Oncologic Head and Neck Reconstructive Microsurgery during the COVID-19 Pandemic in Dharmais Cancer Hospital-National Cancer Center, Jakarta, Indonesia

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Background  Head and neck cancer is one of the leading cancers worldwide. Complex head and neck procedures are potentially aerosol-generating and considered high risk for coronavirus disease 2019 (COVID-19) transmission between the patients, surgeons, and other health-care workers (HCWs). Several adjustments in the microsurgery procedure were needed. The COVID-19 protocol was developed and applied to minimize the COVID-19 transmission. The study objectives were to describe the preoperative, intraoperative, and postoperative protocols applied and the characteristics of patients who underwent head and neck reconstructive microsurgery during the COVID-19 pandemic in Dharmais Cancer Hospital-National Cancer Center.

Methods  This study was a retrospective descriptive study of patients who underwent head and neck reconstructive microsurgery between March 2020 and December 2020 in the plastic surgery department and surgical oncology department, Dharmais Cancer Hospital-National Cancer Center, Jakarta, Indonesia. The patients’ characteristics including sex, age, location of the defects, the flap type, flap survival, and complications were obtained from medical records and analyzed using SPSS version 23.

Results  There were 55 patients, 30 (54.54%) patients were female, and 25 (45.45%) patients were male. The mean age at the time of surgery was 51.32 ± 1.85 years. The most common cancer type was squamous cell carcinoma for 49.09% (n = 27/55). The most frequent location was tongue for 25.45% (n = 14/55). Anterolateral thigh flap was also the most used flap in this study for 50.91% (n = 14/55). The overall survival rate of this study was 83.64% (n = 46/55). There were nine patients (16.36%) who were found with postoperative complications. There was no nosocomial infection with COVID-19 for patients, surgeons, and other HCWs.

Conclusion  Microsurgery can be performed even in the COVID-19 pandemic as the gold standard for oncologic head and neck reconstruction by applying protocols to protect the patients, surgeons, and other HCWs.

Keywords
- head and neck reconstruction
- microsurgery
- free flap
- COVID-19 pandemic

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The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2). The first case of the COVID-19 infection was detected in early December 2019 in Wuhan, China. Since then, the virus has spread very fast globally.¹ The World Health Organization issued a pandemic status on March 11, 2020. SARS-CoV 2 has caused 4,213,580 confirmed infected cases worldwide and 79,755 deaths as of December 28, 2020.² The significant impact on the health care system felt by almost all countries, even in developed countries with established health care systems, caused a high mortality rate.³

The first two cases in Indonesia were reported on March 2, 2020, from the capital city of Indonesia, Jakarta.⁴ After that, the COVID-19 cases multiplied exponentially, and by December 27, 2020, 713,365 positive cases with 21,273 deaths were reported in Indonesia alone.⁵ The COVID-19 pandemic has altered health care services worldwide; early safety precautions and safety protocols were needed in all fields of medicine, particularly surgery.⁶ Developing protocols on health care delivery is continuously evolving to reduce viral transmission and strategically maximize the limited resource of the health care facility. Most hospitals changed their health care service by prioritizing urgent and emergent surgical cases and postponed elective cases. However, there are still several cases that still will require surgery during the pandemic.⁶⁷

Head and neck cancer is the sixth most common cancer globally, with 630,000 cases annually.⁸ Oncologic resection followed by immediate reconstruction is essential for head and neck cancer treatment. Reconstructive free flap is the gold standard for patients with head and neck defects. This procedure is complex and requires a longer operation time compared with other reconstructive modalities.⁹ Head and neck surgery has a higher risk of occupational exposure because the surgical area is at the nasal and oropharyngeal cavities, areas with high viral shedding. Proximity with these areas will increase the risk of spread through small aerosols directly from the infected person to the susceptible person resulting in airborne transmission.¹⁰ Although surgical delay is recommended during the COVID-19 pandemic, every case must be assessed for the risk and benefit of the surgery. Despite the risk, surgery will still be indicated for many cases and strict safety preparation and precaution before performing head and neck reconstruction will be crucial to protecting the patients, surgeons, and all other involved health care workers (HCWs) during the pandemic.¹¹

Dharmais Cancer Hospital-National Cancer Center has adapted a safety protocol to facilitate the head and neck reconstructive microsurgery continuity during the COVID-19 pandemic. In this article, we aim to describe our hospital’s approach for preoperative, intraoperative, and postoperative care to mitigate the risk of the spreading and the profile of the cases, specifically in oncological head and neck reconstructive microsurgery during the COVID-19 pandemic.

Methods

Design and Population

This study was a single-center, retrospective descriptive study conducted at Dharmais Cancer Hospital-National Cancer Center, Jakarta, Indonesia, between March 2020 and December 2020. The study population included patients admitted to the plastic surgery department and the surgical oncology department who underwent microsurgery during the COVID-19 pandemic. This study used a consecutive sampling method. It was approved by the medical ethical committee.

The inclusion criteria were all patients who underwent head and neck reconstructive microsurgery at Dharmais Cancer Hospital-National Cancer Center. Head and neck reconstructive microsurgery was defined as a procedure performed by a surgeon using a microscope or high-powered loupe magnification to anastomose small vessels and/or nerves in an operating room under general anesthesia to restore function and normal appearance located above the clavicle. The exclusion criteria were patients who underwent head and neck reconstructive procedure using the pedicled flap.

Outcome Measure

The outcomes were flap survival rate and postoperative complication within 30 days of surgery. The postoperative complication data included arterial thrombosis, vein thrombosis, and partial necrosis.

Data Collection

The data of this study were gathered from medical records. The demographic variables included sex and age. The microsurgery data included the cancer type, defect location, flap type, and survival of the flap. The postoperative complications within 30 days were categorized and also included.

Statistical Analysis

Data distribution was tested using the Shapiro-Wilk test. The normally distributed quantitative data were presented as means ± standard deviation, while non-normally distributed data were presented as median with data range (minimum to maximum). The categorical data were described as frequencies of counts and percentages. The statistical analyses were performed with SPSS version 23.

Preoperative Care

The surgical management for head and neck cancer has always been challenging, particularly during this COVID-19 pandemic. The risk and benefit of performing head and neck oncologic surgery must be assessed carefully and comprehensively, considering the potential negative impact on patients, surgeons, HCWs, and the health care institutions. A multidisciplinary assessment of the multilevel surgical risk for each case followed by shared decision-making with the patient was recommended.¹¹ The majority of recommendations and guidelines have reported an approach to delay elective surgery, particularly to avoid microsurgery, and instead use local or pedicled flap reconstruction.¹²–¹⁵ Delaying the surgery can be considered for cases that can be treated with radiation and chemotherapy as long as the oncologic outcomes are equivalent to surgery as an alternative.¹¹ American College of Surgeons made guidance on the
triage of nonemergent surgical procedures during the pandemic that was categorized into tiers by case acuity and patient health. The highest tier, tier 3A/B, was for procedures that acutely indicated with significant compromise in patient outcomes if the surgery delayed.  

The majority of patients admitted to our hospital were at an advanced stage of disease with an extensive oncologic resection and a complex defect. Avoiding microsurgery to close complex defects may result in worse form and function outcomes for head and neck cancer patients. Chi et al.17 and other several studies18,19 reported that microsurgery reconstruction following indicated oncologic resections continued to be performed in their hospitals for cases with exposed critical structures or for cases that must be closed with microsurgery, otherwise it will negatively impact the patient outcome. Other microsurgery procedures such as free flap breast reconstruction and lymphatic microsurgery that are categorized as tiers 1 and 2 can be delayed as long as there is no significant negative impact on the outcomes.17 The patients who planned for microsurgery were selected case-by-case basis and after risk and detailed risk–benefit analysis. Free flap reconstructions are still preferred and performed with safety measurements.7,10,19

Dharmais Cancer Hospital-National Cancer Center has designed a standardized protocol to assess COVID-19 preoperatively since the beginning of the pandemic. The COVID-19 protocol in our center was adapted based on the Indonesian Ministry of Health20 and the World Health Organization recommendations.21 When patients first entered the hospital, patients were required to use a face mask, social distancing for over 1 meter, hand washing with running water or hand sanitizer, and were screened initially for COVID-19. The initial screening consists of temperature examination, history taking of clinical symptoms, epidemiologic history, and previous COVID-19 test results (if available). The clinical symptoms included were fever, previous history of fever, and respiratory symptoms (cough, shortness of breath, and sore throat). The epidemiologic history included whether the patient had a history of travel to or residence in a highly epidemic area within 14 days. A patient considered as a suspected COVID-19 if one or more criteria of the epidemiologic history and/or clinical symptoms are present.20,21

If the patient considered as a suspected COVID-19, the patient will be transferred to the emergency room for a suspected COVID-19 patient for further screening. The additional screening consists of a complete blood count (CBC), C-reactive protein (CRP), and chest X-ray. A confirmed case was defined as a positive result by real-time reverse-transcription polymerase chain reaction (RT-PCR) in oropharyngeal and/or nasopharyngeal swab specimens. If the result of the PCR test was negative, the patient was allowed back to the general emergency room for further treatment. If the PCR test was positive for COVID-19, the patient was transferred to the isolation ward immediately. Suppose the patient had no epidemiologic history or clinical symptoms, the patient could enter the emergency room or outpatient clinic.20,21 When the patient was planned for surgery, additional laboratory examinations were mandatory. The preoperative screening protocol at Dharmais Cancer Hospital–National Cancer Center included CBC, CRP, chest X-ray, and COVID-19 PCR swab testing conducted 48 hours before the surgery. If the PCR test result was positive before the surgery, then the surgery had to be delayed and the patient had be isolated for 14 days until the PCR test result was negative.

Until now, there is not yet an outpatient clinic only for COVID-19 patients. If the PCR swab results were positive, the patient was transferred to inpatient care for COVID-19 patients.6,7 A detailed clinical pathway for COVID-19 screening for surgery patients is shown in Fig. 1. Intraoperative Care

Surgeons and other HCWs must wear full personal protective equipment (PPE) even though the patient is COVID negative. False-negative in the PCR swab test was up to 30% because all patients should be treated as suspected COVID-19 positive. A full PPE consists of an N95 mask, a gown, a protective eyewear, and gloves. The number of HCWs in the operating room was reduced to minimize the risk of occupational exposure, especially 20 minutes after the intubation and extubation procedure was done. This strategy also decreased
the number of PPE used. The head and neck cancer surgery was done with a staged approach, one reconstructive microsurgery was usually performed with three surgeons at separated times. First, the surgeon performed the oncologic resection, usually by only one surgeon, with one or two scrub nurses. The second stage is the reconstructive microsurgery that was done with two surgeons and one or two scrub nurses.6,7

Postoperative Care
The postoperative flap monitoring protocol in our center was modified during this pandemic. The frequency of flap checks was reduced to limit the risk of exposure and to limit using PPE needed. Previous flap monitoring protocol was performed every hour for 24 hours for postoperative day 1, every 2 hours for 48 hours for postoperative day 2 until day 3, and every 4 hours for 72 hours for postoperative day 4 until day 6, then every 8 hours until discharge. The new flap monitoring protocol was performed in the first 24 hours, then every 12 hours until 72 hours after the patient was discharged. The flap monitoring routine included clinical examination of the flap (color, temperature, skin turgor, and capillary refill time) and pinprick test.8,9

Result
We included 55 patients who underwent head and neck reconstruction microsurgery in the plastic surgery department and oncology department at Dharmasai Cancer Hospital—National Cancer Center from March until December 2020. The majority were females with 54.54% (n = 30) and 45.45% were males (n = 25). The plastic surgery department admitted 32.72% of patients (n = 18/55), 13 patients were males, and 5 were females. The Surgical oncology department was admitted with 67.27% of patients (n = 37/55), 25 patients were females, and 12 were males. The mean age at the time of surgery for both females and males was 51.32 ± 1.85 years.

The most common cancer found was squamous cell carcinoma (SCC) for 49.09% (n = 27/55), followed by sinonasal carcinoma for 10.91% (n = 6/55), and ameloblastoma for 7.21% (n = 4/55). The most common defect was located at the tongue for 25.45% (n = 14/55), by maxilla for 14.55% (n = 8/55), and mandible for 12.73% (n = 8/55). Fifty-one percent of the operations were used the anterolateral thigh (ALT) flap. ALT was also the most used flap for head and neck reconstruction.

The overall survival rate of this study was 83.64% (n = 46/55). There were nine patients found with postoperative complications (16.36%). Four patients were due to arterial thrombosis, four patients were due to vein thrombosis, and one patient was due to partial necrosis of the flap. Two patients underwent reoperation due to vein thrombosis. One patient with arterial thrombosis was suspected to be caused by disruption of the tunica intima. Of two patients with vein thrombosis, one patient underwent salvage surgery on the 6th day, and the condition of the anastomosis was fine. For the other patient with vein thrombosis, the vein was suspected to be kinked because of a hard cough after the tracheostomy procedure. One patient with arterial compromise was suspected to be caused by inadequate mean arterial pressure. All patients were screened for COVID-19, and only patients with PCR negative were able to have surgery. The characteristics of the 18 subjects are reported in ►Table 1.

There was no postoperative nosocomial infection with COVID-19 detected. No member of our HCWs involved in the microsurgery developed symptoms of COVID-19 or tested positive for COVID-19 during the study period.

Discussion
The COVID-19 pandemic has been a challenge to the health care system, and health resources have been prioritized based on clinical significance. Hospitals were occupied with COVID-19 patients, and the number of patients with reconstructive needs was still present. The balance between hospital supply of limited resources such as PPE, intensive care unit (ICU), and HCWs for COVID-19 cases and elective surgery must be reached because the allocation of these resources is prioritized for managing COVID-19 cases in the larger public health context.22

The surgical management for head and neck cancer has become a clinical dilemma during this pandemic. Therefore, a careful risk–benefit assessment for each patient is necessary, particularly in head and neck reconstructive surgery procedures that were considered as a high risk of disease transmission.23 The majority of elective surgeries have been suggested to be postponed, but a delay could negatively impact the clinical outcome.8 Delaying the surgery may negatively affect the treatment outcome and increasing the time to surgery longer than 42 to 67 days was predicted to have a worse overall outcome.24,25 Immediate reconstruction following oncologic resection was also preferred because it offers easier access to the recipient veins and arteries before the vessels were disrupted by secondary fibrosis and reduces functional disability for the patient.10 There are also other concerns, even though current evidence on the association between cancer and COVID-19 remains inconclusive, and cancer patients are considered to have a higher risk of COVID-19 infection due to lower immunity and several other factors, such as older age and comorbidities. Moreover, patients with cancer had a higher risk of severe events. Twenty COVID Surgery Collaborative reported that postoperative pulmonary complications occurred in almost half of the patients diagnosed with COVID-19 postoperatively with high mortality, particularly in older men. Consideration to delay or avoid the surgery should be carefully made.27 The gold standard in oncologic head and neck reconstruction was microsurgery due to the versatility and reliability, but microsurgery is also a complex procedure that demands a long operative time, requires ICU, considerable donor site morbidity, reliability for revision surgery, longer hospital stay, and relatively higher cost compared with conventional surgery.15,28 However, several centers reported that the head and neck reconstructive microsurgery still can be successfully performed during this pandemic by applying the
protocol to reduce the risk of COVID-19 transmission.\textsuperscript{17–19} Our protocols have been adapted from various sources, including those of the World Health Organization,\textsuperscript{21} Pittsburgh,\textsuperscript{6} Irish Microsurgery Special Interest Group Guide-line,\textsuperscript{7} Baylor Scott & White’s head and neck protocol,\textsuperscript{22} American College of Surgeons,\textsuperscript{16} and a few other guidelines.\textsuperscript{17–19} The Dharmais Cancer Hospital-National Cancer Center has adopted a protocol to safely continue the head and neck reconstructive microsurgery, including preoperative, intraoperative, and postoperative COVID-19 protocols.

The patient selection and COVID-19 testing during the preoperative screening was the key to optimize both patient and operating team safety. The sensitivity for the PCR test is currently reported to be between 70 and 80%.\textsuperscript{29} Our preoperative protocol included PCR swabs 48 hours before the surgery. If the test result was positive, surgery was delayed for at least 14 days until the patient has a negative result on the following PCR. The protocol may vary from one center to another center, but the main principle was COVID-19-positive patients requiring operation will be treated appropriately, but not during the active viral infection to spare both risk and morbidity to the patient and surgical team.\textsuperscript{22} The limitation of our hospital is there is not yet a negative-pressure operating room to operate for COVID-19 patients. Patients with COVID-19 infections will be at increased risk for adverse outcomes, including perioperative mortality rates of up to 16.7% in those with COVID-19 compared with 1.4% in non-COVID-19 patients.\textsuperscript{30}

### Table 1

The characteristic of patients who underwent oncologic head and neck reconstructive microsurgery in Dharmais Cancer Hospital between March 2020 and December 2020

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>N (%) n = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Women</td>
<td>30 (54.54%)</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>25 (45.45%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Mean ± SD</td>
<td>51.32 ± 1.85</td>
</tr>
<tr>
<td>Cancer type</td>
<td>Squamous cell carcinoma (BCC)</td>
<td>27 (49.09%)</td>
</tr>
<tr>
<td></td>
<td>Sinonasal carcinoma</td>
<td>6 (10.91%)</td>
</tr>
<tr>
<td></td>
<td>Ameloblastoma</td>
<td>4 (7.27%)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngeal carcinoma</td>
<td>3 (5.45%)</td>
</tr>
<tr>
<td></td>
<td>Adenoid cystic carcinoma</td>
<td>2 (3.64%)</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous malformation (AVM)</td>
<td>2 (3.64%)</td>
</tr>
<tr>
<td></td>
<td>Laryngeal carcinoma</td>
<td>2 (3.64%)</td>
</tr>
<tr>
<td></td>
<td>Mucoepidermoid carcinoma</td>
<td>2 (3.64%)</td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma (SCC)</td>
<td>1 (1.82%)</td>
</tr>
<tr>
<td></td>
<td>Basalioma</td>
<td>1 (1.82%)</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
<td>1 (1.82%)</td>
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<tr>
<td></td>
<td>Papillary thyroid carcinoma (PTC)</td>
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<tr>
<td></td>
<td>Salivary gland carcinoma</td>
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<tr>
<td></td>
<td>Unknown primary</td>
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<tr>
<td>Defect location</td>
<td>Tongue</td>
<td>14 (25.45%)</td>
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<tr>
<td></td>
<td>Maxilla</td>
<td>8 (14.55%)</td>
</tr>
<tr>
<td></td>
<td>Mandible</td>
<td>7 (12.73%)</td>
</tr>
<tr>
<td></td>
<td>Neck</td>
<td>6 (10.91%)</td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td>5 (9.09%)</td>
</tr>
<tr>
<td></td>
<td>Scalp</td>
<td>5 (9.09%)</td>
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<tr>
<td></td>
<td>Palatum</td>
<td>2 (3.64%)</td>
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<tr>
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<td>Orbita, palatum</td>
<td>1 (1.82%)</td>
</tr>
<tr>
<td></td>
<td>Orbita, palatum, zygoma</td>
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</tr>
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<td></td>
<td>Auricular right</td>
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<tr>
<td></td>
<td>Buccal + mandible</td>
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</tr>
<tr>
<td></td>
<td>Lip + mandible</td>
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</tr>
<tr>
<td></td>
<td>Nose</td>
<td>1 (1.82%)</td>
</tr>
<tr>
<td></td>
<td>Tonsil</td>
<td>1 (1.82%)</td>
</tr>
<tr>
<td></td>
<td>Trigonum retromolar</td>
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</tr>
<tr>
<td>Flap type</td>
<td>ALT flap</td>
<td>28 (50.91%)</td>
</tr>
<tr>
<td></td>
<td>ALT chimeric flap</td>
<td>12 (21.82%)</td>
</tr>
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</table>

(Continued)
comorbidities that are associated with increased risk for adverse outcomes if infected with COVID-19. Studies reported COVID-19-positive patients with cancer has a high mortality rate, and one systematic review reported up to 25.6%. COVID-19 is also reported to be associated with thrombotic-related complications, including disseminated intravascular coagulation, acute coronary syndromes, and venous thromboembolism. Performing reconstructive microsurgery in COVID-19 patients may have a greater risk of flap failure, therefore, delaying the surgery should be considered.

The surgical team should be minimized to those essential for the surgery, especially during the aerosol-generating procedure. The AO Foundation recommends approximately 20 minutes after intubation and extubation before surgical team entry. The reconstructive team should also not be present during major aerosolizing and high-risk procedure such as the oncologic resection and tracheotomy, if possible a staged approach to separate the oncologic resection and tracheotomy from the reconstruction and keeping the patient in the ICU overnight can also be considered in the context of the risk mitigation strategy and if the ICU is available, although it is not a preferred in a pre-COVID-19 setting. In our hospital, we separated oncologic resection with the reconstructive procedure by doing the procedure at a different time but still on the same day. We did not delay the reconstructive procedure overnight due to the limitation of our hospital ICU capacity. We also always cover the airway with a surgical mask or tracheostomy with an occlusive dressing during the surgery and exposed the nose and oral cavity only during flap inset. Adequate PPE must be worn even in a patient who tested negative to protect the surgeon and other HCW from the risk for transmission of the aerosolized virus. Protective eyewear is crucial and must be used at all times because transconjunctival transmission of aerosolized high viral load over a prolonged time is reported possible. Safe donning and doffing of PEE after the surgery also critical. Microsurgical procedures should be performed by the most experienced microsurgical team to achieve more efficient operative time.

Fifty-five patients who underwent head and neck reconstructive microsurgery at Dharmais Cancer Hospital—National Cancer Center during the COVID-19 pandemic. The operation was led by a two-team approach to reduce the time of the operation. The flap survival rate from other centers was reported to be between 93 and 97% and those results were similar to this study (83.6%). Of 55 patients, nine patients were found with postoperative complications, and two patients required reoperation.

Xu et al reported that the most common cause of the defect was SCC for 79.4%, and the most common defect location from the SCC patients was tongue. This result was similar to the result of this study. In this study, SCC was the most common cause of the defect for 49%, and tongue was the most common defect location for 25.45%.

Wong et al reported that the ALT was the most used flap for head and neck reconstruction due to its versatility in harvesting a variable amount of soft tissue and other components by 52.51%, followed by a radial forearm for 15.52%, and fibula osteoseptocutaneous for 15.08%. These flaps also provide a long vascular pedicle, similar to this study; the ALT flap was the most used flap for 97.4% (n = 18).

The ALT flap can be harvested as a skin flap, a myocutaneous flap, or a chimeric flap. The flap’s pedicle, usually the descending branch of the lateral circumflex femoral artery with the length of the pedicle up to 18 cm, allows reaching vessels in the lower neck and even contralateral neck.

Microsurgery reconstruction is a reliable and complex procedure involving many factors that could lead to a wide range of potential complications. Early to recognize and manage the complications are essential to minimize devastating consequences. Pohlenz et al reported that 130 out of 1,000 flaps were failed (7.6%), vascular thrombosis was the primary reason for flap loss, and venous thrombosis was more common than arterial thrombosis. In our study, the complication rate was 16.36%, and the majority of the complications were also due to vascular thrombosis.

Shrikhande et al reported no postoperative death in their series of major oncological surgeries during the COVID-19 pandemic and highlighted the importance of adopting protocols and assessing each patient to minimize the significant complications and mortality.

There was no nosocomial COVID-19 infection found in our patients or our surgeons and other HCWs. We believe that this result was due to the strict preoperative screening strategy, the availability of PPE, and the adherence to using appropriate PPE during the perioperative period.

In our experience, reconstructive microsurgery was still our primary choice of head and neck cancer by applying the COVID-19 protocols safely, starting from preoperative screening, intraoperative, postoperative, and follow-up measures for head and neck reconstructive microsurgery.

**Conclusion**

COVID-19 pandemic has been a challenge to the health care delivery service. This study showed that with adequate preventive and protective measures, cancer surgery was possible by adapting the current safety protocols and multidisciplinary approach to deliver high-quality and efficient head and neck reconstructive care while protecting the patients and the surgical team from the risk of occupational exposure to COVID-19.

**Conflict of Interest**

There are no financial or nonfinancial conflicts relevant to the article.

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**References**


