after the laparoscopic diagnosis of PM was developed[39]. Very high response on ascites by LHIPEC was reported[39]. Penetration distance of drugs into the PM in LHIPEC (closed HIPEC) is longer than that in open HIPEC performed under the laparotomy, because the intraperitoneal pressure in closed HIPEC is significantly higher than that in the open HIPEC[40].

So far, no evidence was reported about the direct effects on PM by HIPEC. Yonemura *et al*[23] first reported a direct effect of HIPEC on PM from gastric cancer. Two cycles of diagnostic laparoscopy and LHIPEC with an interval of one month were done for 50 gastric cancer patients with PM. Ascites completely disappeared or decreased in 64.7% (22/34) of patients and 20 patients with positive peritoneal cytology at the 1st LHIPEC became negative cytology in 14 (70%) patients at the 2nd LHIPEC. Six (12%) patients showed complete disappearance of PM and PCI was significantly reduced from 14.3 ± 10.2 at the 1st LHIPEC to 10.8 ± 10.5 at the 2nd LHIPEC ($P < 0.05$). Furthermore, total PCI scores (6.56 ± 2.92) on small bowel mesentery (BS-PCI) at 1st HIPEC were significantly decreased at 2nd LHIPEC (5.25 ± 3.78) ($P = 0.016$). LHIPEC reduces the SB-PCI before CRS, and the incidence of complete cytoreduction may improve.

Diagnostic laparoscopy is a convenient method to select patients for CRS and neoadjuvant LHIPEC is an effective therapy for the control of ascites and for the eradication of PFCCs. Furthermore, PCI levels can be reduced by LHIPEC and LHIPEC increase the number of patients who will undergo complete CRS. Accordingly,

LHIPEC is recommended to perform as a neoadjuvant induction treatment before CRS.

MECHANISMS OF HIPEC

The first report of CRS and HIPEC in a patient with PC from gastric cancer dates back to 1980s[41-43]. Since then, CRS and HIPEC have been performed to treat for this group of patients. However, there has been only one prospective randomized trial[43]. From the literatures, benefit of the HIPEC is to eradicate micrometastasis left after complete cytoreductio[35,44].

In many institutes, HIPEC is usually performed at the temperature of lower than 42 ℃ for 90 min.

Heat lower than 42 ℃ (mild hyperthermia) can not eradicate cancer cells by the thermal tolerance *via* the upregulation of heat shock protein[45]. Heat shock protein repair degenerated protein by mild hyperthermia, and cancer cells survive. Even in the mild hyperthermia, however, the fraction of hypoxic cells locate apart from vasculature are killed and thus cellular acidity increase thermal sensitivity *in vivo*. Generally, a temperature of Arrhenius "break" temperature of 43 ℃ and treatment time of at least 30 min are recommended. In United States and European institutes, mild hyperthermia of 41 ℃-42 ℃ for 60 to 90 min. is carried out[7,21,24]. In Japan, 43 ℃ to 43.5 ℃ for 30 min. is a standard thermal dose of HIPEC[8]. Thermal dose is a treatment unit provided by the temperature and exposure time during hyperthermia.

Cells are killed according to the exponential manner if the temperature is higher than 43 ℃ *in vivo*. The cytocidal effects by the 43 ℃ hyperthermia are equivalent to those by 42 ℃ hyperthermia for three- to four-fold longer treatment time than by 43 ℃ hyperthermia. Namely, to obtain the same cytocidal effect by 43 ℃ for 30 min requires 90 to 120 min by 42 ℃ hyperthermia[46].

Hyperthermia enhances the cytotoxic effects of some anti-cancer drugs. Melphalan, mitomycin C, cisplatin, docetaxel, gencitabine, and irinotecan[47-50] enhance cytotoxicity when combined with hyperthermia. In HIPEC for gastric cancer, direct cytotoxic agents like mitomycin C, cisplatin and docetaxel are used[33,41,51].

Pharmacokinetic studies revealed that approximately 70% of mitomycin C is absorbed from the perfusate after 2 h HIPEC[52]. In cisplatin, 75% is eliminated from the perfuate after 90 min HIPEC, but only 20% of the cisplatin moves to the systemic circulation[53]. Accordingly, 50% of ciplatinum is absorbed in the PM nodules and peritoneal tissue during 90 min of HIPEC.

In the case of docetaxel, 40% is adsorbed during 40 min HIPEC at 43 ℃-43.5 ℃[51].

Temperature higher than 39 ℃ increases drug penetration distance[54]. The drug penetration into the peritoneal nodules is limited, because stromal pressure in PM is higher than that in normal tissue[54]. Carboplatin and cisplatin penetrate 1-2 mm from the peritoneal surface during intraperitoneal perfusion without hyperthermia, but penetration distance increases up to 2-3 mm when hyperthermia is combined[31]. Penetration depth from the peritoneal surface depends on the treatment time. Membrane permeation index (Paap) is the penetration distance of the drugs from peritoneal surface per minute, and is calculated by the following equation; Papp (cm/h) = CLp (drug clearance from peritoneal cavity, mL/h)/peritoneal surface area (cm^2). From this equation, Papp after 40 min. HIPEC using 40 mg of docetaxel was 1.5 mm/40 min[51]. If the tumors larger than 1.5 mm in diameter are treated by HIPEC with docetaxel, treatment time should be prolonged to increase the penetration distance of drugs.

However, HIPEC increases the operation time and may cause morbidity. A meta-analysis did not show a significant difference in the mortality rates between HIPEC and control group[44]. However, a significant increase was found in the incidence of abdominal abscess and neutropenia after HIPEC.

A randomized control study for colorectal carcinomatosis revealed significant better survival of CRS plus HIPEC group than that of traditional systemic chemotherapy plus CRS group[55].

At present, combination of CRS plus HIPEC is the standard of care recommended for PM from appendiceal mucinous neoplasm and diffuse malignant peritoneal mesothelioma[56].

Before 2011, there was no randomized control study to confirm the effect of HIPEC on survival of gastric cancer patients with PM. Yang *et al*[43] first reported the efficacy of HIPEC on survival by phase Ⅲ randomized clinical trial. They reported that CRS + HIPEC with mitomycin C 30 mg and cisplatin 120 mg improved the survival with acceptable morbidity. Further phase Ⅲ trials should be done to confirm the effects of HIPEC on PM from gastric cancer.

INDICATION OF THE COMPREHENSIVE TREATMENT

A multivariate analysis using Cox proportional hazard model revealed that CC score, PCI threshold, histologic effect after NAC, cytologic status and HIPEC were independent prognostic factors (Table 6)[7,8]. Among these prognostic factors, PCI threshold level after NAC is the strongest prognostic factor. Survival of patients who received incomplete CRS after NIPS was similar to that of patients treated with NIPS alone (Figure 12). Accordingly, patients who are diagnosed as receiving incomplete CRS by laparoscopy should be excluded from the candidates for CRS.

Survival of histological responders after NAC with negative cytology and PCI ≤ 6 after complete CRS and HIPEC is shown in Figure 13. Five-year survival rate was 32.4%.

CONCLUSION

Patients with PM from gastric cancer are recommended to treat with NIPS or BISIC before CRS. Indication

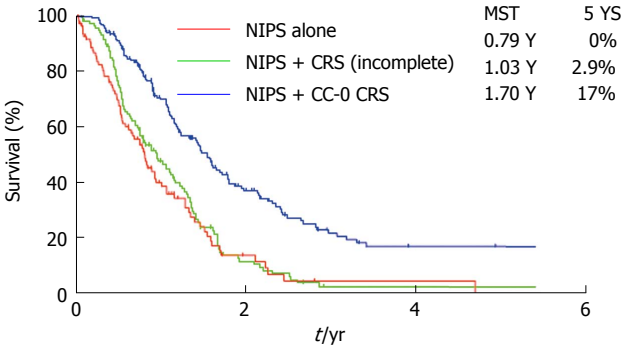

Figure 12 Survival curves of patients treated with cytoreductive surgery and neoadjuvant intraperitoneal/systemic chemotherapy alone. CRS: Cytoreductive surgery; NIPS: Neoadjuvant intraperitoneal/systemic chemotherapy.

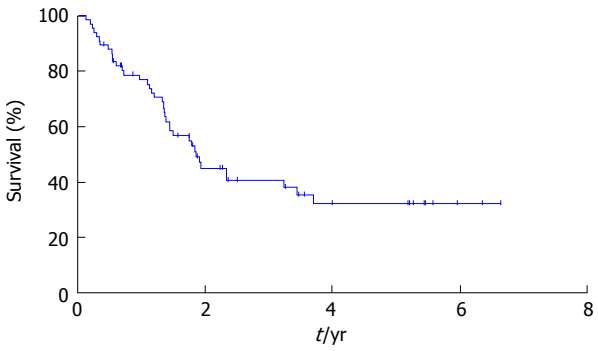

Figure 13 Survival of histological responders with negative cytology and peritoneal cancer index ⩽ 6 after complete cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy.

Table 6 Multivariate analysis of 304 patients with peritoneal metastasis treated with a comprehensive treatmnent

Prognostic factors	χ^2	*P* value	HR	95%CI	
Sex male *vs* female	0.263	0.60752	0.9218	0.676	1.257
CC score: complete *vs* incomplete	4.03	0.04468	1.504	1.01	2.24
Nodal involvement: N0-1 *vs* N2-3	0.445	0.50454	1.1338	0.784	1.639
Neoadjuvant chemo.: negative *vs* positive	2.517	0.11259	1.3445	0.933	1.938
PCI: ⩽ 6 *vs* ⩾ 7	8.809	0.00299	1.7863	1.218	2.621
HIPEC: Not done *vs* done	8.218	0.00414	0.6322	0.462	0.865
Histilogicl effects: EF 0-1 *vs* EF 2-3	12.305	0.00045	0.469	0.307	0.716
Cytology: Negative *vs* positive	8.2163	0.00415	1.8458	1.213	2.806

PCI: Peritoneal carcinomatosis index; HIPEC: Hyperthermic intraoperative intraperitoneal chemotherapy.

of CRS should be determined by laparoscopy. The best indications of the comprehensive treatment are patients with PCI levels within threshold level, and responders after NAC. Patients who satisfy these factors should undergo gastrectomy combined with D2 lymph node dissection and complete removal of PM using peritonectomy techniques. Just after complete cytoreduction, HIPEC should be done[35].

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REVIEW

In utero and *exo utero* fetal surgery on histogenesis of organs in animals

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Abstract

Until recently, fetal surgery was only used for fetuses with very poor prognosis who were likely to die without intervention. With advances in imaging, endoscopic techniques, anesthesia and novel interventions, fetal surgery is becoming a realistic option for conditions with less severe prognoses, where the aim is now to improve quality of life rather than simply allow survival. Until forty years ago, the uterus shielded the fetus from observation and therapy. Rapid changes in the diagnosis and treatment of human fetal anatomical abnormalities are due to improved fetal imaging studies, fetal sampling techniques (*e.g.*, amniocentesis and chorionic villus sampling), and a better understanding of fetal pathophysiology derived from laboratory animals. Fetal therapy is the logical culmination of progress in fetal diagnosis. In other words, the fetus is now a patient. Now-a-days, *in utero* (*IU*) and *exo utero* (*EU*) surgical methods are popular for experimental analyses of the histogenesis of organ development. Using these surgical methods, developmental anomalies can be created and then repaired. By applying microinjection and/or fetal surgery with these methods, models of developmental anomalies such as neural tube defects, temporomandibular joint defects, hip joint defects, digit amputation, limb and digit development and regeneration, and tooth germ transplantation in the jaw could be created and later observed. After observing different types of anomalies, novel *IU* and *EU* surgical techniques would be the best approach for repairing or treating those anomalies or diseases. This review will focus on the rationale for the *IU* and *EU* creation of animal models of different organ defects or anomalies and their repair, based on analyses of organ histogenesis and pathologic observations. It will also focus in detail on the surgical techniques of both *IU* and *EU* methods.

Key words: Myelomeningocele; Microinjection; Rodent; Sheep; Neural tube defect; Temporomandibular joint; Fetal surgery; *In utero*; *Exo utero*

Core tip: Fetal surgery in animal models has become a promising technique for analyses of organ histogenesis

and organogenesis. Using unique *in utero* (*IU*) and *exo utero* (*EU*) methods, developmental anomalies could be created and repaired during the prenatal period. Here, we review the *IU* and *EU* surgical techniques, focusing on methods and outcomes in various experimental animals.

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INTRODUCTION

Fetal surgery has a potential role in managing structural anomalies, where antenatal intervention might theoretically result in an improved outcome for the baby. Many anomalies do not meet these criteria and are likely to remain best managed after birth.

The first attempted intrauterine surgical intervention was a transfusion for Rh incompatibility in 1961. In the 1980s, the developmental pathophysiology of potentially correctable anatomical malformations was studied in animal models. Serial observations, using advances in imaging techniques, helped elucidate the natural history of certain anomalies in human fetuses. Novel obstetric therapies, endoscopic techniques and instruments now make it possible to correct some structural anomalies *in utero (IU)*.

The fundamentals of fetal surgery[1,2] are to (1) understand the natural history of the untreated anomaly *IU*; (2) have a sound pathophysiological rationale for prenatal treatment; (3) demonstrate the safety and efficacy of the fetal procedure in an animal model; and (4) define inclusion and exclusion selection criteria for treatment.

Until recently, only fetuses with a poor prognosis and a life-threatening anomaly were considered for prenatal intervention. Advances in techniques and a better understanding of the natural history of the anomalies have allowed intervention for non-life-threatening conditions, where outcome might be substantially improved. Life-threatening defects include myelomeningocele (MMC), congenital diaphragmatic hernia (CDH), airway obstruction, aqueductal stenosis, twin-to-twin transfusion syndrome, cleft lip and palate, and metabolic and cellular defects. Upadhyaya reviewed how to correct these types of defects[3]. Over the past two decades, the concept of developmental origins of health and disease has gained importance in the medical sciences. Based on the results of several human and animal studies, it is hypothesized that chronic diseases, such as cardiovascular disease and type 2 diabetes, originate from adaptive changes in the epigenetic control of metabolism and organ histogenesis during fetal development[4-6].

The *exo utero* (*EU*) developmental system was introduced by Muneoka *et al*[7]. This experimental system allows researchers to manipulate or operate on mid-to-late-gestation live mouse or rat embryos and to keep them alive *in situ* until the analysis of their effects at a desired pre- or postnatal time point. The *EU* system enables time- and region-specific intervention into developmental phenomena, simply by allowing us to choose the desired time and region for manipulation. This system is far simpler and more time- and cost-effective for *in vivo* functional analyses than establishing genetically altered mouse and rat lines. Compared to the *IU* method, one merit of the *EU* method for embryo manipulation is its clear visualization of the fine details of embryos, making it easier to locate the organs for manipulation. In contrast, because *EU* embryos are not clearly visible before embryonic day (E) 11.5 in mice due to their thick embryonic membranes, use of the *EU* system is mainly limited to the mid-to-late gestational period[8]. However, the *EU* system is a useful method not only for analyses of the developing nervous system but also for investigations of almost all organ systems during the histogenetic period[6,8].

For many genetic disorders, early onset and irreparable tissue and organ damage necessitate innovative methods that allow therapeutic intervention early in development, if a full cure is to be realized. The studies outlined in this review focused on *IU* and *EU* surgery for intervention during organ histogenesis using a variety of animals, including large mammals such as sheep, pigs and primates, and small mammals such as mice and rats. Larger mammals, such as sheep and monkeys, carry on average one embryo per pregnancy and typically tolerate surgical manipulations well, but are more expensive and have longer gestations (145 and 160-180 d, respectively) as well as higher ethical limitations. These factors reduce the number of experiments that can be performed in a given time frame. Most small experimental animals are multiparous, allowing for experimentation on large numbers of embryos, ranging from 3 to 10 embryos per pregnancy and shorter gestational periods of 3-4 wk. Drawbacks include difficulties with the manipulation of the uterus and the subsequent survival of the embryo. To this end, we can use the *IU* and *EU* development systems to screen the functions of various proteins/cells by injecting them into embryos, or to perform fetal surgery and follow up on consequences later in life. Here, we review procedures for mammalian embryo surgery both *IU* and *EU* and highlight technical innovations that have been published using this approach.

GENERAL PREPARATION FOR *IU* AND *EU* SURGERY

Here, we describe in detail *IU* surgical procedures in rodents and briefly describe these in other animals such as sheep, pigs and primates. We will only describe the *EU* surgical procedure in rodents, as thus far no experimental works or reports have been published applying this

method in other mammals. Preparation of pregnant mice or rats and abdominal surgery for *IU* and *EU* surgery are identical, to some extent. Similar procedures in rodents are described below, and later, we separately describe the procedural differences between *IU* and *EU* surgery.

Preparation for IU and EU surgery in rodents

The two generally used approaches are *IU* or *EU* surgery. Both are demanding procedures that require some level of expertise. The post-implantation embryo is encased in its extraembryonic membranes (amnion and yolk sac) within the tubular uterus. The embryo can be accessed by injection, passing through the layers of the uterine wall (perimetrium, myometrium, and endometrium) and the extraembryonic membranes. Intrauterine embryo injections can be successfully carried out on mouse embryonic stages as early as E8[9,10]. For direct surgery on the embryo, *IU* studies require opening and closing the uterus and extraembryonic membranes. This approach is restricted to late embryonic/fetal stages (E14.5 and later) because early embryos are too fragile to survive the postsurgical forces resulting from the contracting uterus. *EU* surgery is based on the finding that embryonic development is not perturbed when the uterine tube is opened but not sutured closed[7]. The embryos remain attached to the open uterus *via* the placentae and develop suspended within the abdominal cavity of the female. When embryos are exposed in this manner, it is possible to perform various embryo surgeries at early embryonic stages. Injection experiments using *EU* surgery have been carried out on stages as early as E8.5[11], and direct surgery on the embryo can be carried out on E11.5 embryos and older[12]. While technically demanding, direct manipulation of the rodent embryo is possible and, in combination with other experimental approaches, provides another avenue for experimental studies of mammalian development.

Preparation of animals and required instruments before surgery were described in detail by Yamada *et al*[13].

Anesthesia: Several different approaches to anesthesia have been used for studies on embryonic and fetal rodents, as reviewed in Ngo-Muller and Muneoka[14]. In all cases, the anesthetic target is the pregnant female and not the embryo/fetus, although the embryo/fetus is exposed to maternal levels of the drug. Anesthesia with ketamine/xylazine (K/X) or pentobarbital induces prolonged anesthesia (30-45 min with K/X; > 45 min with pentobarbital) and is administered by intraperitoneal (*i.p.*) injection. For mice, K/X is administered at a dose of 100 mg/kg of ketamine and 10 mg/kg xylazine (80 mg/kg ketamine and 8 mg/kg xylazine for rats). Reversal of K/X anesthesia can be obtained by injecting the antagonist yohimbine (1.0 mg/kg, *s.c.*) when surgery has been completed[14]. Alternatively, the pregnant female mouse/rat is also anesthetized with sodium pentobarbital (Nembutol) (50 mg/kg body weight *i.p.*)[8,13]. Recently, a combination of anesthetics (Medetomidine/Midazolam/Butorphanol) in solution is widely used. This combination is prepared with 0.3 mg/kg of medetomidine, 4.0 mg/kg of midazolam, and 5.0 mg/kg of butorphanol (M/M/B: 0.3/4/5)[15]. The induction time of M/M/B was identical to the induction time of K/X. The emergence time of M/M/B was the similar to that of K/X. The anesthetic time of M/M/B, however, was longer than the anesthetic time of K/X[15].

Abdominal incision: A sterilized operating aluminum or stainless steel plate is used during operation. Operating field (abdominal skin) of the pregnant dam should be wiped by 70% ethanol after removal of the hair, and the mouse/rat is placed in a supine position on the operating plate. To open the abdomen, an initial large midline incision of the belly skin is made with microdissection scissors. Blunt forceps should be used to handle the skin. A second incision is made along the linea alba to open the abdomen. With the abdomen open, the uterine horns can be found in the lateral regions of the abdominal cavity and simply pulled out onto sterile damp gauze placed on the ventral surface.

IU SURGERY

Mammalian development has been best characterized using rodent (mouse, rat) models. Direct intervention of the post-implantation mouse/rat embryo *IU* represents one of several experimental methods that can be used to probe mammalian embryogenesis. Here, we will elaborately describe the surgical technique in the mouse/rat and also briefly describe it in other animal models.

Rodents

Most studies using *IU* manipulation were performed on mouse embryos, though a few studies have been applied to rat embryos[2,16-18]. *IU* surgery requires that the abdomen be opened to access the uterus. After the surgical procedure, the abdomen is closed and the animal is allowed to recover.

Microinjection

IU manipulations generally involve injections into the embryo that must pass through the uterine wall and the extraembryonic membranes (yolk sac and amnion). The injection should avoid any blood vessels. Embryo manipulation is best performed using a stereo zoom surgical microscope. Injections generally utilize glass needles made from micropipettes of varying size. The making procedure was described in detail by Yamada *et al*[13]. Injection studies include the use of markers, such as carbon particles for establishing fate maps[19] or lipophilic tracers such as DiI (CellTracker; Molecular Probes) to characterize cell migration patterns[10,20-22]. Injection of virus has been used to study cell lineage[23] and the targeted effect of a specific virus on develop-

ment[24,25]. Targeted injection of purified growth factors or signal transduction antagonists directly into the embryo has been used to study signaling during normal and abnormal development[26-28]. Electroporation has been applied to inject plasmids encoding genes for functional studies and/or marker genes for cell labeling studies[29-36], plasmids encoding short hairpin RNA for RNA interference[2,16-18,37], and dual-fluorescence reporter/sensor plasmids for single-cell detection of microRNAs[38].

Recent studies demonstrate that cell transplantation (CT) at progressively earlier embryonic stages resulted in higher levels of chimerism[39]. Clinically relevant studies include the rescue of a genetic mouse model of autosomal recessive osteopetrosis, a human disorder associated with defective osteoclasts, with allogenic fetal liver CT[40], and the rescue of a mouse model of osteogenesis imperfecta with transplantation of adult bone marrow cells[41].

Fetal surgery

Open spina bifida, or MMC, the most common type of neural tube defect (NTD), is defined as a protrusion of the spinal cord and/or meninges through a defect in the vertebral arches. Creating the ideal animal model to study the effects of intrauterine surgery requires that the mechanisms of aberrant primary neurulation, resulting in an open NTD and associated nervous system anomalies, be reproduced. To create the NTD lesion fetus and repair experiments by Heffez, two studies utilized this animal model[42,43]. In the first study[42], pregnant rats at day 18 of a 22-d gestation were anesthetized, and the surgery was performed using an operating microscope. A single horn of the bifid uterus was exteriorized through a midline abdominal incision. Only the fetus being treated was mobilized. Following the opening of the uterus and amniotic membrane, a 2- to 3-level laminectomy was done, and the dura was opened. This group of fetal rats was returned to the uterus with the lesion. In a second study, identical surgical techniques were used by the same authors to lesion fetal rats, and a second group received a repair treatment prior to return to the uterus[42,43]. The rat model utilized two strategies to repair the spinal defect at embryonic day 18[42]. The open spinal cord was either repaired immediately with a nonocclusive peritoneal cover from the mother, or was re-exposed the following day and underwent a primary skin closure. Control embryos did not recover any function and had significant degradation of the spinal cord. The embryos that were repaired by primary skin closure, even after a 24-h delay, demonstrated better outcome than the embryos with closure using peritoneum. The results of this study point to the harmful effects of amniotic fluid, due to the worse outcome after a nonocclusive barrier (peritoneum) was used instead of skin. Stiefel studied the curly tail mouse model of exposed lumbosacral spina bifida and revealed the progressive deterioration of neuroanatomic appearance and neurologic function with increasing gestational age[44]. Danzer developed a retinoic acid-induced MMC model in fetal rats, and histopathology confirmed the entire spectrum of severity observed in human MMC, as well as features of the Arnold-Chiari malformation[45,46]. While these studies support the principle of improved neurologic function with *IU* coverage of the spinal cord, a large animal model with lengthy periods of time *IU* after surgical manipulation is needed before the extrapolation of these findings to humans.

Sheep

Sheep are much easier to breed and maintain and are a well-established animal model of human fetal physiology. Sheep have a consistent gestation period of 145 d, and the development of the fetus and its immune system is very similar to that of humans. Fetal sheep have been used widely to study mammalian fetal physiology, and the results obtained with this model have been directly applicable to the understanding of human fetal growth and development[47]. The first attempt at *IU* gene therapy in the sheep[48] utilized a stem CT based method, in which peripheral blood was collected from 110-d-old fetal sheep by exchange transfusion. Once its full clinical potential has been realized, hematopoietic stem cell-based gene therapy promises to cure a wide array of both inborn and acquired diseases. Both hematopoietic cells and non-hematopoietic cells within the liver and lung are transduced following the direct injection of murine retroviral vector supernatants into the peritoneal cavity of pre-immune fetal sheep, suggesting that the developmental stage of each organ at the time of injection may determine its susceptibility to *IU* gene transfer[49]. Using pregnant sheep, David *et al*[50] have adapted ultrasound-guided injection techniques from fetal medicine practice and established new methods to deliver gene therapy to fetal sheep, including intratracheal injection to target the distal respiratory epithelium[51], intragastric injection to target the intestinal mucosa[52], and fetoscopic techniques including the placement of an intratracheal balloon at the time of vector installation to enhance pulmonary epithelial transduction[53]. The combination of ultrasound guidance and fetoscopic techniques was described in detail[1].

Sheep models have also been used to study the embryopathy and pathophysiology of neurological deterioration in NTD. For NTD treatment, spina bifida lesions were created in fetal sheep by *IU* surgery techniques (reviewed in[54]). The model that most closely simulated the human disease and most clearly demonstrated the feasibility of fetal MMC surgery was the fetal lamb model of MMC introduced by Meuli *et al*[55]. Pregnant sheep were placed under general halothane oxygen anesthesia. The fetuses were then exteriorized through an infra-umbilical midline laparotomy, followed by hysterotomy to expose the backs of the fetuses. A MMC lesion was made using low-power loupe magnification with microsurgical instruments at 75 d. The fetuses with the open spinal defect were then returned to the uterus,

and the amniotic fluid volume was restored with warm sterile saline. The sheep fetuses that underwent repair of the spina bifida defect were lesioned, and the defect was then closed using a latissimus dorsi muscle flap at 100 d of gestation[55,56]. The fetal sheep MMC model was the first large animal model to demonstrate that a spinal cord lesion could be created *IU* and covered at a later time point, with preservation of neurologic function. Unlike previous animal models, this sheep model more closely resembled that of human MMC in the duration of the exposure of the cord to the environment, clinical examination, and histology.

Pigs

IU cell transplantation (IUCT) and potential tolerization are based on the immunologic immaturity of the early developing fetus, leading to the possibility of donor or species specific tolerance to xenogeneic cells. Fisher's group established an IUCT procedure by which piglets are stably engrafted with human hepatocytes during early gestation and explored the possibility of producing a state of hyporesponsiveness in pigs to human hepatocytes by transplanting human hepatocytes into fetal pig livers[57]. Briefly, at gestational day 40, all gilts underwent general anesthesia and lower midline laparotomy. Both uterine horns were exposed. All fetuses in the right uterine horn received direct intrahepatic injection under ultrasound guidance using a 1.5 inch 25 gauge needle.

Furthermore, to determine whether cells could transfer between porcine littermates, McConico[58] performed IUCT. Briefly, at 40-43 d gestation, pregnant pigs/swine were anaesthetised with intra-muscular (*i.m.*) injections of telazol (5 mg/kg), xylazine (2 mg/kg) and glycopyrolate (0.06 mg/kg). Anaesthesia was maintained with inhaled isoflurane (3%-5%). A paramedian incision was made along the dorsolateral margin of the mammary glands, with the pig in lateral recumbency. One horn of the uterus, containing four to eight fetal swine, was then exposed. Guided by ultrasound, 50 million T cell-depleted umbilical cord blood cells were injected into the peritoneum of three to four fetal swine per litter[58].

If an intrauterine event has occurred, then intrauterine interventions, such as surgical repair, might prevent progressive neurological deterioration. Animal models of spina bifida or NTD repair *IU* have been designed by Heffez[42] and reviewed by George[54]. Surgical manipulation of pregnant Hanford mini-pig sows began with sedation *via* intramuscular administration of ketamine and acepromazine. The sows were intubated, ventilated and anesthetized with isoflurane. The fetal pigs were operated on at day 80-85 of the 114-d gestation period. Surgery was performed with an operating microscope. One horn of the uterus was exteriorized. The fetus underwent a two-level laminectomy with opening of the dura. In one group, fetal pigs received repair treatment following lesioning before being returned to the uterus. In the second group, fetal pigs were returned to the uterus with an open wound. The abdominal wall of the sow was closed in two layers[42,54].

Rhesus monkeys

Several animal models of MMC have been developed to test the hypothesis that *IU* intervention can prevent further spinal cord damage and the consequent neurological deficits. Primate (Macaca mulatta) was the first model, developed by Michejda, in which a fetal L3–L5 laminectomy was done late in gestation[59]. Surgical methodologies employed on pregnant rhesus monkeys began with induction of general halothane-oxygen anesthesia. The lumbosacral region of the fetuses was exteriorized *via* hysterotomy. A vertebral opening *via* a lumbar laminectomy in the L3-L5 region was created, and the spinal cord was exposed following the opening of the dura over the spinal cord. The exact techniques, magnification and precise instrumentation were not described in the methodology[59]. A total of 8 fetuses at gestational day 110-125 were manipulated, with full gestational term at approximately day 160-180[60]. The unrepaired embryos showed cystic MMC-like lesions at birth and had neurological deficits. A similar group of monkeys underwent immediate repair of the laminectomy *IU* using allogeneic bone paste to reconstruct the resected dorsal arches. These fetuses, repaired *IU,* were neurologically normal at birth. Unfortunately, the experiment did not include an initial procedure for creation of the defect with a period of exposure to the uterine environment prior to closure.

EU SURGERY

The rodents' *EU* development system is useful for analyzing the roles of molecules or interactions between tissues in the histogenesis of organs from mid to late gestational period. Previously published technical reviews on *EU* surgery are of value to the new investigator, and this surgical treatment has been only performed in rodents (mouse/rat)[8,13,14,61]. The general operation involves making a longitudinal incision along the entire length of the uterus, so that the embryos remain attached to the uterus but are not contained within the uterine cavity. The exposed uterus is returned into the abdominal cavity, where development continues *EU*. In the original study, embryos from E9.5 to E13.5 were found to develop normally to term[7]. In a subsequent study by Serbedzija *et al*[11], *EU* survival of embryos that received injections into the amnionic cavity as early as E8.5 was reported. Early stage embryos are surrounded by a layer of decidual tissue that obscures the visualization of the embryo. Removal of this layer compromises embryo survival. In general, our experience is that the survival rate of mothers is 100%. That of manipulated embryos increases with later stages and with less invasive manipulations, and can reach 100% in cases without invasive manipulation.

Both the *IU* and *EU* surgical procedures were

identical, up to the abdominal incision before the uterine wall was cut. Yamada *et al*[13] described in detail how to relax and cut the myometrial wall, clearly observing the targeting live embryos and how to replace the manipulated embryos into the abdomen. Here, we briefly describe the procedure about how to manipulate the live embryos.

Embryo manipulations

The embryos were enveloped by very thin and transparent amniotic membrane. The amniotic membrane must be kept wet and covered by sterile gauze soaked with sterile saline, otherwise it will become dry and lose its translucency which causes difficulties. *EU* surgery is a lengthier procedure than *IU* manipulation, and not all embryos are manipulated in a single female. In cases where embryo surgery is compromising embryo survival, removing all unoperated embryos can dramatically improve the survival of operated embryos[62]. Two different techniques have been reported for removing embryos from the uterine horn during *EU* surgery.

To increase the viability rate, we have routinely left three embryos on both side of the uterus taking special care for bleeding and adhesion as Yamada *et al*[13] described in detail. Ngo-Muller and Muneoka[14] reported that they removed all but four embryos, leaving two embryos in each horn in positions toward the ovarian end of the uterus. Embryos and placentae are removed by placing a dry cotton-tipped applicator at the placental-uterine junction and gently rolling it across the placenta. This procedure separates the placenta from the uterus and causes a small amount of bleeding from the uterus. Bleeding is controlled by applying direct pressure with the cotton-tipped applicator at the former placental attachment site.

Once embryos are removed and any bleeding is controlled, the abdominal cavity is flushed with saline to remove any tissue debris that might induce a postsurgical fibrotic response. After the abdominal cavity is flushed, it is filled with sterile saline. The embryos are maintained submerged in saline during and after the operation. For older stage embryos, it may not be necessary to keep the embryos submerged. The various types of manipulations that have been accomplished using the *EU* approach are summarized below.

Microinjection

The use of sharp-tipped micropipettes is the most critical for a successful microinjection, since tear of the fetal membrane causes leakage of amniotic fluid. Fetal deaths are often attributable to damages of the embryonic membrane or placenta. Injections generally utilize glass needles made from micropipettes of varying size. Yamada *et al*[13] described how to make glass micropipettes with a beveled point using a microforge. The micropipette is connected to an automated hydrolic (mineral oil) microinjection system (*e.g.*, UltraMicro Pump, WPI Inc.) fitted with a Hamilton-type syringe that allows precise control over injection volume. It is often useful to co-inject a vital dye (*e.g.*, 0.05% Nile blue sulfate or 1% Fast Green) to monitor the injection procedure. Targeted injection of purified growth factors or signal transduction antagonists directly into the embryo has been used to study signaling during normal and abnormal development[26-28].

Cells have been introduced into the embryo by targeted injection for use as *in vivo* reporters, or to characterize the behavior of stem cells in the embryonic and adult environment. Fibroblasts introduced into the embryonic mouse limb proliferate and differentiate in a position-dependent manner[63,64]. The injection of cells that secrete high levels of specific hormones has been used to experimentally perturb embryogenesis[65-67]. Targeted injection of genetically labeled liver stem cells into the embryonic liver results in chimeric livers that persist to adult stages and can be used for both the investigation of liver development and regeneration[62].

Embryonic surgery

In many instances, experimental design calls for direct surgery on the embryo. For early stage embryos, such studies are best performed using the *EU* approach, because it eliminates the need to incise and suture the uterus and avoids postsurgical complications arising from uterine contractions. Clean visualization is the most critical and important factor for embryo manipulation/surgery, thus *EU* is the better option compared to the *IU* surgical procedure. Mechanical strain plays an important role during tissue morphogenesis, and many developmental processes depend on external and internal mechanical forces[68]. In our laboratory, we performed fetal joint movement restriction by surgical techniques using this *EU* method and observed how developmental processes were related to prenatal mechanical forces.

Hip joint movement restriction: Congenital dislocation of the hip (CDH) is one of the most common congenital skeletal deformities. The prevalent type, which constitutes up to 98% of CDH cases, is exhibited at birth by a dysplasia of the hip consisting of a flat acetabular roof and an underdeveloped proximal end of the femur, relatively minor anomalies that predispose to dislocation[69]. In our laboratory, Hashimoto and Kihara created a CDH model[70,71] to clarify its etiology and to develop prevention and treatment therapies. For these purpose, at E16.5 the hind limb of the rat embryos' one side was sutured with 9-0 thread for ophthalmic surgery at the knee joint or more distally to the amniotic membrane, whereas the other side was left unoperated. The hind limbs were tied *in situ* and were not forced into any specific abnormal positions[70,71].

TMJ movement restriction: To observe the proper development of the mandibular condylar cartilage, articular disc and temporalis muscle as related to mec-

hanical forces, we restrained jaw movement by this *EU* surgery technique. In mouse embryos at E15.5, both the upper and lower jaws (mandible and maxilla) were sutured or fixed through the embryonic membrane with 8-0 nylon. The embryos underwent *EU* development[72-75].

Other surgical techniques: Another surgical technique is the resection of parts of the fetal organs. Naruse and Kameyama[76] combined the *EU* system with argon laser irradiation to the extra digits of genetic polydactyly mice. To explore the relationship between agenesis of the olfactory bulb and that of the corpus callosum, Naruse and Keino[77] performed fetal *EU* laser surgery to induce arhinencephaly in mice and clarified that agenesis of the olfactory bulbs induced agenesis of the corpus callosum[78]. In this *EU* system, they induced fetal tissue destruction without damage to the yolk sac membrane and amnion or leakage of amniotic and extra-embryonic fluid to yield embryos with high viability. Sequential observation of NTD by the *EU* method was successfully utilized to analyze the mechanism of generation of anencephaly[46]. In our laboratory, Matsumoto *et al*[46] created anencephaly mouse embryos. Pregnant mice were administered 1 mg/kg body weight 5-azacytidine (Sigma Chemical, St. Louis, Mo.) dissolved in physiologic saline by intraperitoneal injection at E7.5. After that, they observed the sequences of exencephaly, and their subsequent morphological changes, and mechanism of transformation from exencephaly to anencephaly by the *EU* development system at different embryonic days[46]. The most invasive studies to date include amputations of the limb or digit to study regenerative responses. It is possible to transplant tissues between mouse embryos to study cell–cell interactions during development. Examples include studies of the interaction between anterior and posterior tissues during mouse limb development[12] and grafts of digits in association with amputation studies[79]. Amputation studies have also been carried out on mice with targeted mutations to identify genes that are functionally required for a regenerative response[80] and to explore the diastema region of the jaw as a permissive site for the development of a transplanted tooth germ[81]. Other surgical manipulations that have been carried out on mouse embryos using a surgical approach to experimentally induce spina bifida aperta[82].

Restraining movement, amputation, wound healing and tissue grafting surgeries cause significant trauma to the embryo and can compromise embryo survival. In our and other researchers experiences, these types of embryo surgeries can have a high level of success from E13.5 and later, whereas similar manipulations at earlier stages are more challenging yet feasible[12]. This study demonstrates how multiple targeted manipulations can be successfully combined using an *EU* approach.

For both *IU* and *EU* surgery in rodents, Yamada *et al*[13] reviewed in detail about abdominal closure, recovery and post-operative care.

CONCLUSION

Advances in fetal interventions can be predicted over the next decade, driven by novel biological and endoscopic techniques. Developmental biologists have repeatedly used animal models (*e.g.*, mammals such as rodents, sheep, pigs, and monkeys; amphibians; birds) for experimental analyses of histogenesis or organogesis, or to develop powerful tools for studying the function of specific genes during development. We have explained on the methodological procedures of the *IU* (mouse/rat, sheep, pig and monkey) and *EU* (rodents) development system. These systems are useful methods for *in vivo* functional analyses from early/late organogenetic to histogenetic phases. The number of studies using *IU* or *EU* approaches has increased over the past 30 years. Now it is clear that we can successfully probe the *IU* environment of the mammalian embryo both classically (amputation, tissue transplantation, NTD creation and repair) and genetically (electroporation, gene therapy). The *EU* technique is far simpler and more time- and cost-effective than establishing genetically modified mouse/rat lines and provides a convenient experimental design for developmental research. To explore development, especially as it pertains to human health issues, there is clearly a need to develop and expand new strategies that enhance our ability to directly access the post-implantation mammalian embryo.

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MINIREVIEWS

Current management of acute type B aortic dissection

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Abstract

Acute type B aortic dissection (TBAD) occurs as a result of an intimal tear within the proximal thoracic aorta. Patients are typically managed acutely with aggressive antihypertensive therapy. Surgical repair is reserved for those who develop complications such as rupture or malperfusion. The surgical management of acute TBAD has changed considerably in the last decade secondary to the advent of thoracic stent grafting. Thoracic endovascular aortic repair (TEVAR) has improved early mortality and morbidity rates for patients presenting with complicated TBAD. The role of TEVAR in patients presenting with acute and subacute uncomplicated TBAD is less clear. TEVAR has been associated with increased late survival and better aortic remodeling, with low perioperative morbidity in selected patients. Recent literature suggests certain radiographic criteria may be used to predict patients developing late aortic events who would benefit from early TEVAR. The purpose of this article is to review the contemporary management of acute TBAD, discuss controversies in management and evaluate the latest research findings.

Key words: Aorta thoracic; Vascular grafting; Aneurysm dissecting; Aortic rupture; Endovascular procedure; Stent

Core tip: Current recommendations and controversies within the surgical management of acute type B aortic dissection are discussed. The increased use of thoracic endovascular aortic repair has been associated with improved patient outcomes, though data on patients presenting with acute and subacute dissection is less clear. Certain radiographic findings may predict those at higher risk of developing late aortic-related complication.

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INTRODUCTION

Acute type B aortic dissection (TBAD) remains a complex clinical entity associated with a high rate of morbidity and mortality[1]. The majority of patients are able to be managed medically in the acute setting, though a subset of patients require acute surgical intervention. Open surgical therapy has traditionally been associated with high rates of in hospital death and morbidity. Surgical complications have been reduced by endovascular technology, specifically thoracic endovascular aortic repair (TEVAR). Unfortunately strong evidence is lacking regarding the optimal management of patients with acute TBAD. One of the difficulties in interpreting the literature on this topic involves the retrospective, single-institution nature of most studies. Few prospective, randomized trials exist to help guide vascular surgeons in selecting optimal management strategies. This paper will focus on reviewing the contemporary management of acute TBAD, controversies and future directions.

PATHOPHYSIOLOGY

The primary etiology of TBAD is the separation of the layers of the aortic wall from each other, originating at a site known as the entry tear. This injury occurs within the intima at the proximal descending aorta, most often just distal to the origin of the left subclavian artery. A study of hemodynamic forces within the aortic arch by Nathan *et al*[2] demonstrates this area to be particularly susceptible to shear forces. This, in part, explains the frequency with which this location is involved. Microscopic analysis reveals that the dissection occurs into the media, functionally separating the intima from the adventitia. The "false lumen" (between the intima and adventitia) becomes pressurized, and, since the adventitia is stronger than the intima, the true lumen may become compressed. Compression of the true lumen may result in propagation of the dissection in a caudal (or occasionally cranial) direction and compromise of the distal branch arteries to the viscera, spinal cord or extremities. A novel *ex vivo* model for aortic dissection by Faure *et al*[3] highlights the spiral dissection plane that descends caudally. Often the celiac, superior mesenteric and right renal arteries originate from the true lumen while the left renal originates from the false lumen.

Symptoms from malperfusion may result from either static or dynamic obstruction. Static obstruction occurs when a highly pressurized false lumen dissects around, and circumferentially occludes, the orifice of a branch vessel. In contrast, dynamic obstruction occurs when a branch vessel orifice is occluded intermittently by extrinsic compression of the true lumen by pulsatile flow within the false lumen. This phenomenon is best observed using intravascular ultrasound (IVUS) to evaluate a patient with severe true lumen compression (Figure 1).

The initial presentation of dissection is that of tearing chest pain radiating to the back. This may be accompanied by symptoms of end-organ ischemia such as abdominal pain, oligo-anuria, lower extremity ischemia, paresis or paraplegia depending on the end organs involved. When malperfusion occurs, often several vascular territories are involved[4]. In the setting of rupture, patients may develop hypotension, abdominal distention or a left pleural effusion. Diagnosis is most commonly made by computed tomography angiography (CTA) or transesophageal echocardiography (TEE). TEE, when readily available, can identify the proximal entry tear and its origin. It is also effective in differentiating type A and type B dissections, and can assess cardiac function without the use of contrast or ionizing radiation. CTA, however, has the advantage of being readily available in most emergency rooms and is less operator dependent. It can also identify rupture, end organ ischemia, the extent of distal dissection and the relative size of the true and false lumens. For this reason CTA has emerged as the study of choice in acute TBAD[5] (Figures 2 and 3).

MEDICAL MANAGEMENT

Medical management is critical for all patients with acute TBAD, whether or not surgery is performed. Initial management is focused on strict blood pressure and heart rate control. At our institution we favor initiation of anti-impulse therapy with a beta blocker followed by a vasodilator to prevent further propagation of the dissection and to manage the patient's symptoms. These medications are best administered in a closely monitored unit aided by an arterial line and urinary catheter. Target systolic blood pressure goals include 110-120 mmHg, with heart rate goals between 60-80 BPM[5]. These targets may be lowered if the patient's symptoms persist, as long as adequate perfusion as judged by urine output and mentation persists. Patients who respond to this regimen are transitioned to oral antihypertensive medications once their hypertension is controlled. Repeat imaging is typically performed prior to discharge and at regular outpatient intervals, evaluating for patency of the false lumen and aneurysmal degeneration. Established indications to proceed with operative intervention in the acute setting include: rupture, malperfusion, and persistent/refractory pain in the face of maximal medical therapy. The existence of one of these criteria is defined as complicated aortic dissection.

Estrera *et al*[6] evaluated 159 patients presenting with acute TBAD in a single center. In-hospital mortality for patients requiring only medical therapy (*i.e.,* uncomplicated) was 7.3%. Complication rates in medically managed patients included rupture in 5%, stroke in

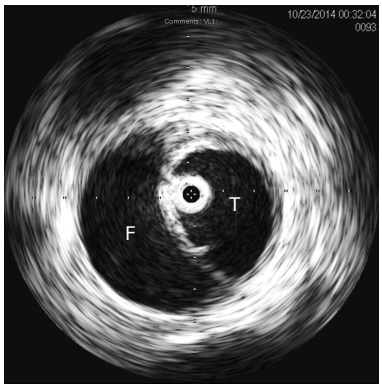

Figure 1 Intravascular ultrasound evaluation during thoracic stent grafting. The IVUS probe (image center) is seen confirming correct orientation within the true lumen. T: True lumen; F: False lumen; IVUS: Intravascular ultrasound.

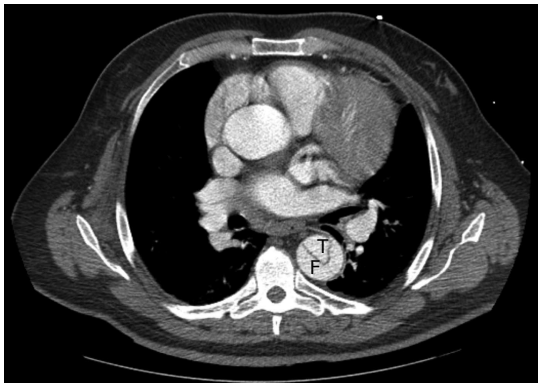

Figure 2 Computed tomography angiogram of a patient presenting with acute type B aortic dissection. T: True lumen; F: False lumen.

5%, spinal cord ischemia in 8.2%, mesenteric ischemia in 5.7%, dialysis dependence in 13.8%, and lower extremity ischemia in 3.8%. Survival at 1 year and 5 years was 83% and 75%, respectively. Approximately 14.5% of patients progressed to complicated aortic dissection requiring intervention; the in-hospital mortality for this cohort rose to 17%. Tsai *et al*[7] reviewed data from the multi-institution International Registry of Acute Aortic Dissection(IRAD). They identified a 10% in hospital mortality rate for patients receiving medical therapy alone. They reported a similar incidence of overall morbidities as Estrera *et al*[6] Approximately 11% of patients in that cohort required surgical intervention. In addition, they reported 1 year and 3 years survival rates for patients treated initially with medical therapy at 90.3% and 77.6%. These data show that the overwhelming majority of patients present with uncomplicated aortic dissection, and they can safely be managed medically. There is, however, a notable incidence of late aortic events and decline in survival in the medically managed patients after several years.

SURGICAL MANAGEMENT

The goals of surgical management are to prevent or treat

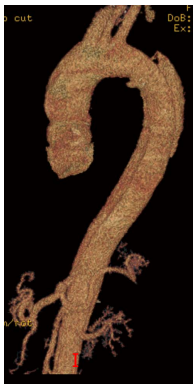

Figure 3 3D reconstruction from a computed tomography angiography of a patient presenting with acute type B aortic dissection, highlighting the entry tear originating distal to the origin of the left subclavian artery. The dissection plan is seen to extend well into the abdominal aorta.

rupture and/or ischemia from vessel malperfusion. This can be accomplished in one of two ways: (1) sealing the entry tear to promote false lumen thrombosis; or (2) equalizing the pressure between the true and false lumen by fenestration of the dissection septum to prevent progression of the dissection and reestablish perfusion to compromised end organs. The choice of therapy depends on the clinical and anatomic presentation of the patient. Efforts at sealing the entry tear are most likely to cause false lumen thrombosis and restore distal perfusion through the true lumen when there is a relatively discrete entry tear with a highly pressurized false lumen. However, when a major branch vessel is perfused exclusively through the false lumen, successfully sealing the entry tear may induce ischemia in the territory that vessel supplies. This can result in renal, intestinal, extremity or spinal cord compromise. Furthermore, when multiple entry and re-entry tears are present, sealing the proximal entry tear alone often will not be sufficient to depressurize the false lumen. Our current diagnostic capabilities make it difficult to definitively predict when such conditions may occur and this uncertainty has tempered enthusiasm for surgery as a first approach.

The principle of fenestration is the opposite of that underlying entry tear coverage. The aim of this technique is to increase communication between the true and false lumen, equalizing pressures within them and stabilizing the dissection process. The technique seeks to create the situation that occurs in many TBADs that respond to medical management alone, *i.e.,* equilibrium between true and false lumens. This technique is most often performed percutaneously and will be described under "endovascular approaches." It is important to recognize that this technique does not "treat" dissection, only malperfusion, and cannot prevent rupture or late aneurysmal dilation of the dissected arterial segment.

Correction of malperfusion may require more than one approach. When the entry tear is sealed and the false lumen depressurized, dynamic malperfusion will be reversed. Equilibration of the pressure in the true and false lumens may also reverse dynamic obstruction.

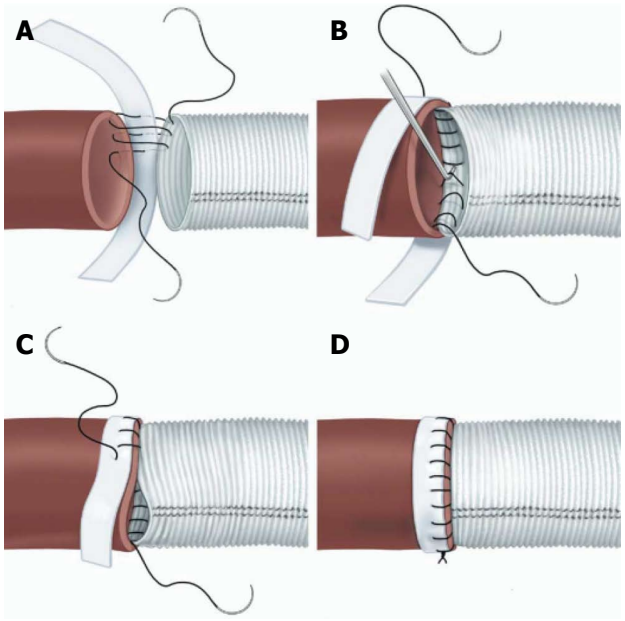

Figure 4 Suture line reinforcement with felt pledgets. A: Performing the posterior wall of the anastomosis first, in a "parachute" fashion. The suture travels from the prosthetic graft, to native aorta, then finally through the pledget; B: The suture line is tightened with the use of a nerve hook, and care taken to place the pledge on the outer surface of the aorta; C: Once the posterior wall of the anastomosis is completed, the anterior wall of the anastomosis is completed. The graft is somewhat invaginated within the aorta; D: The completed anastomosis, whereby the native aorta is buttressed on either end with pledget and graft. Source: "Long-term integrity of teflon felt-supported suture lines in aortic surgery," by Strauch *et al*[9]. Copyright 2005 by Elsevier, reprinted with permission.

Therefore sealing the entry tear, or fenestration of the aorta may be all that is necessary in some cases. However when a static obstruction exists, flow must be restored by another means. When ischemia is restricted to the lower extremities this may be accomplished by extra-anatomic bypass without addressing the aortic dissection itself. However when ischemia persists after initial treatment of malperfusion, vascular reconstruction directed at the ischemic territory is required. When the viscera are involved this is most often done from and endovascular approach using self-expanding stents or covered stents, since aortovisceral bypass in these circumstances is hazardous. These will be discussed in more detail in the "endovascular management" section. When lower extremity ischemia is present either endovascular stents or extra-anatomic bypass may be performed.

OPEN SURGICAL MANAGEMENT

Open surgical management is generally directed at sealing the entry tear and treating any acute complication (rupture or malperfusion) rather than definitive treatment of the aortic pathology. The urgent nature of the operation and unstable character of the aorta dictates a focal approach directed at saving life and limb. Classically, open surgical management of ruptured TBAD involves direct aortic replacement of the ruptured area. When malperfusion is present rather than rupture, management options include a short interposition graft to covering the proximal entry tear, aortic fenestration, or extra-anatomic bypass. Coverage of the entry tear requires a proximal suture line in an area of aorta free of dissection. The graft itself may be relatively short since the goals are simply to seal the entry tear and direct blood into the true lumen. This technique relieves malperfusion secondary to dynamic obstruction. Fenestration involves a transverse aortotomy at or below the location of the branch vessels at risk, with partial resection of the septum to equalize pressure in the true and false lumens[8]. Distal flow is directed exclusively into the true lumen. In both approaches, accurate identification of the distal true lumen and obliteration of the false lumen is critical and this may sometimes be difficult. The suture lines require reinforcement with pledget strips, placed circumferentially (Figure 4), both between the intima and adventitia in the false lumen of the dissected aorta and outside the adventitia at both proximal and distal suture lines, to maintain anastomotic integrity[9]. Aorto-visceral bypass, if required, should originate from the graft itself since the aorta is diseased. Definitive aortic repair is not the goal of open treatment in the acute setting. Spinal cord ischemia, when it occurs, is not reversible.

In patients who manifest only lower extremity ischemia, extra-anatomic bypass grafting, directed at restoring perfusion to the ischemic extremity, may be undertaken without addressing the aortic dissection itself, which is managed medically. In patients with unilateral ischemia a femoral-femoral bypass may be sufficient while in patients with bilateral ischemia axillo-bifemoral grafting is appropriate. As in the thoracic aorta, accurate identification of the distal true lumen is critical to avoid perpetuating the dissection distally. External reinforcement with pledgets may be required.

In a high volume single institution, Bozinovski *et al*[10] retrospectively reviewed 76 patients who underwent aortic replacement. Operative mortality was reported to be 22.4%. The relevant morbidity rates included: stroke (6.6%), paraplegia (6.6%), dialysis dependence (10.5%), left vocal cord paralysis (39.5%) and cardiac complications (43.4%). In their examination of the multi-institution IRAD dataset, Trimarchi *et al*[11] found a 29.3% mortality rate for 82 patients undergoing any open intervention for complicated TBAD. The majority (69.3%) of these patients underwent aortic replacement. Stroke and paralysis occurred in 9.0% and 4.5%, respectively. Sachs *et al*[12] analyzed data from the Nationwide Inpatient Sample (NIS), identifying a 20% in-hospital mortality rate for patients undergoing emergent open aortic replacement, despite being utilized in a younger, less comorbid patient population. Taken as a whole, open surgical intervention is associated with significant mortality and morbidity rates. For this reason it is not recommended in patients without life threatening complications.

ENDOVASCULAR MANAGEMENT

The principles of therapy using endovascular techniques remain the same as those with open surgery: either covering the entry tear to induce false lumen thrombosis or equalizing the pressure in the true and false lumen by fenestration. As with open fenestration, percutaneous fenestration treats malperfusion secondary to dynamic obstruction. Its advantages over open fenestration include avoidance of aortic cross clamping and general anesthesia. It can be performed rapidly in an interventional suite and document the perfusion of branch vessels. Furthermore in patients where visceral vessels are perfused through both the true and false lumens the risk of inducing ischemia by false lumen thrombosis is eliminated. Though the technique is not standardized, common methods include the use of IVUS to determine the locations of the true and false lumens. With a wire passed from one lumen into the other, a fenestration is created then enlarged *via* large balloon angioplasty or balloon-expandable stent placement. When visceral/extremity malperfusion occurs secondary to static obstruction, percutaneous branch vessel stent placement (*via* bare-metal or covered stents) may be utilized alone or in conjunction with other endovascular techniques described in this article.

There has been a robust experience with this technique to treat malperfusion in selected centers of excellence. Patel *et al*[4] published their results in treating 69 patients presenting with acute TBAD with visceral malperfusion. Treatment options included true lumen stenting, branch vessel stenting, fenestration, and a combination of all three modalities. When all ischemic territories were examined, angiographic reperfusion was obtained in 95.7% of cases. Early mortality was reported at 17.4%, with a 4.3% incidence of stroke, 2.9% incidence of spinal cord ischemia, and 14.5% of dialysis dependent renal failure. During the follow-up period, the authors noted 1 year and 3 years survival rates of 76.2% and 63.5%, respectively. Despite the immediate success with endovascular fenestration, the authors documented the technique's shortcomings – the inability to reduce long term aortic-related events. After successful fenestration the dissection will persist, the false lumen will not thrombose and the risk of late aneurysmal dilation persists. At 5 years, the rate of freedom from aortic rupture or repair was 67.7%. With the advent of stent graft coverage of the entry tear, the use of fenestration has diminished.

The biggest change in surgical management of TBAD is the evolution of TEVAR to substitute for open surgical sealing of the entry tear. Like percutaneous fenestration, TEVAR has the potential benefit of an "indirect" intraluminal approach to the dissected aorta as well as the ability to avoid aortic cross clamping and minimize additional end organ ischemia. Through this minimally invasive approach, TEVAR has significantly altered treatment algorithms in patients presenting acutely. The goals of TEVAR use in the acute setting are to seal the entry tear, decompress the false lumen, expand the true lumen, and prevent rupture. Until recently, thoracic endografts were being utilized in an off-label fashion in the United States. In 2014, two endografts, the TAG device (WL GORE) and the Valiant device (Medtronic), received United States Food and Drug Administration approval for use specifically in aortic dissection[13,14]. Several other devices remain under investigation.

Qin *et al*[15] recently reviewed their single center experience performing TEVAR in 152 patients presenting with complicated TBAD. They achieved technical success in 94.7% of cases, with an in-hospital mortality rate of 2%, stroke rate of 1.3%, and paralysis rate of 1.3%. They also reported a 2.6% incidence of type Ⅰ endoleak formation and a 1.3% rate of retrograde dissection. Fattori *et al*[16] reported a slightly higher mortality rate of 10.9% in their review of 290 patients from the IRAD dataset. Rates of stroke (2.3%) and paralysis (1.3%) remained low. In the long term follow up, the group did note that 30.6% of patients required a repeat intervention, and 13.4% developed any endoleak. The 5 year mortality rate was reported at 15.5%. Data from the NIS dataset revealed similar rates of in-hospital mortality (13.1%) and related morbidities[12]. Sachs *et al*[12] also documented a continual increase in the utilization of TEVAR throughout the study period. Hanna *et al*[17] reviewed their experience performing endovascular repair in 50 patients presenting with complicated TBAD. They reported no in-hospital deaths, with low (2%) rates of stroke and spinal cord ischemia. They noted a 20% utilization of adjunct procedures (branch vessel stenting and extra anatomic bypass). Though studied only retrospectively, TEVAR utilized in the acute complicated setting is associated with overall lower rates of mortality and morbidity compared with open repair.

TEVAR and percutaneous fenestration may not completely resolve end organ ischemia and supplemental endovascular techniques may be required[18]. Persistence of visceral malperfusion after true lumen expansion with TEVAR, or in the setting of static obstruction, typically warrants treatment with visceral branch vessel stenting. The choice of using bare-metal, covered, self-expanding or balloon expandable stents is left to the discretion of the surgeon, as all devices have been used to manage branch vessel malperfusion[19,20].

ROLE OF TEVAR IN ASYMPTOMATIC TBAD

The reduced morbidity and mortality of TEVAR compared to open repair raises the question of prophylactic TEVAR in asymptomatic patients. The rationale of such an approach would be to seal the entry tear at an early point in the process, depressurizing the false lumen and thereby reducing risk of rupture and progression to malperfusion in the acute setting or aneurysmal dilation in the long term. It is well known that in chronic dissection the septum between the true and false lumen

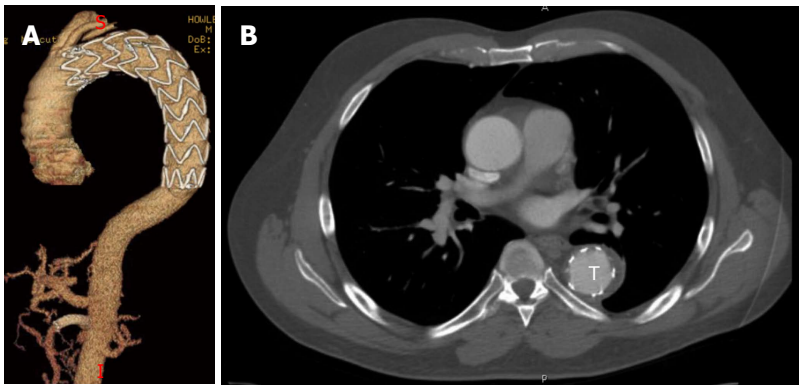

Figure 5 Remodeling after thoracic endovascular aortic repair. A: Follow-up 3D reconstruction from a computed tomography angiography of a patient who underwent TEVAR with adjunct superior mesenteric artery stenting for acute type B aortic dissection with malperfusion. There no evidence of endoleak or aneurysmal degeneration; B: Axial sections from same patient highlighting T expansion with evidence of false lumen thrombosis. TEVAR: Thoracic endovascular aortic repair; T: True lumen.

becomes stiff and repair by endovascular means is more complex and often impossible. The goal of early prophylactic intervention would be to promote false lumen thrombosis, thereby increasing aortic remodeling and reducing the incidence of late aneurysmal degeneration and the frequency of late open repair.

In an attempt to evaluate the role of TEVAR in uncomplicated TBAD, the Investigation of Stent Grafts in Aortic Dissection (INSTEAD) trial randomized approximately 140 patients presenting with subacute (> 14 d) uncomplicated TBAD to best medical therapy with TEVAR or best medical therapy alone[21]. Perioperative mortality rates in the TEVAR group were reported at 2.8%, with a 2.9% incidence of spinal cord ischemia and a 1.5% incidence in major stroke. At 2 years of follow up, the investigators were unable to demonstrate any mortality benefit from TEVAR compared with medical management, with an 88.9% survival in the TEVAR arm and a 95.6% survival in the medical therapy arm. There was no statistical difference seen in the rates of aortic-related deaths (2.9% medical *vs* 5.6% TEVAR), secondary interventions (22.1% medical *vs* 18.1% TEVAR) or spinal cord ischemia (1.4% medical *vs* 2.8% TEVAR) at the end of the 2 years study period. The authors concluded that there was no short or midterm benefit for TEVAR in patients with uncomplicated TBAD and the technique should be reserved for use in those presenting with complications.

There are several shortcomings of the INSTEAD Trial. The major criticisms were that the endpoints of death and complications at two years may not reflect the potential late benefits of TEVAR on false lumen thrombosis, aortic remodeling and late aortic related events and that the trial did not address the role of TEVAR in acute (< 14 d) aortic dissection.

The INSTEAD investigators acknowledged that two years may have been inadequate to capture enough aortic-related deaths within the medical therapy group. To that end, they published outcomes on the same cohort patients followed from 2-5 years from the initial randomization. At 5 years, all-cause mortality statistically differed between the medical (19.3%) and the TEVAR (11.1%) arms[22]. When examining aortic specific mortality, the difference between the medical (19.3%) and TEVAR (6.9%) groups is even more pronounced, with the majority of aortic-related deaths in the medical arm occurring between 2 and 5 years. The authors demonstrated a late survival benefit occurring between 2 and 5 years in patients undergoing TEVAR. It was concluded the survival benefit with TEVAR occurs at a cost of initially increased perioperative morbidity and mortality.

The INSTEAD investigators were also able to demonstrate an improvement in false lumen thrombosis and aortic remodeling in the TEVAR patients. Aortic remodeling is defined as an increase in the true lumen diameter with a subsequent reduction in the false lumen diameter over time, reflecting resolution of the dissection process (Figure 5). No specific criteria exist for objectively quantifying this phenomenon, though several techniques include measuring the true and false lumen diameters at different sites along the thoracic aorta, measuring luminal cross-sectional area, and by volumetric analysis[23]. At 2 years in the INSTEAD trial, only 19.4% of patients undergoing medical therapy were noted to have complete false lumen thrombosis, in contrast to 91.3% of patients undergoing TEVAR[21]. When carried out to 5 years, 22% of patients treated medically showed complete false lumen thrombosis compared with 90.6% of patients undergoing TEVAR[22]. Patterson *et al*[24] attempted to review the available literature on aortic remodeling. Despite being limited by multiple small-sized retrospective series, series with both acute and chronic dissection, and the heterogeneity in which aortic remodeling was quantified, the authors were able to confirm a high (80% to 90%) rate of complete false lumen thrombosis within the proximal thoracic aorta in patients with TBAD undergoing TEVAR. There is evidence to support the connection between aortic remodeling and improvement in long term survival, albeit limited. In a series of patients treated with TEVAR for chronic TBAD, Mani *et al*[25] demonstrated an 89% 3-year survival in

patients with evidence of aortic remodeling, in contrast to a 54% 3-year survival in patients who did not show this feature.

It is important to note that the INSTEAD trial did not address the optimal management of acute TBAD*; i.e.,* all patients survived at least two weeks without developing complications related to their dissection. In patients randomized to TEVAR, the time from diagnosis to treatment averaged 51 d. This may reflect a group of patients in whom the dissection process has already stabilized and who are less likely to develop early or mid-term complications with persistent medical management. Indeed the medical arm had a 95.6% survival and 2.9% aorta related mortality, lower than the 10% mortality reported form the medically managed patients in the IRAD registry[7]. Thus the proper endpoints might have been late rather than early mortality. In fact the 5 years results suggest that the impact of TEVAR is significant in patients who have a longer life expectancy.

INSTEAD did not address the question of how best to deal with patients with acute TBAD who remain asymptomatic but may be at risk for developing complications. While it is clear that this will not occur in the majority of patients, it is equally intuitive that intervention before rupture or malperfusion occurs would be the optimal way to reduce overall morbidity and mortality. The Acute Dissection: Stent Graft or Best Medical Therapy (ADSORB) trial is underway to clarify this issue. A prospectively randomized control study, the ADSORB trial randomized approximately 60 patients presenting with TBAD of less than 14 d duration to either best medical therapy or TEVAR utilizing a Gore TAG device. In contrast to the INSTEAD trial, the ADSORB trial's primary composite endpoint was freedom from either false lumen patency, aortic dilation, or aortic rupture. Mean time to randomization was 4.77 d, with 0.88 d to treatment. Although the study is ongoing, preliminary one year data has been presented. There were no in hospital occurrences of death, stroke or spinal cord ischemia. False lumen thrombosis and freedom from the composite endpoint was reported to be markedly higher in the TEVAR group (57%) compared to the medical only group (3%)[26].

It would be ideal to identify patients at high risk for developing complicated TBAD so that selective use of TEVAR in an asymptomatic setting could occur in at-risk patients, while patients likely to develop false lumen thrombosis with medical management alone could be spared surgical intervention. Several reports have been published that highlight specific cohorts of patients (identified *via* specific radiographic findings) that would potentially benefit the most from early TEVAR. In a recent retrospective review of 228 patients presenting with acute TBAD, Ueki *et al*[27] identified the descending aortic diameter and location of the entry tear as predictors of aortic-related events (dissection-related death, surgical intervention, aneurysmal degeneration or retrograde dissection). In patients treated medically, those with an aortic diameter less than 40 mm and an entry tear located greater than 50 mm from the left subclavian artery experienced an 82.5% rate of freedom from aortic events by 5 years. In contrast, those with aortic diameters greater than 40 mm and a proximal (less than 50 mm from the left subclavian) entry tear experienced a 53.5% freedom from aortic event rate over a similar time period. Marui *et al*[28] also retrospectively examined a group of patients with TBAD treated medically. They identified an aortic diameter greater than 40 mm, persistent false lumen patency and a fusiform dilation index as significantly associated with late aortic events. In a retrospective review of 110 patients presenting with TBAD, Akutsu *et al*[29] identified an aortic diameter of 45 mm on presentation and false lumen patency as independent risk factors for future dissection-related mortality. When examining a series of patients presenting with acute type A and TBADs, Song *et al*[30] identified a false lumen diameter of 22 mm or greater as an independent predictor of late aneurysmal degeneration and aneurysm related death.

FUTURE DIRECTIONS AND CONCLUSION

Management of TBAD has undergone dramatic alterations within the past decade and the management of this problem continues to evolve. The high mortality associated with open repair of patients with complicated TBAD has been reduced by the increasing use of thoracic stent grafts to seal the entry tear and restore perfusion. Initial enthusiasm for percutaneous fenestration is being replaced for the most part by TEVAR, which affords entry tear sealing (and subsequent aortic remodeling) in a minimally invasive fashion. Moreover, the success of TEVAR in managing malperfusion has led investigators to study its use in uncomplicated TBAD. Data supporting this indication is not definitive, but what exists suggests that elective TEVAR in the subacute phase is associated with an improvement in 5 years aortic-related survival, at the cost of some increase in perioperative morbidity. The use of TEVAR also appears to improve aortic morphology over time, potentially explaining its long term survival benefit. This causal relationship, however, has not been definitely proven. Current trials are underway to determine feasibility in applying TEVAR in cases of early (< 14 d) uncomplicated TBAD, although the optimal timing of intervention and criterion for patient selection remain unclear. Observational data has aided in identifying specific radiographic criteria that may select out potential subgroups that may be more likely to benefit from TEVAR than medical therapy alone. Fruitful areas for further investigation include: the development of new devices with lower profile and better conformability to reduce perioperative complications; new techniques to increase incidence of false lumen thrombosis and identifying clinical and radiographic characteristics which can predict patients at high and low risk of developing complications with medical management.

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