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A systematic review on the effect of immediate autologous microsurgical breast reconstruction on the timely initiation of adjuvant therapy

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Abstract

Aim: Postoperative administration of adjuvant therapy is associated with reduced breast cancer recurrence and mortality. Concerns have been raised that immediate reconstruction may lead to a delay in the administration of adjuvant therapy with the risk of compromising survival. This systematic review seeks to evaluate and discuss whether post-mastectomy immediate autologous microsurgical breast reconstruction affects the timely initiation of adjuvant chemotherapy and radiotherapy.

Methods: PubMed and EMBASE were searched to identify studies assessing the impact of immediate autologous microsurgical breast reconstruction on the timely initiation of adjuvant therapy.

Results: Seven studies comprising 267 patients treated with immediate autologous microsurgical reconstruction followed by adjuvant therapy and 2,622 patients treated with mastectomy-only followed by adjuvant therapy were included in this study. Reconstructed patients started adjuvant therapy later, with a mean difference ranging from 2 to 14 days. Adjuvant therapy was initiated after 4-10 weeks in most cases - regardless of reconstruction or not - and only few examples of delays of more than 12 weeks were recorded. Major postoperative complications were found to be associated with delay in the initiation of adjuvant therapy.

Conclusion: The literature generally agrees that delays in adjuvant therapy beyond 12 weeks after surgery are associated with increased breast cancer recurrence and mortality, but uniform data on the clinical effects of delays within this interval are lacking. The association between postoperative complications and delays in adjuvant therapy underlines the importance of careful patient selection, a multidisciplinary treatment approach, and other measures known to reduce the risk of complications.

Keywords: Breast cancer, immediate autologous microsurgical breast reconstruction, immediate free-flap breast reconstruction, adjuvant chemotherapy, adjuvant radiotherapy

INTRODUCTION

Breast cancer is the most common female cancer worldwide, with 2.3 million new cases diagnosed in 2020[1]. The treatment of breast cancer is multidisciplinary and often involves a combination of surgery, chemotherapy, and radiotherapy. Surgery represents the treatment cornerstone, and despite improvements in breast conserving surgery techniques, mastectomy remains the primary surgical treatment for almost 40% of breast cancer patients[2].

Alongside improvements in survival rates, breast reconstruction has become increasingly more widespread in recent decades. In general, breast reconstruction may be performed using implants, autologous tissue, or a combination thereof. To that, autologous flap reconstruction can be based on either a pedicled flap or a microvascular free flap. Free flap reconstruction is commonly used because it provides a life-long natural reconstruction with a good cosmetic result[3]. Examples of commonly used free flaps are the deep inferior epigastric perforator (DIEP) flap, the free transversus rectus abdominis myocutaneous (TRAM) flap, the Inferior/superior gluteal artery perforator (I/S-GAP) flap, the transversus upper gracilis (TUG) flap, and the transverse musculocutaneous gracilis (TMG) flap. Historically, most reconstructions were delayed for months or years after initial mastectomy and adjuvant therapy. However, it has been well established that immediate reconstruction at the time of mastectomy has many advantages for the patient. Most notably, these include avoidance of further operative procedures and maintenance of the patient's body image, resulting in improved sexuality and sense of femininity, improved quality of life, and better cosmetic results[4]. On the other hand, mastectomy combined with immediate reconstruction is a more extensive procedure and many studies have found increased complication rates compared to simple mastectomy[5-7]. It is obvious that this particularly applies to microsurgical free flap reconstruction as these are especially complex procedures with several critical steps and occasionally longer operating times.

As mentioned above, breast cancer surgery is often combined with adjuvant therapy, being it either chemotherapy or radiotherapy and often both treatment modalities are indicated. It has been well established that administration of adjuvant therapy is associated with reduced breast cancer recurrence and mortality[8-10]. Initiation of adjuvant therapy in due time is important, but no randomized trials have determined the optimal time from surgery to the start of adjuvant therapy or evaluated the effect of delays, as this kind of trial would be unethical. However, several retrospective studies have sought to investigate this question. Two recent large-scale multicenter studies[11,12] and one smaller single-center study[13] have shown that delays of more than 90 days in the delivery of chemotherapy are associated with a decline in overall and cancer-specific survival. A meta-analysis by Yu *et al.* including seven studies and 34,097 patients found a 15% decrease in overall survival for every four-week delay in the delivery of adjuvant chemotherapy and commented that adjuvant chemotherapy should optimally be initiated 4 weeks after surgery[14]. Other studies support the perception that chemotherapy should be initiated within four to twelve weeks after surgery[7,15,16], but we do not have solid and corresponding data on the clinical effects of delays within this interval.

The same inconsistency applies concerning the optimal timing of adjuvant radiotherapy. A meta-analysis of 21 retrospective studies has shown an increased risk of loco-regional recurrence if radiotherapy is delayed for more than eight weeks after surgery[17]. In contrast, another large cohort study found no significant difference in survival with delays up to 20 weeks, though it should be noted that this accounts for patients undergoing breast conserving surgery[18]. The Danish Breast Cancer Group (DBCG) suggests that radiotherapy should be initiated as soon as possible and that the maximum time from surgery should not exceed 12 weeks[19].

In general, adjuvant therapy should be initiated as soon as possible, but it should await the complete healing of the surgical wounds[10]. Therefore, concerns have been raised that the increased complication rates associated with immediate reconstruction may lead to a delay in the administration of adjuvant therapy with the risk of compromising the oncological outcome[20]. While psychosocial and cosmetic outcomes both represent important considerations, it is important to keep in mind that a reconstructive procedure should never compromise the overall oncological safety.

Several studies including systematic reviews have investigated the relationship between immediate breast reconstruction and the initiation of adjuvant therapy[20,21]. Most studies are based primarily on implant-based reconstructions or pedicled flap reconstructions and some studies do not even differentiate between reconstructive methods. This systematic review seeks to evaluate and discuss whether post-mastectomy immediate free flap reconstruction affects the timely initiation of adjuvant therapy.

METHODS

Search strategy and selection criteria

The Pubmed and Embase databases were searched to identify studies assessing the effect of immediate breast reconstruction on the time to delivery of adjuvant therapy. A research librarian assisted in the search. Databases were searched on November 22nd, 2023, and December 12th, 2023, respectively, with the terms breast cancer and mastectomy and immediate autologous reconstruction and adjuvant therapy. Both MeSH terms, free text words, and heading/abstract words were used. The search was limited to publications in English. The exact search strategy is presented in Supplementary Table 1.

The inclusion criteria were observational studies reporting some kind of time frame from mastectomy following primary free flap reconstruction to the start of adjuvant therapy, either chemotherapy or radiation. Ideally, studies would also include a control group with women undergoing mastectomy only, but this was not required. Studies that included only implant-based, pedicled-based and delayed reconstructions were excluded. Additionally, studies with children, male patients, patients with metastasis or recurrence, and pregnant or lactating women were excluded. Lastly, animal studies, case reports, editorial articles, author reflection papers, and systematic reviews were excluded. Two investigators independently screened titles and abstracts to identify studies meeting the defined eligibility criteria. Full-text articles were then reviewed by the two plus one additional investigator and disagreements were resolved. The software tool Covidence was used to manage and streamline the screening process.

Data extraction

Extracted data include author, publication year, country, study design, number of patients with free flap reconstruction including type of free flap reconstruction, number of controls (mastectomy-only), and number of patients receiving adjuvant treatment [Supplementary Table 2]. Additionally, complication rates and time to initiation of adjuvant treatment in the two groups were extracted [Supplementary Tables 3 and 4].

RESULTS

Our search identified a total of 1,077 publications. 187 duplicates were removed, some manually and some automatically by Covidence. That left a total of 890 publications for title and abstract screening. In this process, 757 publications were excluded, leaving a total of 133 publications for full text screening. Full text screening led to the exclusion of 126 publications due to criteria which are specified in a PRISMA flow chart [Supplementary Figure 1]. It is worth mentioning that a total of 20 articles had to be excluded because it was not possible, even by a medical librarian, to access the full text version of the article or that the only version published online was a conference abstract. Three articles were excluded because they involved only implant-based reconstructions and 21 were excluded because they only involved reconstructions based on pedicled flaps or did not specify how many patients received a free flap reconstruction. Four articles did specify the proportion of patients with free flap reconstructions, but they did not distinguish between pedicled or free flap reconstructions when evaluating complications or time from surgery to initiation of adjuvant therapy. When screening was completed, seven articles were included in the systematic review[15,16,22-26]. The study characteristics are presented in Supplementary Table 2. Six studies are retrospective case-control studies and compare one group of patients receiving mastectomy immediately followed by a free flap reconstruction (cases) to another group of patients receiving only a mastectomy (controls). One study by Nguyen *et al.* is a retrospective cross-sectional study that sorely investigates 30 patients receiving DIEP reconstructions without comparing to a control group[26]. A total of 267 patients treated with mastectomy followed by immediate free flap reconstruction and 2,622 patients treated with mastectomy-only were included in this systematic review. Most reconstructions were performed using a DIEP flap, but free TRAM-flaps, S/I-GAP-flaps, SIEA-flaps, TUG-flaps and TMG-flaps were also used in some cases.

Complications

Only four studies included data on postoperative complications, specifically on free flap reconstruction. These data are presented in Supplementary Table 3. Lee *et al.* evaluated wound complications including wound dehiscence, infection, skin necrosis, seroma, and skin flap maceration[23]. They found that 22% with DIEP-flap reconstructions and 2.5% with mastectomy-only had a wound complication. O'Connell *et al.* differentiated between any complication and major complications requiring further surgery or hospital readmission[24]. They found that free flap reconstruction was strongly associated with major complications.

Kontos *et al.* did not compare complication rates in the two groups[16]. Instead, they evaluated the group of patients who had a free flap reconstruction and where chemotherapy was initiated later than six weeks after surgery, trying to explain the reason for the delay. Most notably, six patients had complete or partial flap necrosis and three patients experienced abdominal wound dehiscence. Nguyen *et al.* divided complications into three categories based on their location: breast, donor site, and systemic[26]. Four patients had further surgery due to either venous congestion or total flap loss. Two patients suffered abdominal wound dehiscence. Lastly, two patients had a pulmonary embolism and one patient developed pneumonia.

Time to adjuvant therapy

Six of the studies investigated solely adjuvant treatment with chemotherapy. Only one study by O'Connell *et al.* investigated adjuvant radiotherapy as well, specifying that 55% of patients - regardless of reconstruction or not - received chemotherapy as the first adjuvant treatment whereas 46% received radiotherapy as the first adjuvant treatment[24]. Five of the included studies calculated the mean time in days to initiation of adjuvant treatment, whereas two studies recorded time to adjuvant treatment as a categorial variable, describing the proportion of patients who had initiated treatment at a defined point in time. In one study[25], it was six weeks after surgery, and in another study[22], it was eight weeks after surgery. These data are presented in supplementary table 4. In the study by Wilson *et al.*, the median time to initiation of

chemotherapy was 38 days in the free flap group and 28 days in the mastectomy-only group[15]. Another study[16] detected a significant difference in the median time to initiation of chemotherapy in the free-flap group (55 days) compared to the mastectomy-only group (40 days). Additionally, they analyzed the number of patients whose initiation of chemotherapy exceeded a six-week, eight-week, ten-week, and 12-week time point. Significantly more patients in the free flap reconstruction group had not started chemotherapy at week 6, week 8, and week 10. At the 12-week point, there was no significant difference between the two groups. The causes for delays in the free flap reconstruction group were mainly due to surgical complications such as flap necrosis and abdominal wound dehiscence. In four cases, no reason was recorded in the patient's notes. In another study[23], the median time to initiation of chemotherapy was 27 days in the free flap group and 25 days in the mastectomy-only group. There were no cases of delay of more than 12 weeks in either of the groups. The study by O'Connell *et al.* provides extensive data on the time to initiation of adjuvant therapy[24]. They detected a significant difference in the median time to initiation of adjuvant therapy (either chemo- or radiotherapy) in the free-flap group (57 days) compared to the mastectomy-only group (52 days). When looking particularly into delays of chemotherapy, there was no significant difference between the proportion of patients who had started chemotherapy more than 12 weeks after surgery in the two groups. Correspondently, no significant difference was found in the proportion of patients who had started radiotherapy after more than eight weeks. Notably, across all patients, despite surgical procedures, the timing of adjuvant therapy, chemotherapy, and radiotherapy was related to whether the patient had no, minor, or major complications. Likewise, patients experiencing complications were significantly more likely to experience delays of chemotherapy for more than 12 weeks and delays of radiotherapy for more than eight weeks. One study[26] reported that patients with DIEP-flap reconstructions received adjuvant chemotherapy on average, 35 days post-surgery and all within 7 weeks after surgery. Two of the studies[22,25] defined that initiation of chemotherapy was delayed when it was initiated after more than 8 weeks (56 days) and 6 weeks (42 days) after surgery, respectively. 21% of patients in the free flap group had their chemotherapy initiated after more than 8 weeks compared to only 4.4% among controls with mastectomy-only. Overall, 98% of patients who received adjuvant chemotherapy started treatment within 12 weeks[22]. Chemotherapy was delayed for more than six weeks in 47% of cases in the free flap group compared to 22% of cases in the mastectomy-only group[24]. The delay in initiation of chemotherapy was mostly due to wound complications and it was concluded that postoperative complications were a significant risk factor for delay.

DISCUSSION

Adjuvant chemotherapy

The majority of studies in this systematic review present data showing that immediate free flap reconstruction might be associated with a longer time to initiation of adjuvant chemotherapy but that the clinal significance of this delay is open to discussion.

Wilson *et al.* found a median difference of ten days (28 to 38) between the two groups[15]. The study does not perform a statistical test to compare the groups, but comments that the analyses suggest that free flap reconstruction may lead to a delay in chemotherapy. They comment that the reason for delay was not surgical complications, but rather a consequence of fatigue and the need for a longer recovery period among patients in the free flap group. They clarify that data should be interpreted with caution due to the small number of patients in the free flap group (ten patients). It should be noted that five out of ten patients received their chemotherapy within 40 days and that the longest period between surgery and chemotherapy was 52 days. These are both well within the period of 12-week delay, which, in large-scale population-based studies, have shown to be associated with worsening of overall and cancer-specific survival[11,12].

Three studies[16,22,25] found that patients receiving free flap reconstruction started adjuvant treatment significantly later than patients receiving mastectomy only. The cause of this was found to be surgical complications, such as flap necrosis. Kontos concludes that this delay may affect survival for at least a proportion of patients, highlighting the need for microsurgical reconstructive procedures in high-volume centers with experienced teams in order to minimize surgical complications.

O'Connell *et al.* found that free flap reconstruction was associated with a significantly longer time to initiation of adjuvant therapy compared to mastectomy only[24]. The median difference was small, only five days, and the authors comment that this difference hardly carries any clinical significance. Therefore, they conclude that free flap reconstruction does not result in clinically significant delays in the initiation of adjuvant therapy. The study also investigated complication rates and found that patients who developed complications - regardless of surgical procedure - were more likely to experience significant delays of more than 90 days compared to patients with no complications. Correspondently, they found that patients with free flap reconstructions developed significantly more complications, especially major complications resulting in readmission or further surgery, compared to patients treated with mastectomy only.

It is noteworthy that patients with free flap reconstruction do not experience clinically significant delays in the initiation of adjuvant therapy despite the higher rate of surgical complications among these patients. The authors explain this paradox by looking into the patient selection for free flap reconstruction and reconstructive breast surgery in general. Patients selected for reconstructive surgery tend to be younger, have fewer comorbidities, have lower BMI, be non-smokers, and in general, have fewer risk factors for complications. To that, they are less likely to require adjuvant treatment because immediate reconstruction is often performed following mastectomy for low-stage disease where lymph node involvement is not anticipated. This patient- and disease-related pattern is evident in O'Connell *et al.*'s study and it corresponds well with the findings made in the other studies in this review and in general when reading the literature on this subject[24,27]. The tendency to refrain from immediate reconstruction in high-stage disease suggests that surgeons and medical oncologists are cautious in offering immediate reconstruction to patients who are likely to require adjuvant treatment because of the risk that longer recovery time and complications may delay the initiation of adjuvant treatment. This restraint toward immediate breast reconstruction among physicians was presented in a publication as early as 2002, where authors hypothesized that the low number of breast reconstructions performed at the time was partly due to inadequate knowledge and misinformation about breast reconstruction. The study found that nearly 40% of medical oncologists were concerned that immediate breast reconstruction would interfere with adjuvant treatment[28].

Lee *et al.* registered a noteworthy shorter median time to initiation of chemotherapy compared to the other studies (27 days in the free-flap group compared to 25 days in the mastectomy-only group)[23]. No statistical analysis comparing the two groups was performed, but it is evident that the difference is minimal and without clinical significance. Interestingly, they found the shortest median time to initiation of chemotherapy, shortest intervals to drain removal, and fewer admission days among patients with free flap reconstructions compared to patients receiving other methods of reconstruction (LD-flap and tissue expander/implant), although it should be noted that the difference was only significant concerning drain removal. This trend stands in contrast to the findings in, e.g., O'Connell *et al.* and Wilson *et al.*, who both describe a shorter median time to initiation of chemotherapy among patients with implant-based reconstructions compared to free flap reconstructions[24,15]. It should be noted that the analyses concerning especially the free-flap subgroup were particularly limited due to the small number of patients, as only nine patients with DIEP-flap reconstructions were included in Lee *et al.*'s study[23].

Nguyen *et al.*'s study[26] is different from the others because the study designs lack a control group. Despite this, it is still relevant to discuss their experiences with DIEP-flaps and correlate these to the other studies. Adjuvant chemotherapy was initiated after a mean time of 35 days and all within 7 weeks after surgery. These correlate well with the findings of Wilson[15] and Lee[23] but are notably shorter than the other included studies[16,22,24]. The rate of complications was more than 50%, including four patients needing further surgery due to either venous congestion or total flap loss. Those who underwent reoperation still managed to initiate adjuvant therapy within 7 weeks, indicating that the complications did not lead to clinically significant treatment delays. These findings are similar to those by Wilson *et al.* but stand in contrast to the four other studies[15,16,22,24,25] which all describe that complications postpone the initiation of adjuvant therapy to some extent, but not for longer than 12 weeks.

Adjuvant radiotherapy

Only one study by O'Connell *et al.* investigates how immediate free flap reconstruction affects the initiation of adjuvant radiotherapy[24]. It is well known that administering radiotherapy after implant-based reconstruction is not recommended due to the significant risk of developing functionally and cosmetically constraining capsular contractions[29,30]. In fact, there has been a tendency to refrain from immediate reconstruction in general if the patient was expected to need adjuvant radiotherapy. For instance, the Danish Breast Cancer Group (DBCG) has suggested opting for delayed breast reconstruction in these situations[27]. Two meta-analyses in 2017[31] and 2021[32] both conclude that immediate free flap reconstruction should be considered a viable treatment option in patients requiring adjuvant radiotherapy. Late complications were found to be comparable to those of delayed breast reconstruction. Additionally, breast aesthetics and quality of life, evaluated from the patient's perspective, were not compromised by flap exposure to radiation therapy. The optimal timing of adjuvant radiotherapy is not well-established. A meta-analysis of 21 retrospective studies has shown an increased risk of loco-regional recurrence if radiotherapy is delayed for more than eight weeks following surgery[17]. In contrast, another large cohort study found no significant difference in survival with delays of up to 20 weeks, though it should be noted that this accounts for patients undergoing breast conserving surgery[18]. The Danish Breast Cancer Group (DBCG) recommends that radiotherapy should be initiated as soon as possible and that the maximum time from surgery should not exceed 12 weeks[19]. O'Connell *et al.* found that the prevalence of radiotherapy delays for more than eight weeks was similar in the free-flap ground and the mastectomy-only group[24]. There were no examples of treatment delays of more than twelve weeks - regardless of procedure type or complications. This study provides data showing that immediate free flap reconstruction in the setting of adjuvant radiotherapy does not seem to affect loco-regional recurrence rates or survival. These findings support that immediate free flap reconstruction could be considered a viable treatment option in patients requiring adjuvant radiotherapy when the treatment is performed in experienced centers with integrated collaboration between breast surgery, plastic surgery, and oncology.

In general, this systematic review presents data showing that immediate free flap reconstruction is associated with a longer time to initiation of adjuvant therapy compared to mastectomy-only. The mean difference between the two groups spanned from two days in Lee *et al.*[23] to 14 days in Kontos *et al.*[16]. Adjuvant therapy was initiated after four to ten weeks in most cases - regardless of reconstruction or not - and there were only few examples of delays of more than 12 weeks. Patients treated with mastectomy-only were equally likely to experience delays of more than 12 weeks. Authors broadly comment that the clinal significance of this difference between free flap reconstruction and mastectomy-only is expected to be minimal or non-existing in most cases. As presented in the introduction of the review, the literature generally agrees that delays in adjuvant therapy beyond 12 weeks after surgery are associated with increased breast cancer recurrence and mortality, but uniform data on the clinical effects of delays within this interval are lacking. A population-based study by Chaves-MacGregor *et al.* including 24,843 Californian women

found no evidence of adverse survival among patients who started adjuvant chemotherapy up until 90 days after surgery compared with patients starting chemotherapy within 31 days after surgery[11].

Similarly, another retrospective study including 2,594 patients suggests that adjuvant chemotherapy is equally effective up to 12 weeks after surgery[33]. This is in contrast to the findings in a meta-analysis by Yu *et al.* involving seven studies and 34,097 patients. They found a 15% decrease in overall survival for every four-week delay in the delivery of adjuvant chemotherapy and commented that adjuvant chemotherapy should optimally be initiated 4 weeks after surgery[14]. Another meta-analysis by Biagi *et al.* including 14,327 patients found a 6% decrease in overall survival for every four-week delay[34]. The biggest mean difference in time from surgery to initiation of adjuvant therapy between patients receiving immediate free flap reconstruction and patients receiving mastectomy only found in this systematic review was two weeks. Applying the findings of the two meta-analyses, a two-week delay would theoretically result in a 2%-7% decrease in overall survival.

The included studies underline the importance of careful patient selection. These studies and the literature in general extensively describe immediate free flap reconstruction as a potentially complex procedure that carries a considerable risk of surgical complications[35]. Additionally, a majority of the studies agree that complications - especially major complications resulting in re-operation - lead to some degree of delay in the initiation of adjuvant therapy. Based on this, it is obvious that the development of postoperative complications, rather than the type of procedure performed, determines the initiation of adjuvant therapy. When dealing with complex and, to some extent, fragile microsurgical procedures, it is especially important to minimize the amount of patient-related risk factors associated with postoperative complications, such as comorbidity, smoking, and high BMI. This is achieved by careful patient selection. Another way of reducing the risk of postoperative complications is to use per-operative modalities, which can assist the surgeon in intraoperative decision making. One example could be ICG-A, which is a well-known imaging modality that can be applied to visualize the per-operative tissue perfusion. Per-operative application of ICG-A has been reported to correlate with a decreased rate of complications and loss of reconstruction[36].

Study limitations

This review carries certain limitations that should be acknowledged. Most of the studies included in this study can be described as case-control studies, generally recognized as providing an intermediate level of evidence. Randomized controlled studies are recognized to provide the highest level of evidence but cannot be conducted in this setting due to obvious ethical reasons. Two of the included studies[22,24] are multicenter studies, and especially, O'Connell *et al.* provide eligible data based on a substantial study population, resulting in statistically solid and reliable results[24]. The remaining studies are all single-center studies and are based on significantly smaller study populations, especially in the free-flap case group. All studies were retrospective, leaving the possibility of recall bias and record accuracy. Lastly, it is worth noticing that 20 articles had to be excluded during the process of abstract screening and full-text screening because it was not possible to obtain the full text versions. These articles could have contributed with relevant findings and reflections on the subject.

CONCLUSION

This study proposes that immediate autologous microsurgical reconstruction is associated with a longer time to initiation of adjuvant therapy compared to mastectomy-only, varying from 2 to 14 days. Based on this, the clinical significance of the difference between free flap reconstruction and mastectomy-only is predicted to be minimal or non-existing in most cases. Adjuvant therapy was initiated after four to ten weeks in most cases - regardless of reconstruction or not - and there were only few examples of delays of

more than 12 weeks. Solid evidence on the effect of delays within this interval is still lacking and is beyond the scope of this review.

Postoperative complications - especially major complications resulting in re-operation - were found to be associated with delay in the initiation of adjuvant therapy. Based on this, it is evident to reason that the development of postoperative complications rather than the type of procedure performed determines the initiation of adjuvant therapy. This underlines the importance of taking right measures to minimize the risk of postoperative complications. These measures include careful patient selection, a multidisciplinary treatment approach at a highly specialized facility, and possibly the implementation of up-to-date intraoperative modalities such as ICG-angiography. Further research in this field, preferably large multicenter studies, would be appreciated.

DECLARATIONS

Authors' contributions

Contributed to the writing and revision of the manuscript: Dengsoe IB, Sabitovic A, Damsgaard TE

Availability of data and materials

No template data collection forms, data extracted from included studies, data used for analyses, analytic code or any other materials used in this review are publicly available.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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