Combination of radiotherapy and flap reconstruction for cancer treatments (Review)

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Abstract. Flaps are commonly used to repair large tissue defects caused by tumor resection and are often combined with radiotherapy. Relevant explanations for the mechanism underlying the effect of radiotherapy on flaps and the selection of the sequence of flaps and radiotherapy plan have emerged. The combination of flap and radiotherapy is most widely used in breast, head and neck cancers, while free flaps are the most widely used. Although, reduction of the incidence of complications of flap reconstruction, prevention of flap reconstruction failure and best integration of flap reconstruction with radiation therapy remains controversial. In the present review, these questions and debates were addressed by reviewing the literature on radiotherapy and flap reconstruction in cancer treatment.

Contents

1. Introduction

With the continuous advancement of modern medicine and in-depth research on related treatments, comprehensive treatment is often prioritized for tumors (1). For patients with large primary tumors or extensive invasion of metastatic lymph nodes, radical resection of malignant tumors often results in significant defects. To ensure functional restoration and aesthetic appearance of the body, it is necessary to repair these defects through the use of free flap tissue and vascular anastomosis (2,3). Due to the demands of the disease and the principle of comprehensive tumor treatment, a combination of free flap reconstruction and radiotherapy is utilized. In the present study, the current literature on the influence of radiotherapy on flap reconstruction and the integration of both (including the choice of timing and radiation dose) were reviewed. Furthermore, the present review provided relevant experimental data for reference in guiding the selection of skin flap reconstruction and radiotherapy.

2. Application and acquisition of flap

A flap, a tissue block with its own blood supply system and skin, is used for wound repair, functional reconstruction and cosmetic surgeries (4). Resection of advanced tumors and high-dose radiotherapy usually cause large areas of tissue defects that lead to severe deformity. Appropriate skin flaps are necessary to ensure rapid wound healing, restore appearance and function, reduce surgical complications and provide timely post-operative adjuvant treatment (5-7). Various flaps are currently used to reconstruct tumor sites, particularly those found in the breast, head and neck. With the progress in microsurgery and tissue transplantation, this field is developing rapidly, leading to the emergence of free flaps (Table I) (8-32).

3. Effect of radiotherapy on flap

Radiation can affect the function of endothelial cells, causing changes in vascular biology and damage to vascular function (32). Radiation damages endothelial cells, leading to an inflammatory reaction. Correlativity studies have shown that nitric oxide (NO) released from the endothelium relaxes vascular smooth muscle and inhibits platelet aggregation. However, endothelial cell dysfunction caused by radiation reduces NO production. The inhibition of NO production leads to the formation of microvascular thrombosis. Ultimately, the irradiated microvessels appear as thrombi, leading to a microcirculation disorder after radiotherapy, which delays

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wound healing. Related studies have revealed that radiation reduces the proliferation of endothelial cells and fibroblasts, inhibiting the formation of type I collagen and preventing wound contraction. Simultaneously, DNA mutations and apoptosis of endothelial cells increase after irradiation, which blocks the repair process of endothelial cells (33). When the aforementioned events occur in the graft flap, it will cause thrombosis in the blood vessels of the flap and the tissues around the flap, reduce the vascularization, decrease the diameter of the blood vessels and increase the fibrosis, thus leading to a series of flap complications (33-35). The aforementioned pathological mechanism is the process of a series of flap complications caused by radiotherapy. These complications include infection, hematoma, fistula, wound, dehiscence, vessel thrombosis and exposed plate (36). The effects of endothelial cell injury complications have been divided into two major types: Anastomosis-related (flap necrosis) and flap bed-related (infection, fistula and wound dehiscence) (27).

The numbers of blood vessels in the myocutaneous free flap (MCF) and cutaneous free flap (CF) were different. Compared with CF, MCF had a large number of perforators. Regarding the significant effect of radiotherapy on blood vessels, the aggravation of hypoxia in the flap can lead to peripheral circulatory disorders and malnutrition. These changes reduced the flap volume. However, in a previous study by Yamazaki *et al* (37), the volume reduction of CF was greater than that of MCF and the volume of MCF was markedly larger than that of CF. Although there was no statistically significant difference between CF without radiotherapy and MCF without radiotherapy, the difference between CF radiotherapy and MCF radiotherapy was statistically significant ($P<0.05$), which may be because postoperative RT can reduce the transplanted adipose tissue, additionally, there is a tendency to increase muscle tissue (37).

4. Flap of head and neck tumor

Reconstruction of the head and neck flap plays an important role not only in improving the quality of life of patients but also in restoring the function and shape of tumor sites. In addition, the success rate of free-flap reconstruction in the head and neck region is high (40).

Types of flap. Free flaps have been used to repair various types of tissue defects. With the development of surgical reconstruction technologies, flap complications are increasingly being understood. Current flap selections mainly include radial forearm free flaps, anterolateral thigh free (ALT) flaps, rectus abdominis free flaps and free fibular flaps (FFF). The use of ALT flaps and FFF has steadily increased and fibular flaps have become the most commonly used flaps in microvascular reconstruction of the head and neck in recent years (36). FFFs are usually of three types: Fibular bone, fibula osseous-cutaneous and fibular musculocutaneous. A hard bone cortex is observed in the fibular bone flap. Nevertheless, fibular osseous-cutaneous and fibular musculocutaneous flaps are composite flaps that have the advantages of two flaps (41). These are the first choices when mandibular and adjacent buccal skin or oral floor and tongue mucosa defects require repair and functional reconstruction (42). The design of the head and neck reconstruction flap includes the size, shape, length, and the condition of blood vessels and nerves should be determined according to the needs of the recipient area. The surgical incision of the fibular flap is generally located on the outside of the donor site of the peroneal muscle, and the peroneal muscle is entered through the incision. The design of the osteo-myocutaneous flap and its relationship with the neurovascular pedicle are crucial for repairing different parts of a defect. For instance, when repairing lower lip and perioral muscles, suturing the innervated nerve of the muscle flap with either cervical branch or marginal mandibular branch of facial nerve can be conducted. When repairing masseter muscle, the lower part of flexor longus is designed as starting point for masseter muscle repair by suturing it to zygomatic arch. Nerve innervation in this case is sutured to mylohyoid branch of mandibular nerve. Depending on bone flap design, it can be sutured with retained mucosal wound in oral cavity to repair intraoral soft tissue defect or skin tissue defect outside oral cavity. Lateral sural cutaneous nerve can be sutured to inferior alveolar nerve stump to establish sensory function in flap. Extraoral wound at final recipient site should be sutured in three layers: Platysma muscle, subcutaneous tissue and skin. To prevent clot formation from oozing blood that may compress vascular anastomosis within wound area, drainage tube placement allows adequate exudate drainage (38,39).

Selection of operation and radiotherapy plan. Head and neck tumor resection and reconstruction combined with radiotherapy and chemotherapy are common treatments (43). The major argument is the choice between preoperative and post-operative radiotherapy, as scholars mainly consider the influence on the prognosis of flap reconstruction after tumor resection. Klug *et al* (44) reported that radiotherapy before free tissue transfer does not significantly increase flap loss or post-operative mortality but increases post-operative complications and length of hospital stay. Halle *et al* (27) compared complication rates of anastomosis-related (flap necrosis) and flap bed-related (infection, fistula and wound dehiscence) complications between irradiated and non-irradiated patients. This single-center study indicated that preoperative radiotherapy is a risk factor for both infection and fistula formation, most likely related to an impaired flap bed (27). Momeni *et al* (23) concluded that preoperative radiotherapy is associated with a significant increase in post-operative flap-related complications (23). Nevertheless, these outcomes did not result in a prolonged hospital stay because most flap-related complications can be managed on an outpatient basis, as reflected by the researchers. The meta-analysis conducted by Herle *et al* (45), including 24 studies comparing 2842 flap reconstructions performed in irradiated fields and 3491 flap reconstructions performed in non-irradiated fields, yielded statistically significant risk ratios for flap failure, complications, reoperation and fistula. When neck vessels were irradiated, the loss of the free flap increased significantly (46). The aforementioned experimental results support clinical practice in which physicians have taken treatment measures to prevent or reduce the occurrence of complications. For example, surgeons have attempted to prevent wound rupture and dehiscence by anastomosing outside the radiation zone and administering antibiotics prophylactically in the pre-irradiation bed. Although further

Table I. Flap types used in various cancer types.

Types of cancer		Flap type	(Refs.)
Breast cancer		Transverse rectus abdominis musculocutaneous flap	(8)
		Latissimus dorsi musculocutaneous flap	(9)
		Free inferior abdominal artery perforator flap	(10)
		Latissimus dorsi flap	(11)
		Free deep inferior epigastric perforator flap	(12)
		Profunda femoral perforator flap	(13)
		Musculocutaneous flap of gracilis muscle	(14)
Head and neck tumor	Squamous cell carcinoma of buccal fossa	Transverse rectus abdominis musculocutaneous flap	(15)
	Root squamous cell carcinoma of tongue	Forearm fascial flap	(16)
	Laryngeal carcinoma	Pectoralis major fascia flap	(17)
	Hypopharyngeal carcinoma	Free ileocolon flap	(18)
	Right piriform fossa squamous cell carcinoma	Pectoralis major musculocutaneous flap	(19)
	Hypopharyngeal carcinoma	Radial forearm flap	(18)
	Oral cancer	Free forearm flap	(20)
	Parotid gland tumor	Anterolateral femoral free flap	(21)
		Semi-free radial flap of forearm	(22)
		Radial forearm flap	(23)
		Anterolateral femoral fascial flap	(23)
		Fibula and scapula flap	(23)
	Squamous cell carcinoma of the floor of the mouth	Triangular chest flap	(24)
	Laryngeal tumor	Pectoralis major flap	(24)
	Oropharyngeal tumor	Free radial fibula flap	(25)
		Free fibula flap	(25)
	Laryngeal tumor	Pedicled thoracacromial artery perforator flap	(26)
	Head and neck tumor	Radial forearm flap	(27)
	Squamous cell carcinoma of tongue	Pectoral major musculocutaneous flap	(16)
Anorectal and gynecological tumors		Pedicled rectus abdominis flap	(28)
Hemangioma		Expanded flap	(29)
Nasopharyngeal carcinoma		Pedicled pectoralis major musculocutaneous flap	(30)
		Forearm flap	(31)
		Free fibula flap	(31)
		Pedicled tongue flap	(31)
Osteoclastoma		Fibula flap	(32)

research is underway, it has demonstrated certain effects on head and neck reconstruction (47). Similarly, Klug *et al* (45), Benatar *et al* (45) and Schultze *et al* (48) reported a trend between radiation dose and associated flap loss. The aforementioned studies comparing high [>60 gray (Gy)] and low (<60 Gy) radiation regimens revealed an increased risk of free flap loss in the high-dose group, although this did not reach statistical significance. Therefore, the authors suggested that the irradiation dose to the flap should not exceed 60 Gy. Regarding the time interval between radiation and surgery, Bengtson *et al* (49) revealed that when flap surgery was performed <4 months after radiation, the overall complication rate was 36 vs. 14% when performed at >4 months after radiation therapy (49). Halle *et al* (50) reported a linear relationship between the time elapsed after preoperative radiotherapy and the incidence of free flap loss and complications by examining the timing after pre-operative radiotherapy in three groups: i) <4, ii) 4-6 and iii) >6 weeks. The incidence of complications was highest when the flap operation was performed 6 weeks after radiotherapy (50).

Patients with advanced head and neck cancer often require adjuvant radiotherapy. In addition to other side effects of radiotherapy on the surrounding tissues, such as loss of elasticity and flexibility of soft tissues, it may lead to further loss of flap volume (51). Furthermore, due to excessive contraction of the flap, post-operative radiotherapy has side effects on the functional results of swallowing and speaking (52). These findings have led to a consensus that defects should be overcorrected. Cho *et al* (53) studied the use of free anterolateral thigh flaps (ALTF) and regional pectoralis major myocutaneous flaps for head and neck reconstructions. After 24 months of radiotherapy, the estimated volume of free ALTF decreased by 25%, whereas that of the regional pectoralis major myocutaneous flap decreased by 11%. Tarsitano *et al* (54) indicated that 12 months after treatment, patients who underwent reconstruction with an ALT flap had an average volume loss of 44.2% when treated with radiotherapy, whereas an average flap contraction of 19.8% occurred in patients who did not undergo post-operative radiotherapy. For these reasons, they recommended overcorrection by a factor of 1.4 in radiotherapy-treated patients, while a correction factor of 1.2 should be sufficient in patients not undergoing adjuvant radiotherapy. Regarding the influence of radiotherapy on the flap, another important variable to be considered is the flap type which determines the flap contraction. For example, fascial flaps, such as the ALT, have less volume loss than musculocutaneous flaps (such as the latissimus dorsi free flap) (54,55).

The reconstruction of head and neck tumors requires bone flaps. For example, oral squamous cell carcinomas invading the adjacent jaw usually require jaw resection, reconstruction and radiotherapy (56). The ideal timing for jaw reconstruction has been discussed. Gottsauner *et al* (57) discussed the effects of radiotherapy and the timing of radiotherapy on the reconstruction of jaw ossification by free bone transplantation. Researchers have debated the ossification time and influencing factors in patients who received preoperative radiotherapy, post-operative radiotherapy, or no radiotherapy. The results demonstrated that the fastest ossification was observed in the non-irradiated group; that is because the radiation of the head and neck was related to the damage and extension of ossification during the reconstruction of the jawbone with free bone transplantation. Moreover, the closer initial contact between the segments resulted in faster ossification.

5. Flap of breast tumor

Patients with breast cancer not only have to bear the threat of cancer, which may endanger their lives but also bear the blow of losing one breast due to breast cancer treatment, which causes great physical and psychological damage (58). Research demonstrated that both breast-conserving therapy and mastectomy with breast reconstruction for breast cancer can improve the psychological damage caused by mastectomy (59,60). Breast reconstruction with autologous tissue, the so-called flap, comes from the back, abdomen, buttocks, thighs and omentum and can obtain a more natural breast with a certain degree of sag, soft texture, consistent temperature and tolerance to radiotherapy (61). Autologous reconstruction, which has an improved esthetic effect for both physicians and patients, is considered the gold standard by numerous plastic surgeons because it is more flexible, customized for patients and can age more naturally with the opposite breast (61).

Types of flap. In breast reconstruction, latissimus dorsi myocutaneous flaps (LDP), transverse rectus abdominis myocutaneous flaps (TRAM), gluteus maximus myocutaneous flaps, lateral thigh transverse myocutaneous flaps, Taylor Rubens flaps and iliac waist free flaps are used. The most widely used flaps are the LDP and TRAM (62). TRAM is a commonly utilized flap for breast cancer reconstruction due to its ample tissue volume, it facilitates the creation of symmetrical breast shape with the healthy side while simultaneously providing the benefits of both breast shaping and abdominoplasty. Additionally, the post-operative abdominal scar is positioned above the pubic bone, allowing it to be concealed by underwear (63). The main steps of this procedure are as follows: An oblique transverse incision is made on the patient's abdomen, extending from 0.5-cm above the umbilicus to the pubic bone along the boundary formed by the anterior superior iliac crest. Once identification of deep inferior epigastric artery and vein is achieved, separation of TRAM flap commences by excising rectus abdominis muscle containing these vessels at their origin near pubic region. Subsequently, cord-like structures consisting of rectus abdominis muscle fibers along with underlying arteries and veins within deep layer of flap are meticulously dissected and separated from below. After tunneling through thoracoabdominal region, TRAM flap is transferred to affected side for chest reconstruction purposes. Trimmed accordingly, it is then secured in place and shaped according to healthy side before suturing takes place. Defect area undergoes repair using polypropylene mesh while a drainage tube is inserted into reconstructed breast area. After 1, 3, 6 and 12 months follow-up of patients (64,65).

Selection of operation and radiotherapy plan. One of the long-term challenges in plastic surgery, particularly breast cancer reconstruction, is the optimal combination of flap reconstruction and post-tumor resection radiotherapy. Post-mastectomy radiotherapy (PMRT) is a common treatment plan that involves resection of the tumor, subsequent radiotherapy and flap reconstruction. It has been revealed to reduce local recurrence and improve survival rates in patients with lymph node positivity, especially in the treatment of breast cancer (66-68). There are two main treatment options: (i) Immediate reconstruction (immediate flap reconstruction after tumor resection, followed by postoperative radiotherapy) and (ii) Delayed reconstruction (radiotherapy after tumor resection and flap reconstruction 6-12 months later) (68).

Disease-free and overall survival of intermediate-risk women with a tumor size of 50 mm or less and 1-3 positive lymph nodes significantly improved after PMRT and regional node irradiation (69). The optimal time to delay autogenous breast reconstruction after PMRT was discussed. In a study conducted by Baumann *et al* (70), patients who underwent surgery 12 months or longer after PMRT reported significantly less flap loss and repeat surgery than patients who underwent surgery within 12 months after PMRT ($P<0.05$). However, there were no significant differences in partial flap loss, microvascular thrombosis, wound cracking, fat necrosis, or infection between the two groups (70). By contrast, Momoh *et al* (71) observed no significant difference in post-operative complication rates between patients who underwent flap reconstruction within 6 months of PMRT and those who underwent flap reconstruction more than 6 months after PMRT. The optimal timing of PMRT remains uncertain due to the lack of data (71).

In a comparison of immediate and delayed autologous reconstruction, most studies reported fewer complications, including wound contracture, volume loss, fat necrosis and revision surgery (72,73). Because immediate reconstruction preserves the breast envelope and is easier to perform after skin-preserving mastectomy, the goal of reconstruction is to replace the breast volume rather than the lost skin. By contrast, for delayed breast reconstruction after PMRT, a large portion of the skin under the mastectomy incision is often severely fibrotic and needs to be replaced with healthy skin from the donor site to adequately reconstruct the breast contour. In this way, delayed reconstruction not only limits the amount of tissue available for reconstruction but also lengthens the breast scar, making it harder to hide. Patients are increasingly opting for immediate breast reconstruction. However, radiotherapy after mastectomy is an important risk factor for flap complications and irradiated implants have a higher risk of infection and reconstruction failure than unirradiated implants (74). Again, the rates of fibrosis or shrinkage, flap contracture, volume loss and fat necrosis in the irradiated autologous flaps were higher than those in the unirradiated autologous flaps (75). In addition, post-operative complications following immediate reconstruction delayed radiotherapy by an average of 19.7 days, which may affect tumor prognosis (76). Given the limitations of these pathways, clinicians should consider preoperative radiotherapy to avoid the adverse effects of radiotherapy on autologous breast reconstruction. Preoperative radiotherapy may also achieve an antitumor response by eliminating subclinical diseases and improving the pathological complete response rate through the radiosensitization of neoadjuvant chemotherapy (77). Thiruchelvam *et al* (78) initiated preoperative radiotherapy 3-4 weeks after neoadjuvant chemotherapy and the final results demonstrated that the incidence of open breast wounds was similar to that of radiotherapy after mastectomy. It was concluded that skin-sparing mastectomy followed by preoperative radiotherapy and immediate DIEP flap reconstruction was feasible and technically safe (78).

Regarding other studies on preoperative radiotherapy, Brackstone *et al* (77) showed no significant difference in disease-free survival between preoperative and post-operative radiotherapy, whereas Gerlach *et al* (79) reported improved overall survival in patients treated with preoperative radiotherapy (median 19 months) compared with those treated with radiotherapy after mastectomy (median 13 months). The external validity of the heterogeneity of radiotherapy is improved, as radiotherapy plans vary across centers and internationally. Preoperative radiotherapy for breast reconstruction flap complications is limited. In the future, a mastectomy breast reconstruction with radiation timing need more randomized controlled trials to evaluate, and compare their effects on the tumor control and the quality of life.

6. Conclusion

The present review provided insights into the current state of knowledge regarding the integration of radiotherapy and flap reconstruction for cancer treatment. Numerous studies have provided relevant explanations for the mechanism underlying the effect of radiotherapy on flaps and the selection of the sequence of flaps and radiotherapy plan. The combination of flap and radiotherapy is most widely used in breast and head and neck cancers while free flaps are the most widely used. Radiotherapy is often performed after flap reconstruction in clinical practice, with a radiation dose of ≤60 Gy. Although there is a lack of relevant clinical guidelines for flap reconstruction combined with radiotherapy for cancer. There is a need for further research to optimize treatment outcomes and minimize the risk of complications. Further studies could explore different variables, such as timing and dosing of radiotherapy, and compare outcomes among different types of flaps to provide more comprehensive guidance to clinicians.

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Authors' contributions

HX and YL drafted the manuscript. HX, YL and WT reviewed and collected data for the study. XD conceived the study and contributed in the review and edit of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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