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Surgeries and Cardiovascular System



Adjuvant Surgical Oophorectomy

Robotic Surgery versus Laparoscopy

Highlights

Phalloplasty for Transgender Men

Systematic Review of the Rare Disease

Discovering Thoughts, Inventing Future

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Two-Stage Prelaminated Mucosal Neourethra Radial Forearm Flap Phalloplasty for Transgender Men

By Christopher J. Salgado MD, Ajani Nugent MD, Josef Hadeed MD, Maria Lalama BS, Jorge Rey MD & Carlos Medina MD

Abstract- *Background:* Our goal in the construction of the transman phalloplasty is not only to decrease the patient's level of gender dysphoria, obviate the use of an external prosthesis, give the patient the ability to urinate in the standing position and orgasm but also to decrease urinary complications.

Material and Methods: A retrospective review of transmen patients from June 2016 to June 2018 was performed on patients undergoing a two-stage mucosa only prelaminated neourethra radial forearm flap phalloplasty. The surgical technique is detailed in addition to patient demographics including co-morbidities, flap complications, and urinary sequelae.

Keywords: *phalloplasty, transman, female to male, sexual reassignment surgery, gender dysphoria.*

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Two-Stage Prelaminated Mucosal Neourethra Radial Forearm Flap Phalloplasty for Transgender Men

Running Title: Two-Stage Radial Forearm Flap Phalloplasty

Christopher J. Salgado MD [α], Ajani Nugent MD [σ], Josef Hadeed MD [ρ], Maria Lalama BS [ω], Jorge Rey MD [¥] & Carlos Medina MD [§]

Abstract- ***Background:*** Our goal in the construction of the transman phalloplasty is not only to decrease the patient's level of gender dysphoria, obviate the use of an external prosthesis, give the patient the ability to urinate in the standing position and orgasm but also to decrease urinary complications.

Material and Methods: A retrospective review of transmen patients from June 2016 to June 2018 was performed on patients undergoing a two-stage mucosa only prelaminated neourethra radial forearm flap phalloplasty. The surgical technique is detailed in addition to patient demographics including co-morbidities, flap complications, and urinary sequelae.

Results: Twenty-one patients underwent the two-stage prelaminated radial forearm flap phalloplasty. Ischemic complications occurred in four patients and all were salvaged. One flap died due to a late infection at three weeks and was constructed with an anterolateral thigh flap. Urethral cutaneous fistulas requiring surgery occurred in three cases and urethral strictures in four cases. Our operative fistula rate was 14% and urethral stricture rate was 19%. Our fistula rate is smaller than previously published.

Conclusion: Using a two-stage approach for the construction of the transman phalloplasty, we have been able to show acceptable complication rates while accomplishing the goals in our surgical endeavor.

Keywords: phalloplasty, transman, female to male, sexual reassignment surgery, gender dysphoria.

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I. Background

In the United States, there are approximately 1.4 million transgender adults, which makes up 0.6% of the population.[1] Commonly viewed as the "final stage" in the female to male transition, genital surgery has rapidly moved from a metoidioplasty to a phalloplasty operation. Reasons for this change are because of the micropenis appearance of the metoidioplasty and subsequent inability for penetrative intercourse which may contribute to continued gender dysphoria in the patient. Genital surgery can be performed at the age of 18 adhering to guidelines set forth by the Standards of Care for the Health of Transsexual, Transgender, and Gender-Noncomforming People, Version 7.[2] Our main goals in the construction of a phallus for transgender men are to treat their gender dysphoria, allow the patient to have intercourse with their constructed phallus, allow for erogenous sensation and orgasm, allow the patient to urinate in the standing position through their constructed phallus, create an aesthetically pleasing phallus which has tactile sensation and will allow for the placement of a prosthesis without complications. As our surgical technique has advanced, so have the patients' desires. A study reported that more than 98% of transmen desiring phalloplasty reported a desire to stand to void.[3] Although varied options exist for non-autologous tissue, such as packers, external prosthesis, and an osseointegrated epithesis, they have multiple limitations regarding urination, sexual function, and appearance.[4]

Similar techniques used in cis-gender male phalloplasty have been used for transgender men. Flaps, such as the tube-in-tube radial forearm flap, osteocutaneous radial forearm flap, scapular flaps, deltoid flaps, abdominal pedicled flaps, and anterolateral thigh flaps have all been used for phalloplasty.[5,6,7,8,9,10] To date, the free radial forearm flap continues to be the most commonly used tissue for cis and transgender phalloplasty due to its superior erogenous and tactile sensation including versatility in the inset. The urethral portion of the phalloplasty

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construction remains the portion fraught with the most unfavorable outcomes in this very complex procedure. The urethra after phalloplasty construction can be divided into distinct segments, from proximal to distal: native (female) urethra, fixed urethra, anastomotic urethra, phallic urethra, and meatus.[11] The fixed urethra is the portion of the urethra formed after lengthening the native urethra via local vaginal or labial flaps, extragenital flaps, and grafts of skin or mucosa (Figure 1a and b).[12] The phallic urethra can be constructed through a variety of techniques, including prelamination, tube-in-tube techniques, and pedicle flaps.[13,14]

Urethrocutaneous fistulas are the most common urethral complication following surgery with rates ranging from 22% to 75%.[15,16,17] Fistulas occur most commonly at or just proximal to the anastomosis between the phallic urethra and fixed urethradue to vascular insufficiency of the flap, and the decreased lumen of the phallic urethra. At our institution, we have significantly decreased our fistula rates in transgender male phalloplasty by augmenting the paucity of vascularized tissue at this anastomosis using a pedicled gracilis flap at the time of flap transfer.[18] Urethral strictures are an equally as common untoward event following phalloplasty in transgender men with rates ranging from 11-74%and their subsequent management can be challenging.[19,20,21] To decrease unfavorable urologic sequelae following phalloplasty, surgeons have used mucosa, which has characteristics more like uroepithelium, for the urethral reconstruction. Burger used buccal mucosa grafts, which remains the mainstay for the reconstruction of the urethra.[22] Zhang specifically looked at female to male transgender phalloplasty and found vaginal mucosa graft to be an excellent material for urethral reconstruction in patients undergoing phalloplasty. These findings, of a decreased urethra fistula and stricture rate, influenced our conversion to a two-stage radial forearm phalloplasty and flap neourethra prelamination with mucosa (buccal, vaginal, or uterine) that was evaluated in this manuscript.[23]

II. Material and Methods

A retrospective review of transgender male patients undergoing phalloplasty between June 2016 and June 2019 was conducted. Inclusion criteria included age over 18, surgical treatment for gender dysphoria with two-stage radial forearm phalloplasty, and flap neourethra prelamination with mucosa (buccal, vaginal, or uterine). Exclusion criteria included patients opting for single stage tube-in-tube phalloplasty construction, skin graft only prelamination of the neourethra, and cis-male patients undergoing reconstructive phalloplasty.

Patients were identified for inclusion on review of a prospective list of patients treated by the senior author. Charts of patients meeting criteria for inclusion were reviewed for demographic data and complete medical and surgical history. Date of birth, body mass index (BMI), history of or active tobacco use, as well as co-morbid medical conditions were recorded. Operative notes of the phalloplasty procedures were reviewed with the following data recorded: date of operation, tissues used in prelamination including the type of mucosa, neurovascular structures anastomosed during free tissue transfer, and augmentation of the urethral anastomosis with a gracilis muscle flap. Post-operative records were reviewed and final constructive outcomes including length of the phallus as well as complications were recorded.

a) Vaginectomy and Flap neo-urethra prelamination (Stage I)

Our technique for radial forearm phalloplasty has previously been published in detail.[12, 18, 24] The radial forearm flap is our flap of choice due to the superior donor site and sensibility of the flap, in addition to its lower complication rate compared with other commonly used flaps such as the anterolateral thigh flap.[25] The procedure is completed in two stages to facilitate the creation of a neo-urethra. The first stage entails flap prelamination during which the radial forearm flap is designed and the neo-urethra is formed using autologous tissue, typically the vaginal mucosa at the time of vaginectomy and urethral lengthening (Figures 1a and b).

Flap prelamination occurs during the first stage of phalloplasty. The markings for the planned flap are determined pre-operatively after a normal Allen's test (Figure 2). Creating the urethra with mucosal tissue and not using forearm tissue allows for a smaller width in the flap skin paddle compared to the traditional tube within a tube urethra, and therefore if a patient places his upper extremity across his chest with the donor site toward his chest there is no visible skin graft. Also, the patient does not require the out-of-pocket expense of hair removal from the forearm since there will be no hair growth within the urethra. The boundaries for the flap are defined during this stage as the flap is elevated to allow placement of the neo-urethra. The tissue is raised in an ulnar to radial direction in the suprafascial plane. The neo-urethra is formed by circumferentially enveloping a 16 – 24 French Foley catheter with mucosal tissue (Figure 3). The vaginal mucosa is harvested during the vaginectomy for the creation of the neo-urethra. When not previously performed, a hysterectomy may be performed during this stage providing additional mucosal tissue using buccal mucosa if needed (Figure 4).[26] Our technique for urethral lengthening has also been published in detail.[27]

b) Free Tissue Transfer (Stage II)

The design of the radial forearm flap is defined during the first stage. Whereas the flap was elevated in a suprafascial plane for prelamination, the flap is now

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elevated in the subfascial plane to avoid injury to the neo-urethra (Figure 5). The medial and lateral antebrachial cutaneous nerves are preserved during dissection for coaptation to one dorsal nerve of the clitoris for erogenous sensation and the ilioinguinal and or genitofemoral nerves for tactile sensation. The radial artery and venae comitantes are ligated distally and proximally dissected for vascular anastomosis. The basilic and/or cephalic veins are preserved and dissected with the flap.

Using a modification of Monstrey's scrotoplasty technique the clitoris is dissected free from the lengthened urethra and subsequently denuded of skin.[28] The clitoral hood skin is removed and used for the coronaplasty using a technique described by Gottlieb (Figure 6).[29] The recipient arteries harvested for the vascular anastomoses are either the inferior epigastric artery or the descending branch of the lateral femoral circumflex artery. The thigh incision made for the lateral femoral circumflex is also used for the harvest of the saphenous vein.

Absorbable suturesare used for the urethral anastomosis in two layers, which is the first anastomosis performed (Figure 7). The vascular and neural anastomoses are performed next and are all hand sewn using 9-0 nylon suture with the aid of an operative microscope. In addition to a mucosa-only neourethra to decrease urinary complications that we have added to our surgical approach, which is beneficial in decreasing urinary complications, is the deployment of a gracilis flap urethroplasty at the time of flap transfer.[18] Upon closure of all incisions, a coronaplasty is performed with a skin graft obtained for the clitoral hood (Figure 8). The penile Foley catheter is removed once the patient has been discharged and 8-12 weeks after flap phalloplasty upon a normal pericatheter retrograde cystourethrogram revealing no extravasation of dye indicating there is no urinary fistula (Figure 9). Following successful bladder training and urination from the phallus, the suprapubic tube is subsequently removed.

III. Results

A total of 21 transgender male patients undergoing gender affirmation bottom surgery with a two-stage prelaminated radial forearm phalloplasty were identified and included in the study. The average age at the time of the first stage procedure was 35.7 ± 12.2 (range 21-54).The average BMI of included patients was 30.8 ± 7.2 (range 22.3 – 48.5). Demographics and medical history are presented in Table 1. Neo-urethra prelamination was completed with either vaginal and/or buccal mucosa in all cases.

All of the 21 patients completed both the first and second stages of radial forearm phalloplasty. The second stage procedure was performed on average 60.3 ± 27.6 days (range 37 – 126) after the first stage procedure. Donor and recipient vessels used for free tissue transfer are shown in Table 2. Final neophallus length averaged 13.7 ± 2.1cm (range 11 – 17.8 cm).

Among the 21 patients completing second stage phalloplasty, ischemic complications occurred in 4 patients. With 4 of 21 patients developing vascular compromise postoperatively, our take-back rate for this series was 19%. Of note, once we switched to using the descending branch of the lateral femoral circumflex artery as our recipient artery we no longer had re-open procedures due to vascular compromise. In each case, the patients were taken back to the operating room and underwent successful revision of the vascular anastomoses. One patient with a BMI of 40, history of HIV, and diabetes was found to have a urinoma and bacterial infection resulting in thrombosis of both the artery and two outflow veins three weeks following flap transfer. Upon debridement of the flap, an anterolateral thigh flap was performed for his phalloplasty. Our flap loss in this series was 5%.This is a number we quote our patients when they are seen preoperatively.

Our urethral fistulas were commonly detected at the time of the first retrograde cystogram performed however following a subsequent negative study penile catheters were removed. Fistulas developed in 28% of patients however only 14% required operative intervention with a Johannsen urethroplasty. Urethral strictures occurred in 19% of patients and all required urologic cystoscopy and dilation which was readily done with balloon dilation due to the mucosa nature of the urethral conduit. One required a more invasive procedure for repair. Other complications noted in our series are presented in Table 3 however, most notable was our incidence of cellulitis of 33%, the majority of which occurred early in our series prompting our broadening of antimicrobial coverage of all aerobic and anaerobic species including fungus for an extended period of their hospitalization. Due to the proximity of this operative field to the colorectal system and its involvement in the urinary system the tissue is susceptible to a variety of microbes and traditional Surgical Care Improvement Protocols do not apply.

IV. Conclusion

Our two-stage phalloplasty technique with prelamination of the neourethra with mucosa for transgender male gender affirmation bottom surgery was developed to decrease complications after using a one-stage tube within a tube radial forearm flap and a staged skin graft prelamination staged phalloplasty. Our goal was to decrease urinary fistulas and urethral strictures with our modification of technique. With urethral fistula rates ranging from 24% to 83%[11, 19] and stricture rates ranging from 11 to 74%[11, 20] we felt that the creation of a neourethra of mucosa would decrease these complications. Our operative fistula rate was 14%

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and urethral stricture rate was 19%. The fistula rate is smaller than previously published. The gracilis flap which has been used to increase the vascularity of the urethral anastomosis has also been beneficial in the augmentation of the neoscrotum which has been able to obviate the need for testicular implants (Figure 10). Urethral strictures were not uncommon in this series with a rate of 19% of which three of four cases were managed conservatively with dilation only. One reason for stricture development may be the natal female detrusor muscle with aging and its subsequent limitations in channeling urine through a longer conduit, although further studies are warranted.[30]

Although a two-stage technique may be more cumbersome we felt that in our hands we have been able to decrease urinary complications and minimize the commonly large donor site with this technique compared to the previously used skin within a tube radial forearm flap. Approximately 3-4 cm of forearm tissue is spared since this is not used for the urethra. This skin can be used for a phalloplasty of a greater circumference and a donor site that is not visible when patients place their forearm against their chest. Using a pre-laminated urethra our patients do not need to undergo electrolysis since the urethra is not created from forearm tissue, so we do not have the risk of hair growth in the urethra and its associated complications. An additional complication which is seen even with urethras pre-laminated with skin grafts. Although there have not been any blinded, randomized controlled trials comparing single-stage to two-stage phalloplasty, we believe that prelamination using vaginal mucosa for the construction of the transmale phallus urethra is a worthwhile technique that has demonstrated a reduction in the prevalence of complications with this already very challenging procedure.

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iv. Collection and assembly of data: Salgado C, Nugent A
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vi. Manuscript writing: All authors
vii. Final approval of manuscript: All authors

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Consent for publication

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Figures and Legends



Figure 1a: Total vaginectomy is performed and urethral lengthening will be done.



Figure 1b: The urethra has been lengthened with labia minora flaps and reinforced with an anterior vaginal flap.

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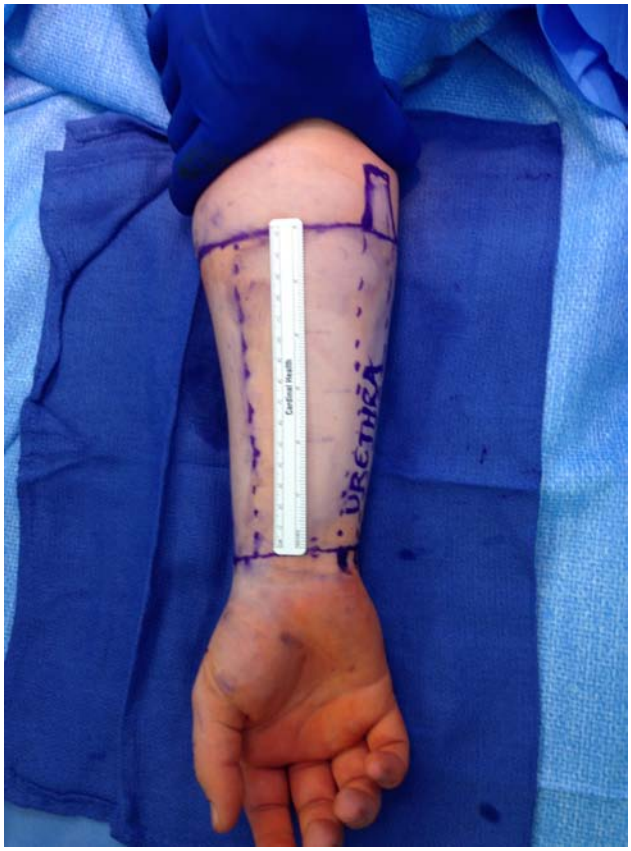


Figure 2: The path of the neo-urethra is marked ulnarly in the forearm flap with a proximal skin extension beyond the planned 6" phallus that will be used for the urethral anastomosis.



Figure 3: A 16 French Foley catheter is shown with both vaginal and buccal mucosa (mucosa surface toward the foley catheter) that will be sutured around the catheter to form the neo-urethra.

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Figure 4: Right buccal mucosa is seen in a patient before harvest.

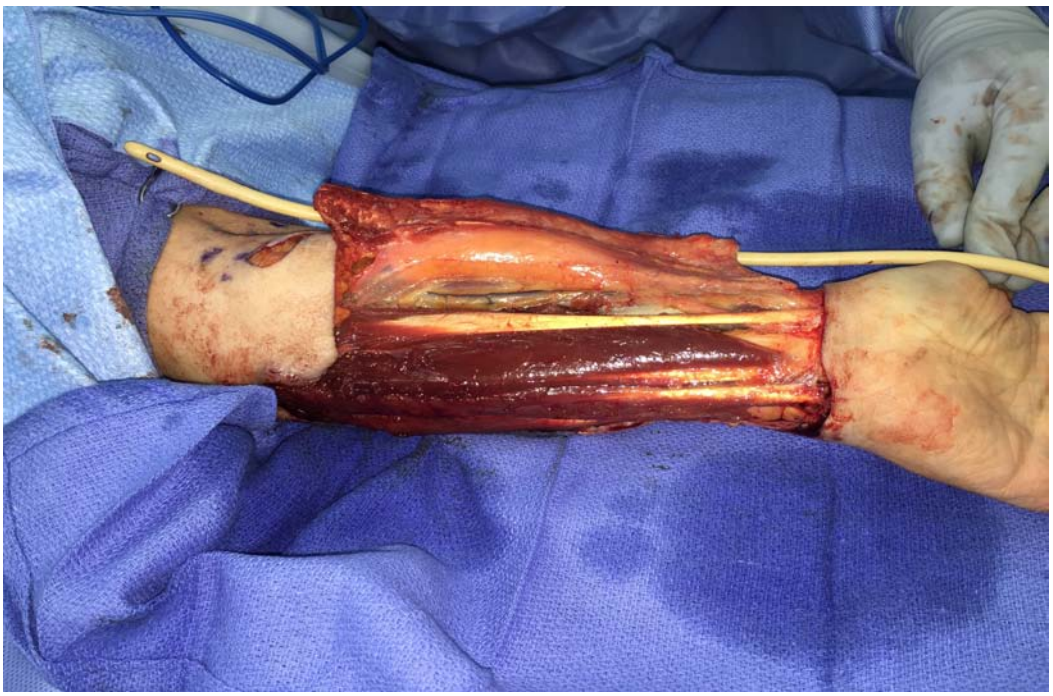


Figure 5: The nearly completely elevated radial forearm flap is shown harvested in a subfascial plane with the neourethra.

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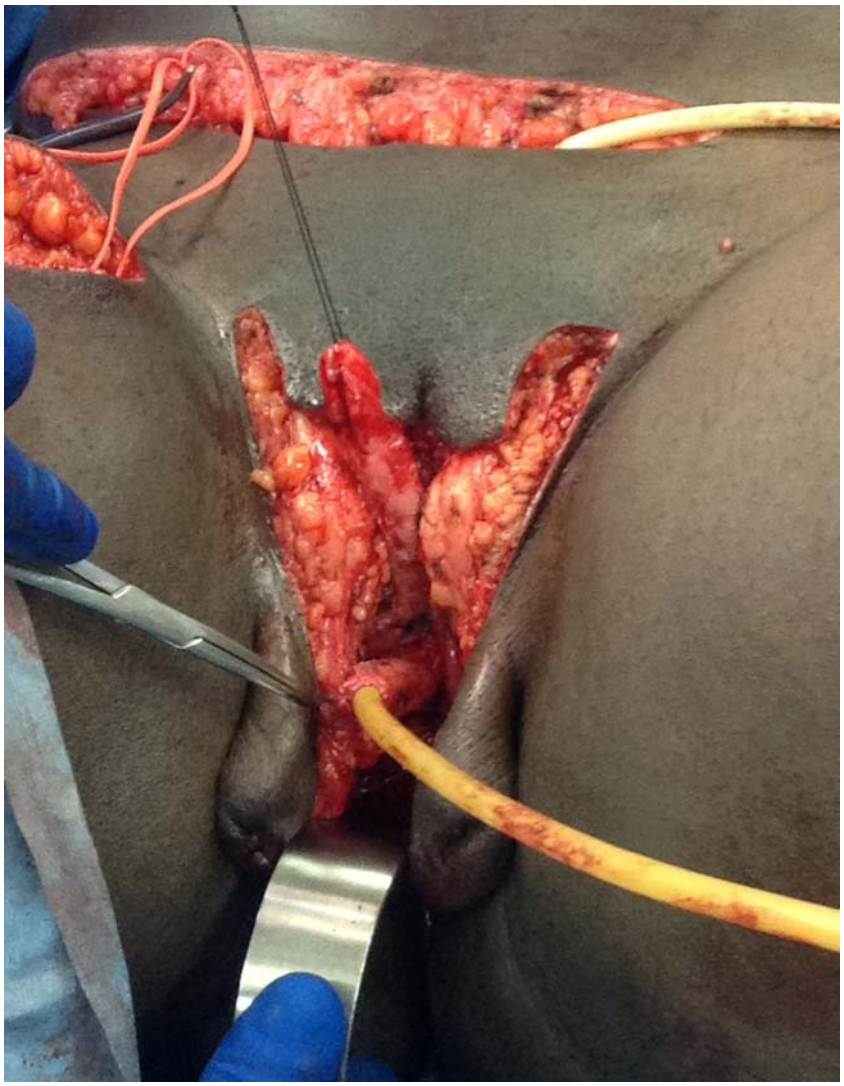


Figure 6: Scrotoplasty with denuded clitoris and extended urethra visible. The inferior epigastric artery harvested and the saphenous vein harvest.

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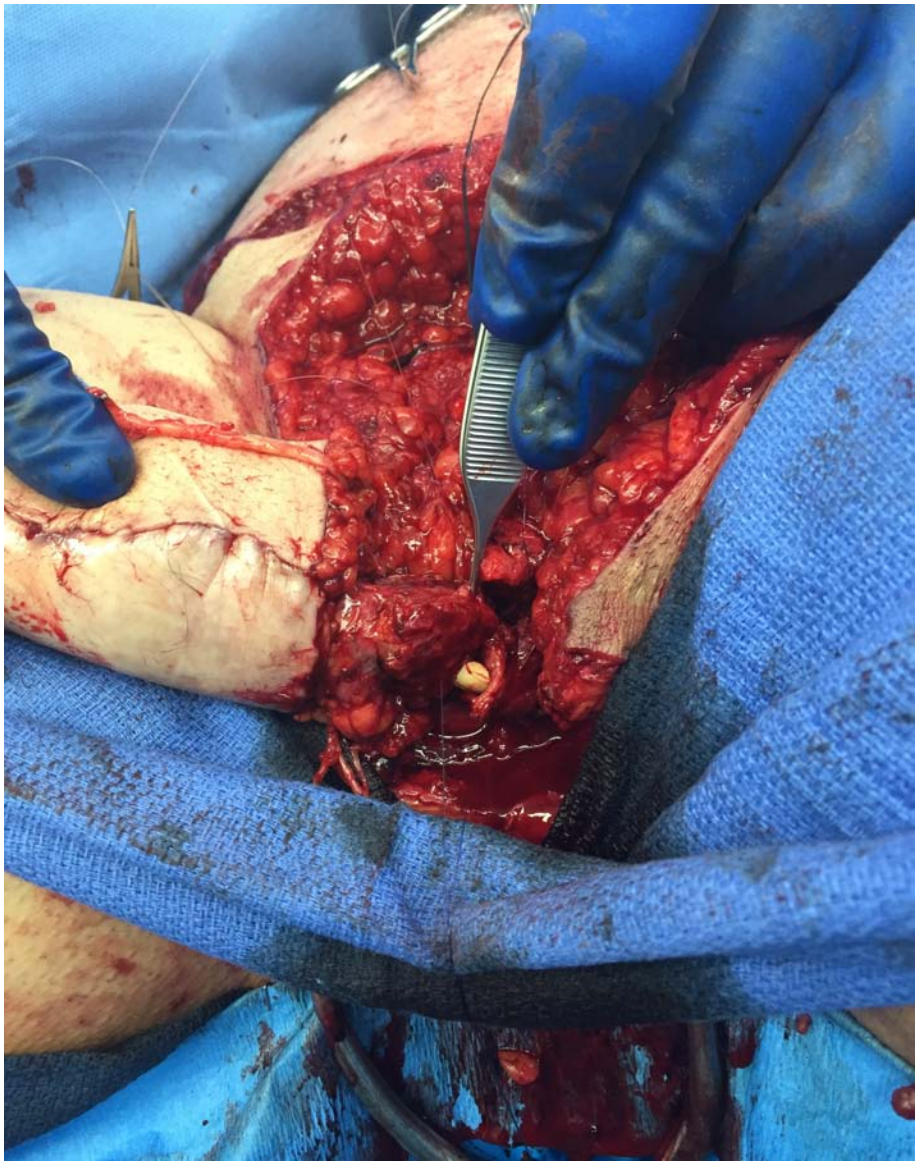


Figure 7: Urethral anastomosis is performed with absorbable suture and will be done in two layers. A sensory donor nerve is also shown on the surface of the flap.

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Figure 8: Pre-laminated radial forearm flap phalloplasty.

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Figure 9: Normal pericatheter retrograde cystourethrogram is shown indicating no urinary fistula.

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Figure 10: 34-year-old transman following radial forearm flap phalloplasty with gracilis and augmentation of the neo-scrotum with the muscle.

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Synchronous Vaginal Metastasis in Patient with Clear-Cell RCC. A Case Report and Review of the Literature

By Hevia Palacios M, Gómez Rivas J, Tueti Silva D, Aguilera Bazán A, Martínez-Piñeiro L & Gonzalez Peramato, P.

Universitary Hospital Ramon y Cajal

Abstract- *Background:* Vaginal metastasis, despite being rare, are more common than primary tumors and as presentation of the disease is extremely rare. At the time of diagnosis metastasis by hematogenous or lymphatic spread in 20-30% of patients.

Case presentation: 68 years old female patient that debuted with haematuria. In the extension study we can objectify a left renal mass treated by laparoscopic radical nephrectomy.

During admission the patient presented and episode of metrorragia. A lesion was found in the lower thrid of the vagina, which was biopsed, resulting a vaginal metastasis of clear cell carcinoma. The patient presented a favorable evolution being discharged four days after de surgical intervention. The subsequent extension study revealed progression of the underlying disease with mediastinal nodes and bone metastases.

Keywords: *renal cell carcinoma. vaginal metastases.*

GJMR-I Classification: *NLMC Code: WJ 140*



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Synchronous Vaginal Metastasis in Patient with Clear-Cell RCC. A Case Report and Review of the Literature

Hevia Palacios M[α], Gómez Rivas J[σ], Tueti Silva D[ρ], Aguilera Bazán A[ω], Martínez-Piñeiro L[¥] & Gonzalez Peramato, P.[§]

Abstract- Background: Vaginal metastasis, despite being rare, are more common than primary tumors and as presentation of the disease is extremely rare. At the time of diagnosis metastasis by hematogenous or lymphatic spread in 20-30% of patients.

Case presentation: 68 years old female patient that debuted with haematuria. In the extension study we can objectify a left renal mass treated by laparoscopic radical nephrectomy.

During admission the patient presented and episode of metrorragia. A lesion was found in the lower thrid of the vagina, which was biopsed, resulting a vaginal metastasis of clear cell carcinoma. The patient presented a favorable evolution being discharged four days after de surgical intervention. The subsequent extension study revealed progression of the underlying disease with mediastinal nodes and bone metastases.

The patient died 9 months after surgery having received treatment with tyrosine-kinase inhibitors.

Conclusions: About 30% of patients diagnosed with renal carcinoma have metastases at the time of diagnosis. Vaginal location is extremely rare and usually occurs with episodes of metrorrhagia and mass effect. Treatment consists on removal of the lesion or local radiotherapy. The prognosis of these patients is conditioned by metastases in other organs.

Keywords: renal cell carcinoma. vaginal metastases.

I. Background

Vaginal metastases in patients with clear cell renal carcinoma are rare. There are fewer than 100 cases currently described as the revised literature. At the time of diagnosis, we observe metastasis by hematogenous or lymphatic spread in 20-30% of patients [1].

Vaginal metastases, despite being rare, are more common than primary tumors and as presentation of the disease is extremely rare.

We present the evolution and treatment of a patient with renal cell carcinoma and vaginal metastasis.

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II. Case Presentation

We report the case of 68 years old caucasian female, with a history of hypertension, Sjögren's syndrome, vitamin D deficiency, mild mitral regurgitation and mild aortic regurgitation.

The patient has constitutional syndrome associated with macroscopic hematuria for 4 months evolution.

On physical examination we find a palpable mass in the left flank and evidenced gross hematuria. We performed a pelvic abdominal CT scan that evidence a heterogeneous mass of 10 x 16 x 9 cm dependent on the back side, the middle and lower third of the left kidney. Also striking, the presence of bilateral pulmonary parenchymal involvement with multiple nodular formations compatible with mestastasica involvement (the greater than 4 cm) and apparent hilar and mediastinal infracarinal lymph nodes. The clinical stage was cT3 No M1. This case was discussed in the uro-oncology committee and despite being classified as intermediate risk according to MSKCC/Motzer's criteria [2], the patient was intervened because she had symptomatic disease.

The patient underwent a left laparoscopic radical nephrectomy.

The study of the specimen reveals a mass of 9x6x8 cm located in the middle third and lower pole, infiltrating the renal capsule, the renal sinus, perirenal fat, renal vein and numerous segmental renal veins. In addition, numerous tumor thrombosis in lymphatic vessels of renal sinus were observed (Figure 1).

Regarding lymph node staging, lymph node metastases were seen in one of the two extracted hilar lymph and in two of the three nodes obtained from the specimen of regional lymphadenectomy. On microscopic analysis we observed a renal clear cell carcinoma, grade 4 (ISUP 2014/WHO 2016) in 90% of the tumor, Fuhrman IV (90%), with 40% tumor necrosis with negative surgical margins. The pathological stage was pT3a N2.

In the first postoperative day, the patient has an important episode of metrorragia. On genital examination we found a solid mass of 2x2 cm in the left lateral surface of the vagina, on the lower third.

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The patient underwent emergency surgery to suture the vaginal tear and excisional biopsy of the lesions.

The pathology of both lesions revealed metástasis of clear cell renal cell carcinoma with high grade nuclear atypia and abundant lymphovascular tumor thrombosis (Figure3 and 4). The patient had a favorable evolution getting discharged from hospital four days after nephrectomy.

One month after discharge the patient begins treatment with pazopanib (800 mg / day). A thoraco-abdomino-pelvic CT control done two months after surgery reveals an acute pulmonary embolism on lobar artery on right lower lobe as well as progression of the underlying disease with increased number and size of hiliar lymphnodes and mediastinal conglomerates adenopathicas well as lytic lesion in the posterior arch of the 5th costal left rib with probable metastasic origin. The patient died 9 months after surgery.

III. Discussion and Conclusions

Since the 1970s the incidence of RCC has increased given the use of ultrasound and CT routinely for the diagnosis and evaluation of various abdominal disorders.

The classic triad of hematuria, flank pain and palpable mass is observed between 5% and 15% of patients and may also debut as different paraneoplastic syndromes like Cushing's syndrome, Stauffer syndrome, deep vein thrombosis or amyloidosis among others.

At the time of diagnosis, we can observe metastasis by hematogenous or lymphatic spread in 20-30% of patients [1]. The most frequent locations are retroperitoneal nodes, lung, liver and bone.

Vaginal adenocarcinomas are rare entities (5% vaginal cancers) and almost always metastatic (91%). In young women, they are often related with exposure to diethylstilbestrol. In older women, as in our case, they are almost always metastatic.

The appearance of the vaginal lesion usually precedes the diagnosis of the primary tumor, and the presenting symptoms, usually metrorrhagia, vaginal discharge and mass effect.

Vaginal metastases are more common in tumors located in the left kidney and generally, these metastases occur ipsilateral to the primary kidney tumor. Less than 90 cases of vaginal metastasis of RCC were reported. In most of these cases, vaginal metastases were diagnosed as metachronous metastatic disease that discovered long term after radical nephrectomy. There are only four cases of synchronous vulvo-vaginal metastases from RCC in medical literature[3-6].

As for the way of disemnicacion, JJ Mulcahy proposed the theory that even today remains the most plausible explanation for this phenomenon [7].

The spread is caused by retrograde venous extension from the renal vein to the ovarian vein, ovarian plexus and uterovaginal plexus[8].

In this study they demonstrated angiographically that the contrast flow retrograde from the left renal vein on the left ovarian vein, the uterovaginal plexus and therefore the right ovarian vein.

The fact that approximately 60% of RCC with vaginal metastases are located on the left side favors this hypothesis.

The most important prognostic factor in these patients is the presence or absence of metastases in other organs. No conclusive studies in the literature that support the realization of Pap smear for the diagnosis or monitoring of these patients.

The treatment of metastatic renal cancer has varied over the last decade. Currently, target therapies such as tyrosine kinase inhibitors and immunotherapy are used depending on the risk of the disease. Cytoreductive nephrectomy is reserved for those patients with a more favorable prognosis or those with symptomatic disease.

As therapeutic recommendations premature ovarian vein ligation during nephrectomy it is recommended in order to limit the migration of tumor cells from the renal vein[9].

Local excision and / or radiotherapy are the standard treatments for vaginal metastases in patients undergoing radical nephrectomy[10].

About 30% of patients diagnosed with renal carcinoma have metastases at the time of diagnosis. Vaginal location is extremely rare and usually occurs with episodes of metrorrhagia and mass effect. Treatment consists on removal of the lesion or local radiotherapy. The prognosis of these patients is conditioned by metastases in other organs.

List of Abbreviations

Abbreviations: RCC, Renal cell carcinoma; CT, Computerized tomography; MSKCC, Memorial Sloan Kettering Cancer Center, ISUP, International Society of Urological Pathology; WHO, World Health Organization.

Declarations

Ethics approval and consent to participate: The hospital ethics committee endorsed the review of this case. Hospital La paz Ethics Comitte.

Availability of data and material: The data was collected from the electronic medical record of the hospital

Competing interests: The authors declare no competing interests.

Funding: No funds were used to study this case.

Authors' contributions: J.G.R and D.T.S operated the patient with a laparoscopic nephrectomy. A.A.B. made the diagnosis of vaginall metastasis and L.M.P contribute to the revision of the manuscript and the literature. P.G.P performed the anatomopathological

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analysis of the specimen. All authors read and approved the final manuscript.

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Figure Legends

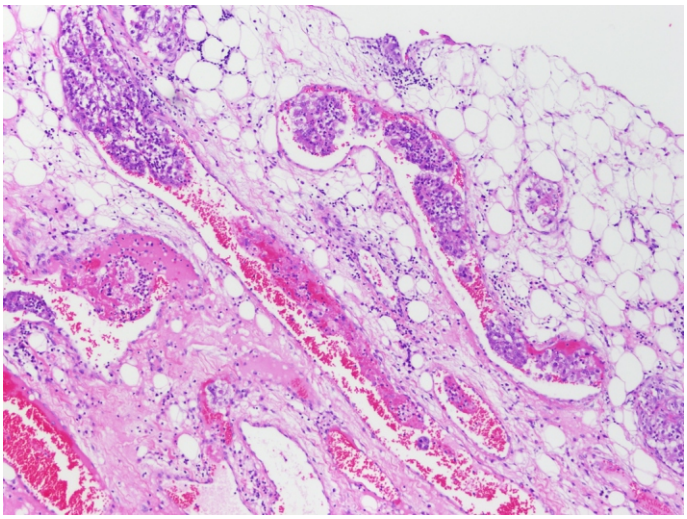


Figure 1: Numerous tumor thrombosis of clear cell renal cell carcinoma in lymphatic vessels of renal sinus.

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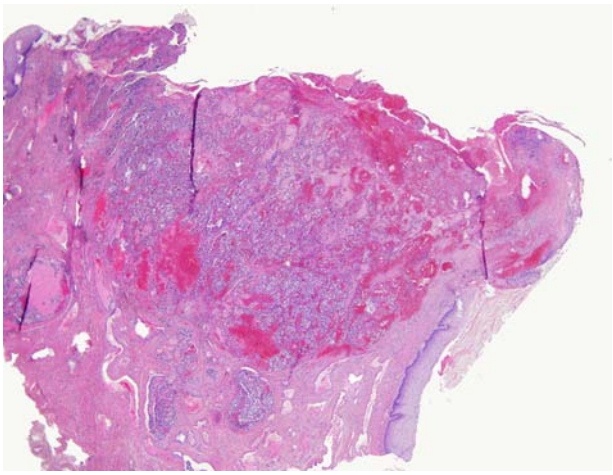


Figure 2: Vaginal metastasis seen at low magnification

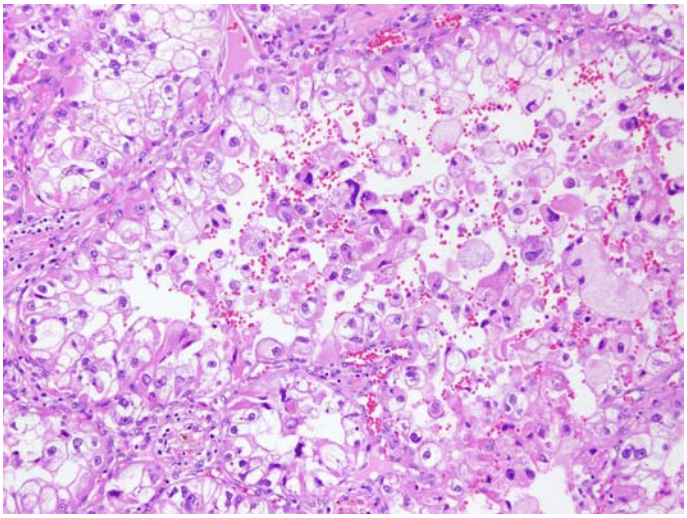


Figure 3: Metastasis of clear cell renal cell carcinoma in vagina. Note the squamous epithelium of the vagina at the bottom right corner. The stroma is infiltrated by a tumor with hemorrhagic areas. Tumor thrombosis of lymphatic vessels is evident at lower part of the figure.

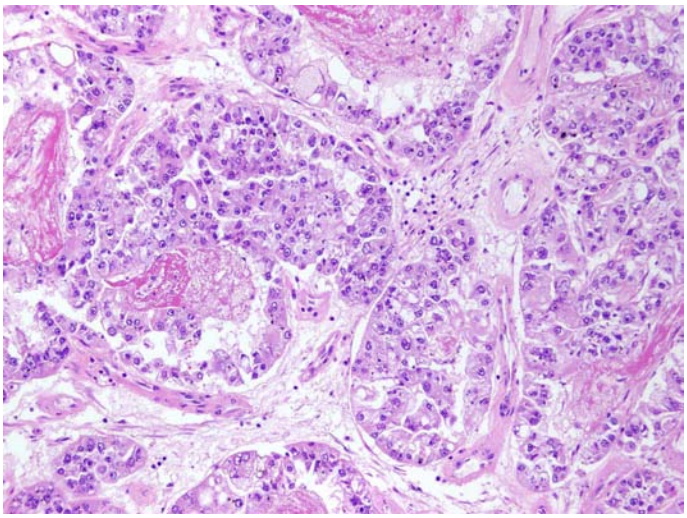


Figure 4: High power field of high-grade clear cell renal cell carcinoma metastatic in the vagina nested and alveolar

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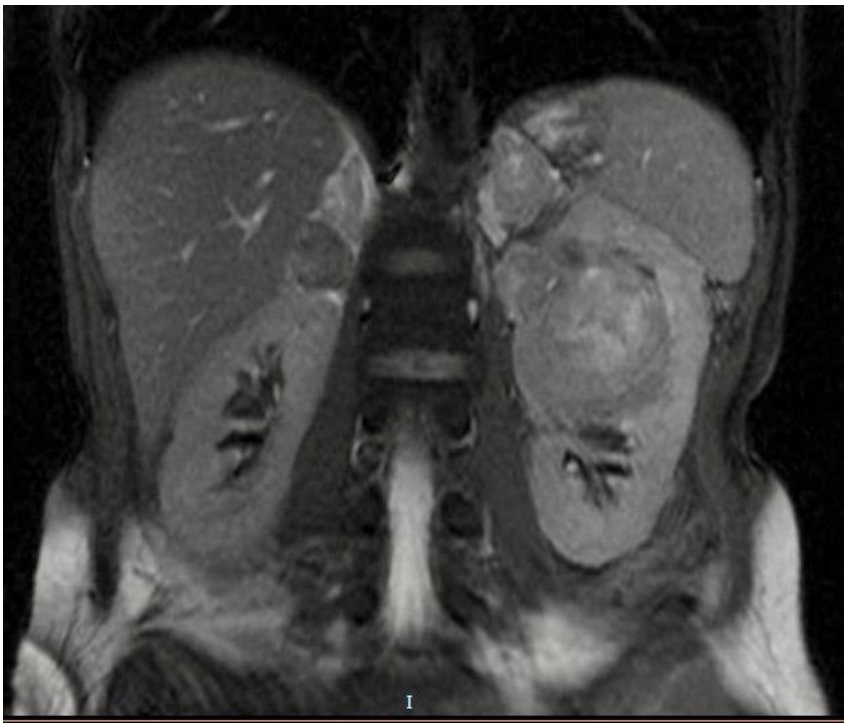


Figure 5: Coronal section of left renal tumor

Table 1. Published case report of synchronous vaginal metastasis in patients with renal cell carcinoma.

Literature	Age	Symptoms	Side tumor	Metastasis in other organs	Treatment
Chibuzo et al. 2016	43	Flank pain	Right	-	Nephrectomy
Pisavadia et al. 2017	79	Vaginal bleeding	Left	Liver	Pazopanib (400 mg)
Jimenez et al. 2018	54	Vaginal bleeding	Left	Both adrenal glands, retroperitoneal lymph nodes	Nephrectomy + Sunitinib (50 mg)
Asaad et al. 2020	40	Vaginal bleeding	Left	-	Nephrectomy + Sunitinib

Figure 6: Literature review

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Robotic Surgery versus Laparoscopy in Colorectal Cancer Resection: A Systematic Review

By Guilherme Gomes Gil De Menezes

Abstract- *Menezes, GGG. Robotic surgery versus laparoscopy in colorectal cancer resection*: A systematic review [final paper]. Salvador. Medicine course, Bahiana School of Medicine and Public Health, Bahia 2019.

Introduction: Colorectal cancer is a malignant disease, more predominantly observed in men and the third most incident tumor among all cancers, with an estimated risk of 26.6 / 100 thousand. Despite its high incidence and prevalence, it is amenable to treatment, and in most cases, it is curable - when detected in early stages.

Objective: To compare the safety and efficacy of performing robotic surgery with traditional laparoscopic surgery in patients undergoing colorectal cancer resection regarding the variables: intra and postoperative complications, surgical conversion, and mortality.

Keywords: *colorectal neoplasm. colectomy. laparoscopy. robotics.*

GJMR-I Classification: *NLMC Code: QZ 20.5*



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Robotic Surgery versus Laparoscopy in Colorectal Cancer Resection: A Systematic Review

Guilherme Gomes Gil De Menezes

Resumo- *Menezes, GGG. Cirurgia robótica versus laparoscopia na ressecção de câncer colorretal:* Revisão sistemática [trabalho de conclusão de curso]. Salvador. Curso de Medicina, Escola Bahiana de Medicina e Saúde Pública, Bahia 2019.

Introdução: O câncer colorretal é uma doença maligna, observada mais predominantemente em homens e o terceiro tumor mais incidente entre todos os cânceres, possuindo um risco estimado de 26,6/100 mil. Apesar das suas elevadas incidência e prevalência, é passível de tratamento e, na majoritaridade dos casos é curável – quando detectado em estágios iniciais.

Objetivo: Comparar a segurança e eficacia da realização da cirurgia robótica com a cirurgia laparoscópica tradicional em pacientes submetidos à ressecção de câncer colorretal, quanto às variáveis: complicações intra e pós-operatórias, conversão cirúrgica e mortalidade.

Métodos: Trata-se de uma revisão sistemática caracterizada pela busca de artigos na literatura, com aplicação de metodologia sistematizada, através de bases de dados *MEDLINE/PubMed*, *Scielo*, *Embase* e *Cochrane*, por meio da combinação de descritores, incluindo termos do Medical Subject Headings (MeSH) e dos Descritores em Ciência da Saúde (DECs), incluindo publicações em inglês e português: *robotic-assisted conventional laparoscopic surgery colorectal cancer resection*, além de busca ativa. Foram incluídos ensaios clínicos randomizados, estudos de coorte e estudos retrospectivos publicados partir de 2010, em português e inglês, que compararam o emprego das técnicas laparoscópicas minimamente invasiva e a ressecção colorretal pela abordagem robótica. Foram excluídos revisões, relatos de casos, série de casos, comentários e correspondências. A análise e aplicação das ferramentas CONSORT e STROBE foram feitas por dois avaliadores separadamente.

Resultados: Foram encontrados 20 artigos na estratégia de busca, e 07 foram selecionados. As amostras variaram de 56 a 471 participantes (n total = 1589), com variação de idade de 61,2 - 69,0. Todos os estudos incluíram ambos os gêneros e, dentre estes, apenas um20 relatou uma proporção maior de mulheres. Dentre os trabalhos selecionados, cinco estudos se caracterizam como coortes retrospectivas e dois estudos como ensaios clínicos randomizados. A variação de duração das intervenções foi de 12 - 120 meses. Realizando uma comparação entre as abordagens laparoscópica e robótica acerca da taxa de complicações intraoperatórias, o percentual apresentado pelo grupo da cirurgia robótica (6,0%) foi maior que a taxa de complicações relacionadas à cirurgia laparoscópica (5,2%). Sobre as taxas de conversão, a cirurgia robótica apresentou percentual consideravelmente menor: 0% - 8,1% contra 0% - 37%. Em relação à morbidade pós-operatória as prevalências foram de 22,6% – 60% para a laparoscopia e 8,9% – 42,3% para a cirurgia robótica, sendo observada uma notória variação em ambas as abordagens. No que tange ás taxas de mortalidade foi identificada prevalência que variou entre 0% - 5,6% na cirurgia laparoscópica, enquanto que na cirurgia robótica as taxas variaram entre 0% e 0,8%.

Conclusão: Frente aos achados descritos, evidências de boa a moderada qualidade, sustentam que a cirurgia robótica para a ressecção de câncer colorretal, apesar de promover melhor ergonomia e conforto para o cirurgião, produz resultados peri e pós-operatórios semelhantes. A cirurgia robótica, no entanto, possui menor taxa de conversão cirúrgica e mortalidade. Contudo, diante de uma literatura ainda carente de evidências mais abrangentes sobre o tema, outros trabalhos se fazem necessários para uma maior constatação das inferências reproduzidas nesse estudo.

Palavras-Chave: *neoplasias colorretais. colectomia. laparoscopia. robótica.*

Abstract- *Menezes, GGG. Robotic surgery versus laparoscopy in colorectal cancer resection:* A systematic review [final paper]. Salvador. Medicine course, Bahiana School of Medicine and Public Health, Bahia 2019.

Introduction: Colorectal cancer is a malignant disease, more predominantly observed in men and the third most incident tumor among all cancers, with an estimated risk of 26.6 / 100 thousand. Despite its high incidence and prevalence, it is amenable to treatment, and in most cases, it is curable - when detected in early stages.

Objective: To compare the safety and efficacy of performing robotic surgery with traditional laparoscopic surgery in patients undergoing colorectal cancer resection regarding the variables: intra and postoperative complications, surgical conversion, and mortality.

Methods: This is a systematic review characterized by the search for articles in the literature, with the application of systematized methodology, through MEDLINE / PubMed, Scielo, Embase and Cochrane databases, by the combination of descriptors, including terms from the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DECs), using publications in English and Portuguese: robotic-assisted conventional laparoscopic surgery colorectal cancer resection, besides active search. Randomized clinical trials, cohort studies, and retrospective studies published since 2010 were included, in English and Portuguese, which compares the application of the techniques minimally invasive laparoscopy

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and colorectal resection by the robotic approach. Revisions, case reports, case series, comments, and correspondence were excluded. The analysis and application of the tools CONSORT and STROBE were made by two evaluators separately.

Results: Twenty articles were found in the search strategy, and 07 were selected. The samples ranged from 56 to 471 participants (total n = 1589), with an age range of 61.2 - 69.0. All studies included both genders and, of these, only one reported a higher proportion of women. Among the selected works, five studies are characterized as retrospective cohorts and two studies as randomized clinical trials. The variation in the duration of interventions was 12 - 120 months. By comparing the laparoscopic and robotic approaches concerning the rate of intraoperative complications, the rate of the robotic surgery group (6.0%) was higher than the rate of complications related to laparoscopic surgery (5.2%). Regarding the conversion rates, robotic surgery showed a considerably lower percentage: 0% - 8.1% against 0% - 37%. The prevalence of postoperative morbidity was 22.6% - 60% for laparoscopy and 8.9% - 42.3% for robotic surgery, with a noticeable variation in both approaches. Regarding mortality rates in the subgroup of laparoscopic surgery, a prevalence ranging from 0% - 5.6% was identified, while in robotic surgery, the rates varied between 0% and 0.8%.

Conclusion: Given the findings described, evidence of good to moderate quality supports that robotic surgery for colorectal cancer resection produces similar perioperative and postoperative results, despite promoting better ergonomics and comfort for the surgeon. However, robotic surgery has lower surgical conversion and mortality rates. Nevertheless, in the face of literature that still lacks more extensive evidence on the topic, other studies are needed to verify further the inferences reproduced in this study.

Keywords: colorectal neoplasm. colectomy. laparoscopy. robotics.

I. Introduction

Since the 1980s, when the first robotic surgery was performed[1], much has been said regarding this new technology and its potential future capabilities. Over the years, robotic surgery has broken the boundaries of innovation in health technology for better clinical outcomes. Thus, linked to a growing need for more precise and minimally invasive surgeries, robotics was developed to meet these demands. Nowadays, it performs several functions related to surgical practice - from assisting in the conduct brain biopsies to performing resection of malignant colorectal tumors. Several specialties such as urology, gynecology, cardiology, neurosurgery, and general surgery can use robotic surgery[1].

Among the technical advantages offered to surgeons are: the potential for three-dimensional visualization of the structures analyzed, elimination of the physiological tremors produced by the movements- allowing greater accuracy- improved surgical maneuvers permitted by the "robotic wrist" mechanism (positioning of surgical instruments at angulations not previously allowed by the laparoscopic technique), less fatigue of the surgeon, faster surgical recovery and with fewer complications compared to laparoscopy[1-3]. However, robotic surgery should be reserved for procedures in which technology can provide maximum benefit, in general when it is necessary to perform precise dissections in confined areas, due to its current high operational cost[3].

This procedure has been becoming more popular since Pigazzi et al.[3] described for the first time the total excision of a malignant rectal tumor performed through robotic surgery in 2006. However, there is still not enough evidence in the literature regarding the safety and effectiveness of robotic surgery compared to traditional laparoscopy in cases of resection of malignant colorectal tumors[2, 3].

II. Objectives

a) Primary objective

To compare the safety and effectiveness of robotic surgery with traditional laparoscopic surgery in patients undergoing colorectal cancer resection.

b) Secondary objective

To compare intraoperative complications rates, surgical conversion, postoperative complications, and mortality of robotic surgery with laparoscopy in colorectal cancer resection surgeries.

III. Literature Review

a) Colorectal cancer

Colorectal cancer is a tumor that affects the large intestine, which is divided into colon and rectum. An essential aspect of this pathology is that the vast majority originates from polyps - small elevations in the colon and/or rectum wall - which grow slowly, starting with an aberrant crypt and developing into a neoplastic precursor lesion and then, finally becoming colorectal cancer. This process can take 10 to 15 years to occur. Thus, these polyps can be palliatively identified and removed before they can even produce malignancy characteristics.

However, some decades ago, colorectal cancer was rarely diagnosed due mainly to a lack of preventive practices and technological resources. Hence, this pathology used to be diagnosed at extremely advanced stages when no therapy could reverse the existing problem[4].

Currently, colorectal cancer is the fourth most lethal cancer globally, causing the death of about 900,000 people each year, accounting for about 10% of the incidence of all cancers diagnosed annually and of cancer-related deaths worldwide [4, 5]. It ranks as the second most common cancer among women and the third most common cancer among men. Its major risk factors are lifestyle-related. Intake of red meat, processed meat, fats, sedentariness, obesity, smoking,

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alcoholism, family predisposition, previous polyps, and age over 50 are conditions that predispose new polyps to appear and consequently increase the likelihood of developing colorectal cancer[4].

The most common signs and symptoms associated with this pathology are hematochezia, anemia with no apparent cause, abdominal discomfort, mild fever, severe weight loss, bowel habit changes, a continued desire to evacuate even after the evacuation, and gas or colic. Nevertheless, colorectal cancer can progress as a silent and asymptomatic disease until it reaches an advanced stage[4].

The diagnosis is based on the association of clinical findings with performing a colonoscopy and other imaging examinations such as computed tomography and laboratory tests such as blood count and concentration of carcinoembryonic antigen that can be used as complementary tests[4]. Colonoscopy should regularly investigate rectal bleeding in patients over 45 years of age. In younger patients, some additional factors should be considered for increasing diagnostic suspicion: the presence of unfavorable family history, marked and unexplained weight loss, and changes in intestinal habit[4].

Through technological advances and the increased possibility of early diagnosis, some cancers are only amenable to local treatment. Incipient polyps can be resected endoscopically, also allowing precise evaluation of risk characteristics, such as the depth of submucosal invasion, lymphatic invasion, presence of the tumor, and its differentiation[4].

Surgery is the main therapeutic procedure for treating colorectal cancer, often with radio- and chemotherapy support. The optimal resection of the tumor is fundamental and can be evaluated through safe and objective parameters. Rectal cancer surgery is a complex process because of the difficult access to the surgical site, provided by the limiting pelvic anatomy. Total mesorectal excision is the standard oncologic approach for rectal cancer, and its extent depends mainly on the involvement of the sphincter complex and other surrounding structures.[4]

Several factors are associated with better prognosis and increased quality of life after surgical treatment. These factors are mostly the same related to colorectal cancer prevention. Thus, patients who adapt to a healthy lifestyle after definitive diagnosis had a 33% lower risk of death during follow-up than those who did not include this habit in their daily practices[4].

b) Robotic versus laparoscopic surgery

During the years of development of surgical practice, minimally invasive techniques allowed laparoscopic interventions in the treatment of colorectal cancer patients. Subsequently, several randomized studies have shown that laparoscopic colectomy is associated with lower morbidity rates, less surgical trauma, and better immediate postoperative results, with shorter recovery times and hospital stays compared to surgery performed through laparotomy[6].

However, a laparoscopic approach in rectal cancer patients is significantly different and more difficult than laparoscopic procedures in patients with colon cancer[6]. This is explained by the difficulty of visualization and surgical access at the pelvic anatomic site where the procedure should occur. Deep dissection in the pelvis to perform a total mesorectal excision and obtain a sample with intact margins, making a safe anastomosis are demanding techniques, besides promoting a considerable probability of reoperation[6].

Corroborating the hypothesis that the laparoscopic approach for rectal neoplastic procedures is a complex and laborious procedure, the British randomized clinical trial CLASICC[7] in 2006 compared laparotomy and laparoscopy performing 794 colorectal cancer surgeries. This study indicated that rectal excision by laparoscopy resulted in a high conversion rate (38% in the first year, decreasing up to 16% in the last year) and a tendency for greater positivity of the circumferential excision margin. Some other studies also present the same conclusion regarding high conversion rates during colorectal laparoscopic surgery[8-10].

The recent introduction of the robotic surgical system has revolutionized the field of minimally invasive surgery. This new technology allows surgeries with a three-dimensional visual field, better ergonomics for the surgeon (by reducing the fatigue), more extensive and better movement amplitudes of the forceps and other surgical instruments, besides eliminating the physiological tremors produced by human arms [1-3,11,12]. Thus, adopting a robotic surgical system to perform colorectal cancer resection procedures seems attractive from this perspective. Since this new technique can be safer for patients submitted to it - mainly concerning the greater ease of management of an area as confined as the pelvic region - always aiming at a safe surgical procedure, free of complications, with higher overall survival, disease-free survival, and quality of life, which are the most relevant objectives of colorectal cancer treatment.

Another advantage related to the robotic surgical procedure is the possibility of using an infrared fluorescent intraoperative imaging system with indocyanine green. This system allows the best identification of noble structures such as vessels, nerves, and lymphatic ducts, thereby facilitating solid organs' partial resection, without damaging their neighboring anatomical structures[13].

Nevertheless, robotic surgery still demands a high financial investment to be performed[14], besides counting on some practical obstacles such as the long learning curve, longer surgical time, and size of the robotic system[15]. Hence, within a publicly funded health system, the replacement of laparoscopic surgeries by

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robotic ones in colorectal operation requires a complete and thorough analysis so that their benefits are indeed validated.

The current literature evidence is that robotic rectal excision has been verified as feasible and safe, but these conclusions were mostly based on statistically non-significant differences. Therefore, this systematic review has great value to clarify the evidence available in the literature about the advantages of robotic surgery in comparison to traditional laparoscopic surgery in cases of colorectal cancer resections.

IV. Material and Methods

a) Study design

Systematic literature review.

b) Search strategy

The literature review was carried out on September 10, 2019, in the electronic databases MEDLINE/PubMed, Scielo, Embase, and Cochrane, through the combination of descriptors, including terms from Medical Subject Headings (MeSH) and Health Science Descriptors (DECs), using publications in English and Portuguese: robotic-assisted conventional laparoscopic surgery colorectal cancer resection. The terms used for the search were related to the population of interest, the parameters to be studied and the outcomes of morbidity and mortality: robotic-assisted [All Fields] AND conventional[All Fields] AND ("laparoscopy"[MeSH Terms] OR "laparoscopy"[All Fields] OR ("laparoscopic" [All Fields] AND "surgery"[All Fields]) OR "laparoscopic surgery"[All Fields]) AND ("colorectal neoplasms" [MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms" [All Fields]) OR "colorectal neoplasms" [All Fields] OR ("colorectal"[All Fields] AND "cancer" [All Fields]) OR "colorectal cancer"[All Fields]) AND resection[All Fields]. References in the articles identified by the search strategy were also manually searched to add to the study and literature review.

c) Inclusion criteria

There were included studies, with a sample size greater than 30, published from October 2006 to December 2018, comprising patients who underwent robotic or laparoscopic surgery to perform cancer resection in the colorectal region. The clinical outcomes of interest were: surgical time, surgical conversion, other intraoperative and postoperative complications, length of hospital stay, and mortality.

d) Exclusion criteria

Reviews, case reports, case series, comments, and correspondence were excluded.

e) Identification and selection of studies

The authors read each pre-selected article's titles and abstracts from the electronic database research to identify only those studies that correctly fulfill the inclusion and exclusion criteria. Subsequently, the full texts were read, ensuring the criteria for the systematic review.

Both authors discussed the divergences trying to respect the inclusion and exclusion criteria previously defined.

f) Data extraction

Two authors collected the data using a predefined collection form. The characteristics of interest of the studies included: geographical origin, title, type of study, duration of the study, number of participants, and mean age of the sample. Finally, data were collected related to surgical time, intraoperative and postoperative complications, conversion, length of hospital stay, and mortality. The quality of each study characterized as a randomized clinical trial was evaluated by the Cochrane Tool - Consolidated Standards of Reporting Trials (CONSORT)[16] to assess the risk of bias, which contains the following criteria: adequate randomization; allocation of participants; blinding of participants; blinding of the outcome evaluator; integrity of results; incomplete data; selective outcome reports; and other sources of bias (e.g., the effect of small studies). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[17] was used for the methodological evaluation of observational articles.

V. Results

a) Identification and selection of studies

Through the search strategy, 20 records were identified after the exclusion of duplicate studies. Based on the reading of the title and abstract, 8 articles were left for a full reading. Of these, one study was excluded because it did not reach the minimum sample size. Therefore, 7 articles were selected for the systematic review (Figure 1).

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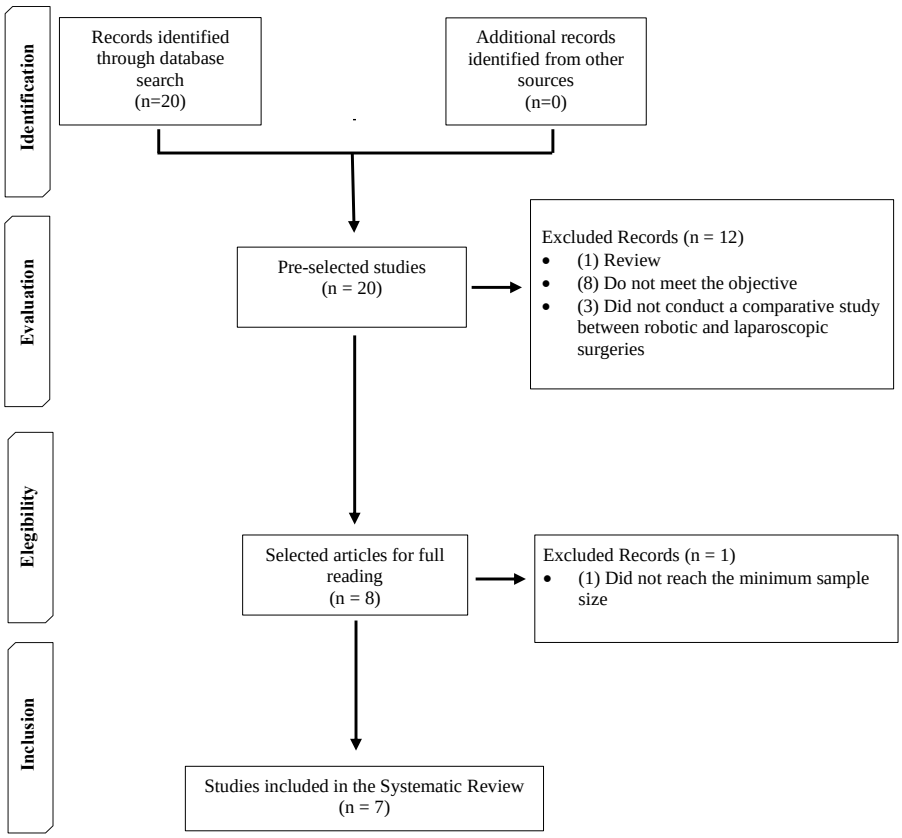


Figure 1: Flowchart for identification, screening, eligibility, and inclusion of studies in the systematic review.

The selected articles were retrospective cohorts and randomized clinical trials. The general characteristics of the studies included in the systematic review are summarized in Chart 1.

Chart 1: General characteristics of the selected studies, ordered by year of publication

Authors	Study design	Year	Country	Sample size		Gender (M/F)	Mean age (years)		Study time (months)
				Laparoscopy	Robotics		Laparoscopy	Robotics	
Park et al.[6]	Retrospective cohort	2010	South Korea	41	82	(73/50)	63.0	61.2	120
Rodríguez et al.[18]	Randomized clinical trial	2011	Spain	28	28	(29/27)	61.5	68.0	19
Levic et al.[19]	Retrospective cohort	2014	Denmark	36	56	(51/41)	69.0	65.0	24
Ramji et al.[14]	Retrospective cohort	2015	USA	27	26	(38/15)	63.7	62.1	24
Yamaguchi et al.[20]	Retrospective cohort	2015	Japan	239	203	(294/148)	65.9	64.8	45
Jayne et al.[21]	Randomized clinical trial	2017	United Kingdom	234	237	(234/237)	65.5	64.4	12
Crolla et al.[22]	Retrospective cohort	2018	Netherlands	184	168	(216/136)	68.1	67.0	60

Source: The author (2020)

b) General characteristics of the obtained studies

The samples ranged from 56 to 471 participants (n total = 1589), with an age range of 61.2 - 69.0. All studies included both genders, and among these, only one20 reported a higher proportion of women. Among the selected studies, five are characterized as retrospective cohorts and two as randomized clinical trials. The length of interventions varied from 12 to 120 months. All articles reported the presence of the variables: surgical time, length of hospital stay, surgical conversion, other intra-and postoperative complications. The risk of bias classification of randomized clinical trials was performed with the CONSORT16 tool, available in the Cochrane Collaboration, shown in Chart 2.

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Chart 2: Quality assessment - CONSORT tool [16]

Item	Checklist item	Rodríguez et al.[18]	Jayne et al.[21]
1a	Identification as a randomized trial in the title	●	●
1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	●	●
2a	Scientific background and explanation of rationale	●	●
2b	Specific objectives or hypotheses	●	●
3a	Description of trial design (such as parallel, factorial) including allocation ratio	●	●
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	●	●
4a	Eligibility criteria for participants	●	●
4b	Settings and locations where the data were collected	●	●
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	●	●
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	○	○
6b	Any changes to trial outcomes after the trial commenced, with reasons	○	○
7a	How sample size was determined	●	●
7b	When applicable, explanation of any interim analyses and stopping guidelines	●	●
8a	Method used to generate the random allocation sequence	○	○
8b	Type of randomization; details of any restriction (such as blocking and block size)	○	○
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	○	○
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	○	○
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	○	○
11b	If relevant, description of the similarity of interventions	○	○
12a	Statistical methods used to compare groups for primary and secondary outcomes	○	●
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	○	●
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	●	●
13b	For each group, losses and exclusions after randomization, together with reasons	○	●
14a	Dates defining the periods of recruitment and follow-up	○	○
14b	Why the trial ended or was stopped	○	○
15	A table showing baseline demographic and clinical characteristics for each group	●	●
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	●	●
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	●	●
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	●	●
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	●	●
19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	●	●
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	○	○
21	Generalisability (external validity, applicability) of the trial findings	○	○
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	●	●
23	Registration number and name of trial registry	●	●
24	Where the full trial protocol can be accessed, if available	○	●
25	Sources of funding and other support (such as supply of drugs), role of funders	●	○
	TOTAL	**15**	**16**

Source: The author (2020)

Legend: (●) Scored (○) Not mentioned/not applicable

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The quality assessment of the selected observational studies was performed with the STROBE17 tool, available in the STROBE initiative, verified in Chart 3.

Chart 3: Quality assessment of selected studies, based on the essential items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative[17]

Topic	Item	Park et al.[6]	Levic et al.[19]	Ramji et al.[14]	Yamaguchi et al.[20]	Crolla et al.[22]
Title and abstract	1	◉	◉	◉	◉	●
Introduction						
Background/Rationale	2	●	●	●	◉	●
Objectives	3	●	●	●	●	●
Methods						
Study design	4	●	●	●	●	●
Setting	5	●	●	●	●	●
Participants	6	◉	●	●	●	●
Variables	7	●	●	●	◉	●
Data source/Measurement	8	◉	○	○	◉	●
Bias	9	◉	○	◉	●	◉
Study size	10	◉	◉	◉	●	●
Quantitative variables	11	●	●	●	●	●
Statistical methods	12	◉	○	◉	◉	●
Results						
Participants	13	○	○	○	●	●
Descriptive data	14	●	◉	●	●	●
Outcome data	15	●	◉	●	●	●
Main results	16	◉	◉	◉	◉	◉
Other analysis	17	●	●	●	◉	○
Discussion						
Key results	18	●	●	●	●	●
Limitations	19	●	●	●	●	○
Interpretation	20	●	●	●	●	●
Generalisability	21	●	●	●	●	●
Other Information						
Funding	22	○	●	●	●	●

Source: The author (2020)

Legend

- ● Item fully covered by the article
- ◉ Item partially covered by the article
- ○ It was unclear the item's compliance with the article

In 2010, Park et al.[6] conducted an analysis exclusively related to low rectal cancer. The records were collected and prospectively acquired from all patients at Kyungpook University Hospital with rectal cancer located 8 cm from the anal margin. After this process, the information was reviewed retrospectively. Patients with tumors causing intestinal obstruction or perforation, local resectable tumor with transanal access, invasion of adjacent organs requiring multiple organ en bloc resection, and distant metastasis were not considered suitable for laparoscopy or robotic surgery.

The choice between the two different surgical approaches was based on a joint decision between patients and physicians, and the use of robots did not modify the criteria for selecting individuals. The patient's preoperative evaluation comprised physical examination, complete blood count, electrolytes and liver function tests, serum carcinoembryonic antigen (CEA), chest X-ray, and electrocardiogram. Colonoscopy, abdominopelvic computed tomography, and pelvic magnetic resonance imaging were routinely performed to evaluate distant metastases, local infiltration of the disease, and tumor characteristics. This study had limitations due to its retrospective nature and its inherent selection bias. Another established limitation is related to the lack of a detailed economic comparison between the two groups. Some differences in short-term results were considered insufficient to justify the costs of using the new technology.

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Rodríguez et al.[18], in 2011, besides analyzing rectal cancers, evaluated the occurrence of tumors in the sigmoid. All patients underwent preoperative analysis, including hemogram, liver function, and biochemical tests, chest radiographs, and electrocardiograms. Patients diagnosed with rectal cancer were also submitted to colonoscopy with biopsy for the histological diagnosis of the lesion, accompanied by thoracoabdominal computed tomography, magnetic resonance imaging, and ultrasound examinations. This study analyzed patients' clinical conditions through the American Society of Anesthesiology (ASA) classification and performed histological analyses to define the distance of the distal margin, the total number of resected lymph nodes, and the total length of the sample. This research did not present its eventual limitations.

Levic et al.[19] conducted a retrospective and multicenter analysis in 2014. The patients considered appropriate for the laparoscopic technique were over 18 years old and had rectal cancer without metastasis. Exclusion criteria were magnetic resonance imaging (MRI) or preoperative computed tomography (CT) showing tumor size >4 cm in diameter or evidence of local invasion (T4 cancer); ASA class IV/V; the anticipated need for intensive care unit (ICU); a history of major anterior abdominal surgery and obese patients with body mass index (BMI) >32 kg / m2. Inclusion criteria for robotic surgery were practically the same, except that high BMI was not a reason for exclusion. The tumor staging and preoperative evaluation consisted of a digital rectal examination, proctoscopy, histopathological examination, thoracoabdominal computed tomography, and pelvic magnetic resonance imaging. All patients were discussed at the multidisciplinary team conference before the treatment decision.

This study's limitations were the restricted number of patients in each group and the short follow-up, which made it impossible to reach satisfactory conclusions about the long-term oncologic effects and any possible differences in late complication rates. Moreover, the authors presented the selection bias as a limitation since the study was not randomized, as well as the learning curve of surgeons for both techniques since this can cause distorted results in any direction.

The retrospective study by Ramji et al.[14], in 2015, additionally compared robotic and laparoscopic surgical procedures to laparotomy. The analysis was the only one that compared the economic feasibility between the surgical techniques. This study also analyzed the patients' tumor characteristics according to the ASA classification and comorbidities' existence through the Charlson score. The included cases required a confirmed histological diagnosis of rectal adenocarcinoma and could not be associated with recurrent or synchronous disease. Cases with multivisceral involvement and palliative intention were excluded. The study showed limitations related to the small number of cases assisted by robotics concluded until its institution.

In their study in 2015, Yamaguchi et al.[20] included all patients who underwent proctectomy for rectal adenocarcinoma at Shizuoka Cancer Center Hospital. Patients undergoing open surgery, high anterior resection, lateral lymph node dissection, or multiple resections were excluded. The preoperative tumor staging was carried out according tocolonoscopy findings, computed tomography, magnetic resonance imaging, and barium enema. The rectal cancers were staged using the tumor-node-metastasis (TNM) classification. The surgical method to be performed was decided through a physician's discussion with the patient. After providing informed consent, the patients selected their preferred approach - however, rectal cancer surgery with lateral lymph node dissemination was performed by the open method if the patient did not desire to undergo robotic surgery - a condition that reproduces a selection bias, somehow restricting the internal validity of the study. The first limitation present in the study was related to the fact that it was a retrospective analysis that potentially included several selection biases. The second limitation was established because of the lack of evaluation of sexual function after surgery.

Jayne et al.[21] conducted a randomized multicenter study in 2017, which included 29 different medical centers in 10 countries and 40 surgeons. The patients included were those with an indication for resection and were diagnosed with rectal adenocarcinoma. Patients with benign lesions of the rectum, anal canal cancers, locally advanced cancers, or those requiring multivisceral block resection or multiple surgical resections were excluded from the study. The study additionally evaluated bladder function and sexual function through the International Prostate Symptom Score (I-PSS), International Index of Erectile Function (IIEF), and Female Sexual Function Index (FSFI). This research presented limitations related to the low number of patients analyzed - conferring statistically insignificant results among the treatment groups. No blinding was established for this study, consequently affecting the study's primary outcome and mortality measures.

In 2018, Crolla et al.[22] carried out their study using a prospectively filled database - with data routinely collected from patients. Multiple organ resections were excluded. Regarding its limitations, this study presented several diagnostic and therapy protocol changes throughout the development period. The randomization process was not performed. This study also did not consider the surgeons' learning curve or adequacy. Besides, the authors showed that confounding factors related to general morbidity might have been neglected.

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Table 1: Surgical time in minutes, surgical conversion, postoperative morbidities and intraoperative complications

Study	Surgical time (in minutes)		Surgical conversion (n)		Morbidities postoperative (n)		Intraoperative complications (n)	
	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics
Park et al.[6]	168.6	231.9	0	0	19	12	2	0
Rodríguez et al.[18]	135.1	159.4	2	2	NR	NR	4	4
Levic et al.[19]	295	247	0	3	10	12	0	8
Ramji et al.[14]	240	407	10	3	7	8	1	0
Yamaguchi et al.[20]	227.6	232.9	8	0	54	18	NR	
Jayne et al.[21]	261	298.5	28	19	73	78	34	36
Crolla et al.[22]	172	219	23	3	111	71	NR	

Source: The author (2020)

Legend: NR: Not referred

The main intraoperative complications recorded by the studies, besides the surgical conversion, were: significant hemorrhage, need for intraoperative transfusion, injury and/or perforation of the rectum, equipment failure, fecal contamination, and inadvertent perforation of the tumor. Rodríguez et al.[18], in 2011, and Ramji et al.[14], in 2015, did not detail the intraoperative complications analyzed in their studies.

The most significant postoperative complications described by the studies included in this review: anastomotic dehiscences, urinary retention, need for reoperation, anemia with the need for transfusion, and infection of the wound or surgical region. Rodríguez et al.[18], in 2011, did not perform an analysis of postoperative morbidities, and Yamaguchi et al.[20], in 2015, did not specify the postoperative morbidities recorded besides anastomotic dehiscence and infection of the surgical site.

From the studies added to the systematic review, Park et al.[6], in 2010, Ramji et al.[14], in 2015, and Yamaguchi et al.[20], in 2015, classified patients through Clavien-Dindo postoperative complications severity classification system, verified in Table 2. Park et al.[6], in 2010, divided patients into two groups: the first integrating classifications I and II, while the second joined classifications III and IV. The other researches did not make any reference to this classification tool.

Table 2: Length of hospital stay in days, postoperative Clavien-Dindo classification and mortality

Study	Length of hospital stay (days)		Postoperative Clavien-Dindo classification		Mortality (n)	
	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics
Park et al.[6]	9.4	9.9	I/II: 76 III/IV: 6	I/II: 37 III/IV: 4	0	0
Rodríguez et al.[18]	9.2	9.3	NR	NR	0	0
Levic et al.[19]	7	8.0	NR	NR	2	0
Ramji et al.[14]	11.3	7	0:14 I:6 II: 0 III: 0 IV: 4	0:15 I: 4 II: 4 III: 3 IV: 0	0	0
Yamaguchi et al.[20]	9.3	7.3	0: 1 I: 107 II: 41 III: 73 IV: 17	0: 1 I: 98 II: 20 III: 72 IV: 12	0	0
Jayne et al.[21]	8.2	8	NR	NR	2	2
Crolla et al.[22]	7	6	NR	NR	9	1

Source: The author (2020)

Legend: NR: Not referred

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The most used type of surgery among the studies was the low anterior resection, followed by the abdominoperineal resection, shown in Table 4. Most studies included only rectal cancer in their analysis. Park et al.[6], in 2010, were even more specific and analyzed only low rectal cancers. Only Rodríguez et al.[18], in 2011, additionally analyzed colon cancers in their study - totaling 44 patients.

Table 4: Types of surgery and tumor location

Types of surgery	Study						
	Park et al.[6]	Rodríguez et al.[18]	Levic et al.[19]	Ramji et al.[14]	Yamaguchi et al.[20]	Jayne et al.[21]	Crolla et al.[22]
Low anterior resection	●	●	●	●	●	●	●
Abdominoperineal resection	●	○	○	●	○	○	●
Hartmann	○	○	●	○	●	○	○
Hartmann' anterior	○	○	○	○	○	○	●
High anterior resection	○	●	○	○	○	●	○
Abdominoperineal resection	○	○	●	○	●	●	○
Intersphincteric resection	○	○	○	○	●	○	○
Abdominoperineal intersphincteric resection	○	○	●	○	○	○	●
Coloanal anastomosis	●	○	○	○	○	○	○
Sigmoidectomy	○	●	○	○	○	○	○
Amputation	○	●	○	○	○	○	○
Low anterior resection with protective ileostomy	○	○	●	○	○	○	○
Tumor location	Low rectal cancer	Colorectal Cancer	Rectal cancer	Rectal cancer	Rectal cancer	Rectal cancer	Rectal cancer

Source: The author (2020)

Legend: (●) Performed, (○) Not performed

VI. Discussion

The present study aimed to select four main variables related to the efficacy and safety of different surgical approaches: prevalence of intraoperative complications, surgical conversions, postoperative morbidities, and mortality. This systematic review obtained a total sample of 1,589 patients submitted to colorectal cancer surgery, either by laparoscopic or robotic technique.

The prevalence of intraoperative complications from laparoscopy ranged from 0% to 14.8%, and the most prevalent among the complications mentioned in the studies were: significant hemorrhage, damage to some organ or structure, low rate of anal sphincter preservation and surgical equipment failure. Yamaguchi et al.[20], in 2015, and Crolla et al.[22], in 2018, showed no results for this variable. Park et al.[6], in 2010, Ramji et al.[14], in 2015, and Levic et al.[19], in 2014 presented prevalence below the average of studies included in the review, while in the studies by Rodríguez et al.[18], in 2011, and Jayne et al.[21], in 2017, showed above average results. The reason for Rodríguez et al.[18], in 2011 and Jayne et al.[21], in 2017 being the only studies with an above-average prevalence of intraoperative complications is because most studies did not present an adequate sample size in order to obtain statistically significant results and avoid type II error - this being the main limitation mentioned in the studies. Thus, Jayne et al.[21], in 2017, probably because of a more significant sample number (230), was the study that most closely resembled the data available in the literature, which present an approximate average prevalence of intraoperative complications of 16.5%[23-27].

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The prevalence of intraoperative complications related to robotic surgery ranged from 0% to 15.3%. Yamaguchi et al.[20], in 2015, and Crolla et al.[22], in 2018, also showed no results for this variable. Park et al.6, in 2010 and Ramji et al.[14], in 2015 reported no intraoperative complications related to robotic surgery, while Rodríguez et al.[18], in 2011, Levic et al.[19], in 2014, and Jayne et al.[21], in 2017 presented similar results with those found in the literature, which has an average prevalence of approximately 14%[28-32]. The rationale used by these studies is related to the lack of tactical sensitivity that the robotic system transmits to the surgeon, especially to those who are at the beginning of their learning curve, consequently causing damage to the patient's organs and structures. To prove this rationale, Rodríguez et al.[18], in 2011, went further, and performed a brief review on the possible causes of intraoperative complications in robotic surgery, finding a result that corroborates with the rationale mentioned above.

Comparing the laparoscopic and robotic approaches concerning the rate of intraoperative complications, the rate related to the robotic surgery group (6.0%) was higher than the rate of complications related to laparoscopic surgery (5.2%), being registered 7 more cases.

As mentioned by Crolla et al.[22], in 2018, "a low conversion rate is important because, in general, the conversion is associated with more complications, longer hospital stay and worse long-term outcome". Thus, regarding surgical conversion rates during laparoscopic surgeries, a prevalence ranging from 0% to 37% was found. Park et al.[6], in 2010, and Levic et al.[19], in 2014, registered no surgical conversion. Rodríguez et al.[18], in 2011, had a conversion rate of 7.14% and reported no statistical differences about robotic surgery. Other studies that found significant differences about laparoscopy varied their prevalence between 3.3% - 37% and reported that the main reasons for the occurrence of surgical conversions in this type of technique were: difficulty of visualization, visible anastomotic leaks, adhesions, stapler complications, tumor invasion of adjacent structures and difficulty in manipulating the target organ.

The robotic technique's prevalence of surgical conversion rates was found to vary between 0% - 8.1%. Park et al.[6], in 2010, and Yamaguchi et al.[20], in 2015, did not report surgical conversion. The study by Levic et al.[19], in 2014, was the only one that presented more conversions (3 versus 0) during robotic surgery. The other studies always showed a lower conversion rate compared to laparoscopic surgeries. The leading causes for surgical conversion during the robotic approach were: the presence of severe fibrosis in the pelvis as a sequel to radiotherapy with a rectal lesion, tumor fixation, and perforation of the rectum due to a narrow pelvis. The studies justified a better performance of robotic surgery in this field by the improved visualization with the 3D camera and a better capacity to maneuver the surgical instruments. Jayne et al.[21], in 2017, still mention that the benefits of robotic surgery for surgical conversion rates are enhanced when surgeons already have some experience in the practice of robotic surgery itself, i.e., when they are at a high level in their learning curve.

By making a parallel between the two approaches analyzed, robotic surgery compared to conventional laparoscopic surgery in colorectal cancer improved the conversion rate, presenting a considerably lower percentage. However, the authors showed that although data related to robotic surgery have achieved better blood loss rates and fewer conversions compared to laparoscopy, this may be less a reflection of the surgical tools used and more a result of the surgeon's improved skill and experience in minimally invasive surgery, which can be considered a confounding bias.

The prevalence of morbidity after surgery related to laparoscopy ranged from 22.6% to 60%. Rodríguez et al.[18], in 2011, presented no results for this variable. he other studies presented similar prevalence, ranging from 22.6% to 31.7% - except Crolla et al.[22], in 2018, who reported a rate of about 60% - well above the average of approximately 29% found in the literature [21,31-33]. This discrepant result was established due to the introduction of an additional variable combined with the postoperative complications mentioned, called by the study of "any other complications" without, however, describing what these possible complications would be. The most mentioned postoperative complications in the analyzed studies were: anastomotic dehiscence, urinary retention and other urinary complications, the need for reoperation, infection of the surgical site, bleeding with the need for transfusion, and cardiorespiratory complications.

Regarding postoperative morbidity related to robotics, the prevalence varied between 8.9% - 42.3%. Rodríguez et al.[18], in 2011, presented no data for this variable. Yamaguchi et al.[20], in 2015, showed the lowest prevalence of morbidity. The study identified fewer occurrences of urinary retention, wound infection, small bowel obstruction, anastomotic dehiscence, intra-abdominal or intraluminal bleeding, and enteritis. Among these complications, the least recurrence of urinary retention was emphasized, and the rationale found for such an event was that "[...] This is probably due to the superior free-moving multi-joint forceps, high-quality three-dimensional imaging, and steady "traction and counter-traction" allowing easier recognition and preservation of the pelvic splanchnic nerves and inferior hypogastric plexus". Crolla et al.[22], in 2018, presented a 42.3% prevalence - a result above the average found in the literature of approximately 27%[28,34,35], but no plausible rationale was found for such a result - only the existence of the additional variable "any other

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complications", which was not detailed by the authors to establish what these possible complications could be. The other studies established a prevalence between 23.2% and 33% and presented the same complications about the laparoscopic technique.

Furthermore, it is worth mentioning that colorectal cancer surgery is a high-risk intervention, which depends significantly on the patient's tumor characteristics and good general condition. Therefore, it is expected that about 1/3 of the patients present postoperative complications in less than 30 days[21]. This data agrees with the selected studies' variation and is valid for both the laparoscopic and robotic techniques, with no significant difference being observed concerning general postoperative morbidity.

The mortality variable in the laparoscopic surgery subgroup was identified as a prevalence ranging from 0% to 5.6%, similar to data found in the literature, which defines average mortality of 2%[33,36]. Park et al.[6], in 2010, Rodríguez et al.[18], in 2011, Ramji et al[14], in 2015, and Yamaguchi et al.[20], in 2015, reported no deaths, while Levic et al.[19], in 2014, Jayne et al.[21], in 2017, and Crolla et al.[22], in 2018, showed a mortality rate of 5.6% , 0.9% and 4.9%, respectively. Levic et al.[19], in 2014, despite recording the highest percentage of mortality, presented only two deaths in a total of 36 patients, not representing statistical significance. In all studies reported in this review, there were a total of 13 deaths related to laparoscopy. Most of the deaths were associated with organ and structure perforation- causing extensive hemorrhage during surgery and postoperative sepsis.

Regarding robotic surgery, mortality prevalence variation was between 0% - 0.8%, a result compatible with the average found in the literature of about 1%28, 37. The only studies reported deaths were conducted by Jayne et al.[21], in 2017, and Crolla et al.[22], in 2018, recording 3 negative outcomes. The rationales for the deaths involving robotic surgery were the same as for laparoscopy.

By comparing the mortality rates of the two surgical techniques, robotics presented 3 deaths out of a total of 789 patients included in the study, which represents a percentage of 0.38%, while laparoscopy showed a total of 13 deaths out of a universe of 800 patients, representing a percentage of 1.6%. Thus, robotic surgery proved promising since the researches revealed a lower mortality rate compared to laparoscopic surgery.

The different methodologies presented by the studies, besides the low sample value of some of them during the analysis of the variables, indicate the need for additional research on the comparison between laparoscopy and robotic surgery in colorectal cancer resection. Larger samples and clearly defined methodological criteria are needed to establish the safety and efficacy of each approach. Also, this present study has not been extended to a meta-analysis to obtain a better statistical result is defined as a limitation.

VII. Conclusion

Given the described findings, evidence of good to moderate quality supports that robotic surgery for colorectal cancer resection produces similar perioperative and postoperative results, even though it promotes better ergonomics and comfort for the surgeon. However, robotic surgery reflects lower surgical conversion and mortality rates. In the face of the literature still lacking more extensive evidence on the topic, other studies are necessary for more significant verification of the inferences reproduced in this study.

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Appendixes

Chronogram

ACTIVITIES	SEPT 2019	OCT 2019	NOV 2019	DEC 2019	JAN 2020	FEB 2020	MAR 2020	APR 2020	MAY 2020	JUN 2020
Choice of theme and										
Meetings with the supervisor										
Preliminary bibliographic research										
Project elaboration										
Research project delivery										
Complementary bibliographic review										
Final considerations										
Official delivery of the paper										
Presentation of the paper in the examining committee										

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Budget

Item	Value (R$)
Computer	R$ 2700,00
Printer	R$ 450,00
Binding	R$ 15,00
Articles	R$ 400,00
Total	R$ 3565,00

Data Collection Tables

	Reference	Country/year	Study design	Sample size, gender (M/F)	Mean age (years)
1	Park et al.	South Korea, 2010	Retrospective cohort	123 (73/50)	62.1
2	Rodríguez et al.	Spain, 2011	Randomized clinical trial	56 (29/27)	64.75
3	Levic et al.	Denmark, 2014	Retrospective cohort	92 (51/41)	67
4	Ramji et al.	USA, 2015	Retrospective cohort	53 (38/15)	62.9
5	Yamaguchi et al.	Japan, 2015	Retrospective cohort	442 (294/148)	65.35
6	Jayne et al.	United Kingdom, 2017	Randomized clinical trial	471 (234/ 237)	64.95
7	Crolla et al.	Netherlands, 2018	Retrospective cohort	352 (216/136)	67.6 (± 10.2)

	Types of surgery	Pathology	Study time (months)
1	Low anterior resection Coloanal anastomosis Abdominoperineal resection	"Low rectal cancer"	120
2	Sigmoidectomy Anterior resection Amputation	"Colorectal cancer"	19
3	Low anterior resection with protective ileostomy Low anterior resection Abdominoperineal resection Abdominoperineal intersphincteric resection Hartman	"Rectal cancer"	24
4	Abdominoperineal resection Low anterior resection	"Rectal cancer"	24
5	Low anterior resection Intersphincteric resection Abdominoperineal resection Hartman	"Rectal cancer "	45
6	Low anterior resection High anterior resection Abdominoperineal resection	"Rectal cancer"	12
7	Hartmann' anterior Low anterior resection Abdominal perineal resection Intersphincteric abdominoperineal excision	" Rectal cancer "	60

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	Surgery time (min)		Surgical conversion		Postoperative morbidities (Extra Table? Describe which ones?)		Length of hospital stay (days)		Postoperative complications (extra table?) - Clavien Dindo		Mortality	
	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics	Laparoscopy	Robotics
1	168.6	231.9	0	0	19	12	9.4	9.9	Dindo I/II: 76 Dindo III/IV: 6	Dindo I/II: 37 Dindo III/IV: 4	0	0
2	135.1	159.4	2	2	x	x	9.2	9.3	NR	NR	0	0
3	295	247	0	3	10	12	7	8	NR	NR	2	0
4	240	407	10	3	1	0	11.3	7	Dindo 0: 14 Dindo I:6 Dindo II: 0 Dindo III:0 Dindo IV:4	Dindo 0: 15 Dindo I: 4 Dindo II: 4 Dindo III: 3 Dindo IV: 0	0	0
5	227.6	232.9	8	0	54	18	9.3	7.3	Dindo 0: 1 Dindo I: 107 Dindo II: 41 Dindo III: 73 Dindo IV: 17	Dindo 0: 1 Dindo I: 98 Dindo II: 20 Dindo III:72 Dindo IV:12	0	0
6	261	298.5	28	19	73	78	8.2	8	NR	NR	2	2
7	172	219	23	3	223	178	7	6	NR	NR	9	1

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Aldosterone Producing Adrenocortical Carcinoma: A Case Report and Systematic Review of the Rare Disease

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Abstract- *Introduction:* Functional adrenocortical carcinoma is very uncommon. Aldosterone producing adrenocortical carcinoma (APAC) is rare malignancy with incidence of less than 10% among adrenal tumor. The diagnosis of APAC is done based on clinical findings, radiological features, and hormonal assay. Most of the cases of APAC were in isolated case reports since 1955. Due to the rarity of the disease the clinicopathological details is less known. The impact of the functional varieties of the adrenal malignancy on disease prognosis is less explored. We present here a case report of an APAC surgically managed in our institution and review of the published data on APAC.

Methods: A case history, clinical and treatment details of an APAC in 40 years gentleman is presented. Online search of the literature on APAC was done and details were extracted to construct database for statistical analysis. The summary measures were done in mean, median, or range after testing for normality. Kaplan Meier analysis and Cox regression proportional hazard analysis were done to evaluate the survival and the survival covariates respectively.

GJMR-I Classification: *NLMC Code: WP 460*



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Aldosterone Producing Adrenocortical Carcinoma: A Case Report and Systematic Review of the Rare Disease

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Abstract- ***Introduction:*** Functional adrenocortical carcinoma is very uncommon. Aldosterone producing adrenocortical carcinoma (APAC) is rare malignancy with incidence of less than 10% among adrenal tumor. The diagnosis of APAC is done based on clinical findings, radiological features, and hormonal assay. Most of the cases of APAC were in isolated case reports since 1955. Due to the rarity of the disease the clinicopathological details is less known. The impact of the functional varieties of the adrenal malignancy on disease prognosis is less explored. We present here a case report of an APAC surgically managed in our institution and review of the published data on APAC.

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Results: A total of 93 cases were included for analysis. The mean age of the study population was 45.7±15 years. APAC is more common in female than male gender. Muscle weakness, headache, and hypertension were the common clinical features. Hypokalemia (mean- 2.3±0.5 meq/l), high plasma aldosterone level (median 45 ng/dl), Low plasma renin activity (median- 0.25 ng/ml/hr) were the biochemical abnormalities observed in the study cases. Majority of the disease were in stage II (38.7%) at presentation, followed by stage I (21.5%). The median disease free survival was 25 months and overall survival was 36 months. Age at presentation and the disease stage were the significant covariates of the disease survival.

Conclusion: Aldosterone producing adrenocortical carcinoma is one of the rare types of functional adrenal malignancy. Any suspected case should undergo thorough clinical, radiological and biochemical evaluation. Surgery is the mainstay treatment and adjuvant therapy has no conclusive role in disease free survival. A large cases series and multicenter study could further add scientific evidence for management of the APAC.

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I. Introduction

Most of the adrenal tumor are benign non-functional incidentaloma.(1) Cortisol hypersecretion (9.2%) followed by pheochromocytoma (4.2%) and aldosteronoma (1.6%) is the most common hormonal abnormality in functional adrenal incidentaloma. The prevalence of the primary and secondary adrenal malignancy was 1.9% and 0.7% among adrenal incidentaloma.(2-4)

The incidence of the adrenocortical carcinoma (ACC) is 1-2 per million population per year which is more common in age group 40- 50 years. Approximately half to two third of the adrenocortical carcinoma is functional and fewer than 10% present with hyperaldosteronism (5,6) Aldosterone producing adrenocortical carcinoma (APAC) is responsible for about 20% of resistant hypertension in adult and is also called as mineralocorticoid hypertension.(7) The diagnosis of APAC is based on presence of hypokalemia, high serum aldosterone level, and suppressed plasma renin activity associated with adrenal computed tomography radiographic findings suggestive of malignancy(7-9)

Apart form a single review on the disease published by Seccia(10) on 2005, there is not another conclusive analysis of APAC cases. Many cases have been reported and published since then. We herein present a case managed in our institute, and have searched and analyzed the online data base (1955-2020) of APAC cases to review demographic characteristics, clinical and histological features, and treatment outcomes of the APAC.

II. Case Report

A 40 years gentleman with one year history of hypertension under medication presented with left sided lumbar pain and non projectile vomiting in April 2020. He gave history of weight loss of 21 kg in past 7 months and had polydipsia. There was no history of headache, muscle weakness, loss of consciousness, chest pain or shortness of breath. He was smoker and consumes mixed diet. On examination the blood pressure was 170/100 mmHg. Other general physical and systemic examination was unremarkable. The total blood count was within normal limit. Blood sugar was 120mg/dl. The

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blood sodium and potassium level was 145 meq/L and 2.0 meq/L respectively. The ultrasound abdomen revealed left adrenal mass which was confirmed by contrast computed tomography of abdomen. Contrast enhanced Computed tomography (CECT) [figure 1 (a)] revealed heterogeneously enhancing left adrenal mass that was 5x6x5.7 cm in size with well defined margin abutting the spleen, pancreas and posterior abdominal wall. The mass had displaced the left kidney inferiorly. There were no enlarged lymph nodes and metastatic lesion elsewhere in the body. The serum aldosterone concentration was 535 ng/dl (normal 2.52-39.2 ng/dl) and the plasma renin activity was 0.5 ng/ml/hr with aldosterone renin ratio (ARR) 1070 ng/dl/ng/ml-hr. The serum and urinary metanephrine and nor-metanephrine was normal. The serum cortisol level was 10.6 ng/ml (normal 6.4-21 ng/ml).

With diagnosis of aldosterone secreting adrenal tumor patient underwent transperitoneal laparoscopic left adrenalectomy, figure 1 (b) and (c). The intraoperative and postoperative period was uneventful. The histopathological report revealed adrenocortical carcinoma stage II with low mitotic count. The serum aldosterone level and Plasma renin activity done one week post surgery was normal. The CECT scan done 9 months post surgery had normal findings and patient was normotensive and normokalemic during the follow up.

III. Methods

The online literature search on aldosterone producing adrenocortical carcinoma was performed through Pub Med, Google scholar, and Scopus search engine. The study design of this review is depicted in figure 2. The cited references were cross examined for APAC cases. Full article with confirmed diagnosis of adult aldosterone producing adrenocortical carcinoma were included in this review. The patient's information pertaining patient demography, clinical presentation, biochemical investigations, histopathological findings, and treatment outcomes, and follow up details were extracted. A database was then constructed for statistical analysis.

The summary statistics; mean ± SD, median (and range) were calculated as appropriate after testing for normality. The difference in distribution of the categorical variables were evaluated using Chi Square test and $P<0.05$ was considered significant. The disease free survival time was defined as the time between initial treatment with curative intent and the first radiological evidences of adrenal tumor, local recurrence or metastasis. While overall survival interval was defined as the time between initial treatment (or initial diagnosis if initial treatment date is not available or if the treatment was not offered) to censoring at death or end of study. Kaplan Meier analysis was done to plot the disease free survival and overall survival. Cox regression proportional hazard analysis was performed to evaluate the correlation between disease variables and outcomes (disease free or overall survival)

IV. Results

We identified 100 cases from 71 academic articles on aldosterone producing adrenocortical carcinoma published in year between 1955 and 2020. Out of 100 only 93 were eligible for data base construction and analysis. More than half of the cases were from American region (after World Health Organization). The mean age of the study population was 45.7±15.0 (Range 17-79 years). Majority of the patients were between 17- 60 years (77.4%) with male female ratio of 1:1.4.The clinical presentation of the patients were listed in table 1. Muscle weakness (40%) and headache (14%) were the most common symptoms. Dependent edema and hypertension were the most common clinical signs. 33.3 % of the patient had locally advance (T3) or metastatic disease at presentation. The range of systolic and diastolic blood pressure in hypertensive patient were 130-270 mmHg and 72-150 mmHg.

The tumor size and weight range from 2.3 -35 cm and 18.5-1400gm respectively. The functional and physical characteristic of the tumor were listed in table 2. 84% of the patients became normotensive and had normal potassium postoperatively. 13% were on anti-hypertensive medications even after surgery. According to American Joint Committee on Cancer (AJCC) 8th edition the adrenocortical carcinomas of the study group were classified into Stage I-21.5%, Stage II-38.7%, Stage III-16.1%, and Stage IV- 17.2%. The staging details were not available in about 6.5% (n=6) cases. 89% of the patient underwent surgery irrespective of the disease stage.

Median disease free survival was 25 months (95% CI- 16.5-33.5) and median overall survival was 36 (95% CI- 18 - 54). Female had higher median overall survival than male (27 vs 18 months). Patient age > 60 years had significantly lower median disease free survival (14 months) than age group ≤ 60 years (30 months). The overall recurrence rate was 55%; Liver (35%), Lungs (22.5%), local recurrence (15%), Bones (12.5%) and abdominal lymph nodes (12.5%). In Cox regression analysis patient age at diagnosis, and the staging characteristics (size, lymph nodes involvement, invasion and distant spread) were the significant (p=0.05) covariates of the disease free and overall survival.

V. Discussion

The first case of adrenocortical carcinoma presenting with hyperaldosteronism was published in 1955 by Foye(10) and Jerome W. Conn further

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elaborated the spectrum of clinical features of hyperaldosteronism in 1965.(11) The largest series were published by Mouat and Kendrick in 2019 and 2002 respectively.(12,13) Aldosterone hypersecretion is the least common (0-7%) among the functional adrenocortical carcinoma (ACC). Though surgery remain potentially curative in early stage ACC, the recurrence and metastasis post surgery were common. The effect of functionality on tumor behavior and outcome is not quite predictable.(6, 14-16) The analysis and review was done to highlight and update the clinic-pathological behavior of the APAC.

Majority of the cases reports and case series reported were from United States and Europe reflecting possible publishing bias. Approximately half of the cases reports were published during 2000 to 2020. The age group and sex distribution of APAC is consistent with the adrenocortical carcinoma in general.(6) APAC cases were not reported in pediatric age group. Advance diseases (stage III and IV) were significantly higher in older age population in this series (71% in age >40 years and 56% in age > 60 years).

The demographic and biological features of the APAC remained same when we moved from series of 58 cases published in 2005 (10) to 93 cases in this review. Hypertension and hypokalemia were the most consistent sign of Conn's syndrome (17) and the later was commonly associated (83%) with muscle weakness. Contrary to the ACC in general (15), APAC was predominantly found on right side. CECT characteristics are the mainstay of diagnosing malignant adrenal mass. At cutoff of 4 cm, sensitivity and specificity of diagnosing malignant adrenal incidentaloma was 93% and 76%.(18,19)

The characteristic CECT findings of the APAC were heterogeneous enhancement, calcification, capsular invasion, irregular margin, local infiltration, renal or inferior venacava thrombosis, and metastatic lesion. The published research showed that the unenhanced CT attenuation ≤10 HU or a combination of tumor size ≤4 cm and HU ≤20 almost excludes adrenal malignancy.(20,21) There is increase probability of adrenal malignancy with the increase size of the tumor (55% for tumor >10 cm).(22) However, 26.7% of the reported APAC size in this analysis were ≤ 5 cm and 20% (2/10) of the stage IV tumor were size ≤ 5 cm. Positron emission tomography (PET) scanning with fluorodeoxyglucose (FDG) is valuable tool for diagnosing malignant adrenal tumor. PET-CT (with an SUV cutoff value of 3.1) has sensitivity, specificity, positive predictive value, and negative predictive values for malignant adrenal tumor of almost 100%.(23) Radiological imaging has limitation in diagnosing tumor less than 1 cm, and bilateral tumors. A systematic review of 38 studies found inappropriate management of 37.8% of primary aldosteronism cases when diagnosis was determined by CT/MRI alone.(24) Adrenal venous sampling for hyperaldosteronism is indicated to confirm unilateral disease if the CT scan is not abnormal, shows bilateral disease, or unilateral disease in patient age > 35 years.(25)

The primary hyperaldosteronism manifest with triad of hypertension, spontaneous hypokalemia, and metabolic alkalosis. Primary hyperaldosteronism is suspected when serum potassium < 3.5 meq/L, plasma renin activity less than 1 ng/ml/hr, and plasma aldosterone concentration ≥ 10ng/dl, and PAC/PRA >20 ng/dL per ng/mL/hour.(7, 21) The combination of a PAC > 20 ng/dLand a PAC/PRA ratio > 30 ng/dL per ng/mL/hour have a sensitivity and specificity of 90 percent for the diagnosis aldosterone producing tumor (26), and was consistent findings in this study. Study says 9-37% of the primary hyperaldosteronism can present with normal serum potassium level.(27) In this review 7%-9% of APAC had normal laboratory findings (normokalemic, normal PAC and PRA level). In normokalemic but hypertensive cases the diagnosis of APAC is confirmed with additional testing (23); 24 hour urine aldosterone, sodium, and creatinine on high sodium diet, fludrocortisone suppression testing, and or saline suppression testing can confirm the diagnosis in suspicious cases.

Most of the adrenocortical carcinoma are sporadic and some are components of several hereditary cancer syndrome.(28) Less than 10% ACC present with virilization alone or feminization or hyperaldosteronism.(5, 28) 70% of the reported APAC in this study were pure aldosterenoma and 30% were mixed (hyperaldosteronism with hypercortisolism-20%, hyperaldosteronism with hypercortisolism and hyperandogeniemia-7%, and hyperaldosteronism with hyperandrogenemia-3%).

It is not always easy to confirm benign and malignant adrenal tumors based on histopathological features. The differentiation of malignant form benign adrenal mass essentially depends on local invasion and distant metastasis. Tumor size larger than 5 cm and greater than 100 gm has malignant potential. Weiss criteria is the simple and reliable system to diagnose malignant adrenal tumor with threshold of total score ≥ 3. The five criteria used in the updated Weiss system include: >6 mitoses/50 high-power fields, ≤25 percent clear tumor cells in cytoplasm, abnormal mitoses, necrosis, and capsular invasion.(26-28) In this review 80% (55/75) of the APAC were larger than 5 cm, 60% (24/35) were larger than 100 gm and 57 % (33/58) had mitotic count > 20/high power field. Histopathological and molecular diagnosis of APAC often has limitations. A total of three cases of adrenal tumor diagnosed as adenoma presented with metastatic adrenocortical carcinoma one and half year after primary surgery. (10,29,30) There are several marker(alpha-inhibin, Melanin A, SF-1) that can identify the origin of adrenal tumor as well as differentiate the benign from malignant

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adrenal tumor (Ki67 proliferation index, overexpression of *TP53*, IGF-2, and cyclin E) however, they are not sufficiently discriminatory. (31,32).

According to German ACC registry the fiver year disease specific survival of adrenocortical carcinoma for stages I, II, III, and IV were 82%, 61%, 50%, and 13% respectively.(33) We found that the aldosterone producing adrenocortical carcinoma had more dismal prognosis with mean and median disease free survival of 49 months and 25 months respectively. Incoherence in the stage specific median disease free survival (Stage I < Stage II) might be due to variable follow up duration of the heterogeneous and small number of cases in each stage (figure 3 and 4). Occult micro metastasis is presumably responsible for the early recurrence and disease progression.(34) In this series the recurrence rate among the size group of 0-5 cm; 6-10 cm; 11-15 cm; and > 15 cm were found to be 50%, 55%, 42%, and 100% respectively.

Surgery is the mainstay treatment for potentially resectable stage I to stage II adrenocortical carcinoma. (35,36) Routine lymphadenectomy had shown improved recurrence free survival and decreased disease specific death (hazard ratio [HR] 0.54, 95% CI 0.29-0.99).(37) Open surgery is recommended method of surgery for ACC.(38,39) European clinical practice guideline recommends laparoscopic surgery for adrenal tumor less than 6 cm in absence of local invasion.(36) However studies had shown comparable outcome from open and laparoscopic adrenalectomy even for tumors upto 10 cm.(40,41)

We found patient age at diagnosis and staging characteristics significant ($p<0.05$) predictors of disease free survival and overall survival. Metastasis at presentation; capsular, vascular, and adjacent organ invasion; tumor necrosis; mitotic activity were proven significant covariates of disease specific survival in adrenocortical carcinoma. Markers of proliferation like mitotic rate, and Ki67 expression has prognostic value as well.(42,43) Recurrence rate of APAC was 55% which is comparable with the recurrence rate of ACC (60-80%) in general. Liver and lungs were the two most common site of APAC recurrence. Adjuvant mitotane therapy has shown improved recurrence free survival and indicated for histologically high-grade disease, intraoperative tumor spillage or fracture, and some large tumors with vascular or capsular invasion.(44-46) However National Comprehensive Cancer Network (NCCN) guidelines suggest that mitotane be "considered" (category 3 recommendation) for all patients with resected low- or high-grade localized ACC regardless of stage or tumor size.(47) We found no uniform criteria of using adjuvant therapy in this study 14/93. Cytotoxic chemotherapy (etoposide, doxorubicin, and cisplatin) in combination with mitotane is suggested in rapidly progressive, high grade and metastatic disease.(48-50) Post operative radiation therapy is beneficial in local control of disease and suggested in incompletely resected ACC, stage III disease, those who have tumor spillage, and for all patient with high grade ACC.(36)

VI. Conclusion

APAC is a rare adrenal malignancy that requires meticulous evaluation before offering definitive surgery. Recurrence rate is high with dismal prognosis. Further research on tumor biology, natural history, and treatment outcome can add more to the understanding of this rare variant of adrenal malignancy.

Declarations

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Conflicts of interest/Competing interests
We declare no conflict of interest or competing interests

Ethics approval
Not applicable

Consent to participate
Not applicable

Consent for publication
All authors consent to publication of this paper

Availability of data and material
All data is available for review by contacting Dr. Bikash Thapa

Code availability
Not applicable

Authors' contributions
BT and BB both has made substantial contributions to the conception or design of the work; the acquisition, analysis, interpretation of the data, and manuscript writing.

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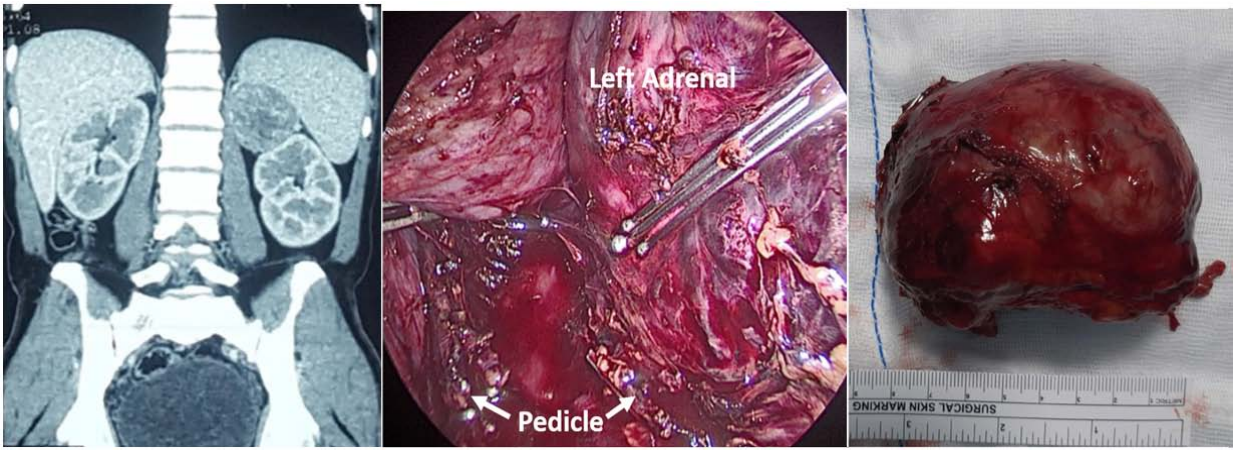
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(a) (b) (c)

Figure 1: (a) CECT abdomen of Left Adrenal tumor; (b) Laparoscopic adrenalectomy-division of pedicles; (c) Resected specimen of left adrenal tumor

Figure 2. Study Design

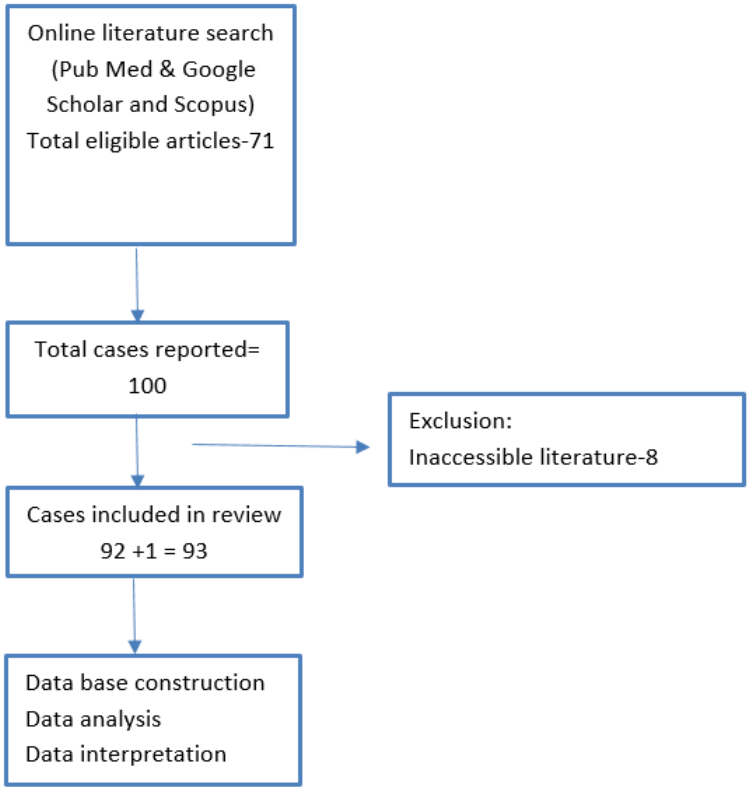


Figure 2: Study Design

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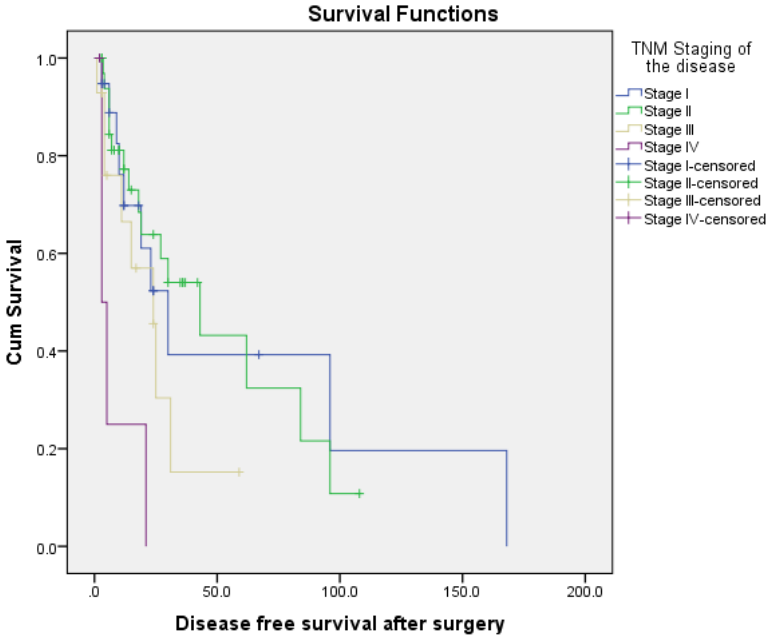


Figure 3: Disease free survival (DFS) in different stages of APAC

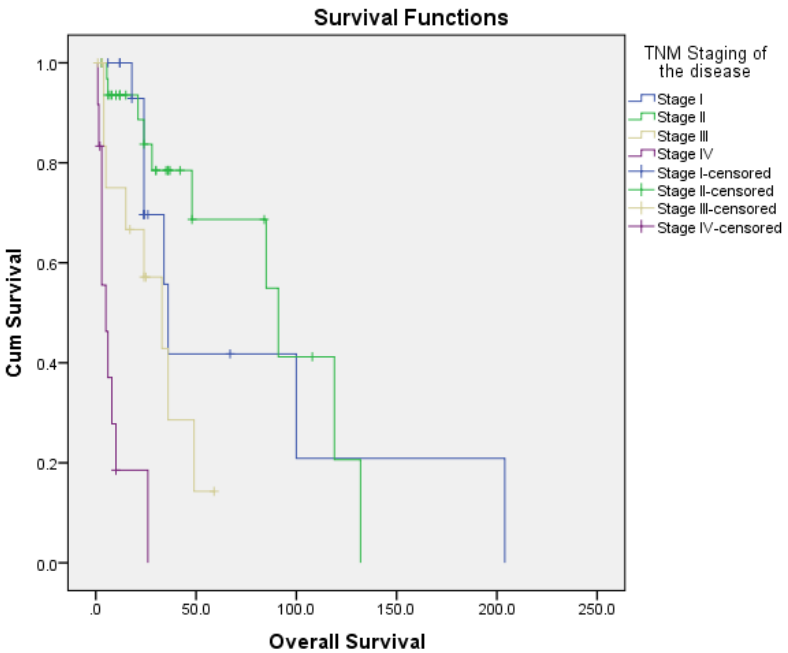


Figure 4: Overall Survival (OS) in different stages of APAC

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Table 1: Clinical and Biochemical presentation of the Aldosterone producing Adrenocortical Carcinoma

Clinical and Biochemical Details	Incidence and Measurement
Hypertension	93.4% (mean 184±34/ 107±18 mmHg)
Hypokalemia	93.4% (mean- 2.3±0.5 meq/l)
Muscle weakness	40%
Features related to sodium retention (polyuria, nocturia, dependent edema)	18%
Headache	14%
Locally advance disease (T3)	16.1%
Metastatic diseases	17.2%
Serum Aldosterone (ng/dl)	Median-45 (IQR; 26.9-107.5)
Plasma renin activity (ng/ml/hr)	Median-0.25 (IQR; 0.12-0.72)
Aldosterone Renin Ratio (ARR) (ng/dl-ng/ml/hr)	Median 165 (IQR; 43-620.8)

Table 2: Characteristics of the aldosterone producing adrenocortical carcinomas

Tumor details	Incidence and Measurement
Pure aldosterone secreting	68 % (n=63/93)
Mixed hormonal type	29% (n=27/93)
Right side APAC	60.2% (55/93)
Left side APAC	37.6% (34/93) * Bilateral - 2
Size of (Mean)	8.7±5.3cm ; IQR 5-11.7 cm
Weight (Median)	180 gm; IQR 70-470 gm
Local Invasion (T3)	17%; (n=16/70)
Venous Thrombosis	3.2%; (n=3/70)
Regional lymphadenopathy	9.7% (9/70)
Metastasis	16% ; (n=15/71)
Surgery performed	85% (n=80/93): Open 90 %; Laproscopic-10%

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Adjuvant Surgical Oophorectomy Efficacy According to Hormonally-Determined Menstrual Cycle Phase

By Richard R. Love
Marquette University

Abstract- *Purpose:* While there is now considered to be no significant outcome impact of the timing of breast surgery in the menstrual cycle of premenopausal women with breast cancer, the data with respect to adjuvant surgical oophorectomy in women with breast cancer have received limited exposition and attention. In a trial investigating the timing of surgical oophorectomy in women with metastatic disease, we observed a trend for poorer overall survival in women in women in prolonged follicular phases of the menstrual cycle, with low progesterone levels.

Methods: The data from a previously reported adjuvant randomized clinical trial addressing the timing of surgical oophorectomy in the menstrual cycle have been examined in detail, presenting here new data from pre-planned secondary analyses. Multivariable Cox models were used.

Keywords: *adjuvant therapy, surgical oophorectomy, tamoxifen, menstrual cycle timing.*

GJMR-I Classification: *NLMC Code: WJ 768*



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Adjuvant Surgical Oophorectomy Efficacy According to Hormonally-Determined Menstrual Cycle Phase

Short Title: Surgical Oophorectomy Plus Tamoxifen

Richard R. Love

Abstract- ***Purpose:*** **While there is now considered to be no significant outcome impact of the timing of breast surgery in the menstrual cycle of premenopausal women with breast cancer, the data with respect to adjuvant surgical oophorectomy in women with breast cancer have received limited exposition and attention. In a trial investigating the timing of surgical oophorectomy in women with metastatic disease, we observed a trend for poorer overall survival in women in women in prolonged follicular phases of the menstrual cycle, with low progesterone levels.**

Methods: **The data from a previously reported adjuvant randomized clinical trial addressing the timing of surgical oophorectomy in the menstrual cycle have been examined in detail, presenting here new data from pre-planned secondary analyses. Multivariable Cox models were used.**

Results: **In this adjuvant trial, among randomized subjects, women in prolonged follicular phases (>14 days) with low progesterone levels at the times of their surgeries derived minimal survival benefit from surgical oophorectomy plus tamoxifen treatments. The differences at 5 years compared with luteal phase patients with elevated progesterone levels, were, for disease free survival (DFS) 20% less, multivariable p=0.02; and for overall survival (OS)15 % less, multivariable p=0.036.Other sub-group comparisons in this trial support these findings.**

Conclusion: **Because one third of women undergoing surgical oophorectomy have worse outcomes if they are in prolonged follicular phases at the time of their surgeries, major outcome benefits are suggested to accrue to women undergoing this treatment in hormonally confirmed follicular and luteal menstrual cycle phases.**

Keywords: adjuvant therapy, surgical oophorectomy, tamoxifen, menstrual cycle timing.

I. Background

Globally, 500,000 premenopausal women annually present with hormone receptor positive breast cancer. For these women with operable disease, surgical oophorectomy or ovarian function-suppression plus tamoxifen are the most effective adjuvant therapies[1, 2, 3]. Secondary analysis of women in a clinical trial receiving surgical oophorectomy treatment suggested that if the oophorectomy surgery was performed during the luteal phase of the menstrual cycle, long term disease-free and overall survival were significantly better than if the surgery was done in the follicular phase[4]. We have conducted and reported two phase III trials, one in metastatic and one in adjuvant patients, to investigate this finding in which we presented some data from secondary pre-planned analyses of outcomes according to hormonally confirmed menstrual cycle phases[5, 6].

In the reported metastatic study, the primary analysis showed that the randomized luteal history (beyond day 14 since beginning of last menstrual period) and follicular history (from beginning day of menstrual period through day 14) surgical oophorectomy patients had equivalent overall survival ($L^H=F^H$ for OS) [6]. In pre-planned analyses of all randomized patients with hormonal levels, based on confirmed hormonal status L^H patients with high progesterone (Pg) levels had better overall survival than L^H patients with low progesterone levels: 27 versus 17 months (multivariable p=0.14) [6].

The primary analysis of the adjuvant trial showed that luteal phase by history(L^H)patients, did not have better survival than patients in historical follicular phase, F^H, by strong trends (multivariable overall survival p=0.05)[5, Figure 2]. That is, contrary to the study hypothesis, L^H patients had worse disease-free (DFS) and overall survival. One exploratory analysis result was presented: In patients randomized to receive mid-luteal phase surgery, patients with higher Pg≥(2ng/ml) had better DFS than those with < 2ng/ml (aHR 0.53; 95% CI 0.34 – 0.84; p=0.006) [5].

This communication reports new data from the adjuvant study, other data, and interpretations relevant to our findings.

II. Methods

Reports of two phase III clinical trials of surgical oophorectomy plus tamoxifen (SO +T) in adjuvant and metastatic populations have been published with the detailed designs, eligibilities, IRB approvals, treatments, laboratory studies and statistical methods[5, 6]. A

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consort figure for the adjuvant trial populations that are the subject of this report is presented in figure 1. In this study, 383 patients (of 509 randomized because they would not be by history in luteal phase-that is beyond day 14 since last menstrual period began-for the next 1-6 days) had: 1. menstrual cycle history data; 2. day-of-surgery blood hormone level determinations showing levels of <2ng/ml or 5 or greater ng/ml; and 3. complete follow up data. In the current report, Cox model subgroup analyses are based on data from these 383 subjects. In this adjuvant trial are three subgroups of the combined two randomized groups, defined by menstrual cycle dates history and hormonal levels on the dates of oophorectomy surgery (Figure 1). In this report luteal phase history patients with progesterone levels of >=2 but < 5 ng/ml have been removed to provide information on the most well-defined follicular and luteal groups. The three subgroups of patients are: Follicular phase patients-by-history with progesterone levels <2ng.ml—"F^H confirmed"; luteal phase-by-history patients with progesterone levels = >5ng/ml—"L^H confirmed"; and luteal phase-by-history patients with progesterone levels <2 ng/ml or prolonged follicular phase patients, or anovulatory patients—"L^H unconfirmed". If the less well-defined subgroup of 49 luteal phase by history patients with progesterone levels of between 2 and 5 ng/ml, half of whom were in follicular phase by history, is included as confirmed luteal phase patients, the results reported here are unchanged.

A multivariable Cox proportional hazards model was used to estimate adjusted hazard ratios between pairs of luteal phase-confirmed and unconfirmed, and luteal phase-unconfirmed and follicular phase-confirmed groups. In these analyses, the other prognostic variables included were: adjuvant radiotherapy, stage, nodal status, tumor size and patient age. As in the report of the primary analyses "proportionality assumptions for the Cox models were assessed by diagnostic plots of the scaled Schoenfeld residuals and log-minus-log survival plots. Substantial deviations from proportionality were not observed."

In all comparisons of these randomized patient subgroups, treatment group assigned at random assignment was compared regardless of the treatment received(5). P values are reported for completeness: because these are exploratory/explicatory analyses, they cannot be considered hypothesis testing results.

III. Results

In pre-planned analyses based on history-confirmed hormonal status, the explanation for the definitive primary analysis result is clear.[The result described above: luteal phase by history patients, did not have better survival than patients in historical follicular phase, (multivariable overall survival p=0.05)].

The subgroups of unconfirmed and confirmed luteal phase status had markedly different survival experiences. Among all combined randomized patients, L^H patients with high progesterone levels ("L^H confirmed", n=150) had better survival than L^H patients with low progesterone levels ("L^H unconfirmed", n=112): the differences at 5 years were for disease free survival, 20%, HR=1.60 (95% C.I.:1.07-2.38), multivariable p=0.02; and for overall survival,15%, HR=1.63 (95% C.I. 1.03-2.56), multivariable p=0.036.The differences between F^H confirmed (n=121) and L^H unconfirmed (n=112) for both DFS and OS were marginally greater.

Among all randomized L^H patients: those with high progesterone had better survival than those with low progesterone (p=0.001).

IV. Discussion

a) Interpretation

The reported new results show that in pre-planned exploratory analyses in a second phase IIIadjuvant study, among the randomized patients, those patients found to be in prolonged follicular phase (that is beyond day 14 of their menstrual cycle) with low progesterone levels at the times of their oophorectomy surgeries, showed limited evidence of long-term disease-free and overall survival benefits, despite receiving additionally tamoxifen treatment. A conservative interpretation is that these observations define a new hypothesis. The major limitation of the results is that they are secondary study findings, whose statistical significance cannot be reliably estimated. The major strength of the results is that they have been found among randomized patients in two studies (5, 6).

As I have previously written, which critically bears repetition here: "the corollary to this new observation is that were such unconfirmed luteal phase patients (in these and other studies usually one third of patients) identified a priori, and not treated with this surgery at this time, those patients treated in hormonally-confirmed follicular or luteal phases would be expected to have better outcomes that the average outcomes that are seen from this treatment applied to all premenopausal women regardless of hormonal status and menstrual cycle phase. Thus, if in a high-risk group of women with operable breast cancer receiving SO (+T) (without paying any attention to their menstrual cycle history and blood levels of progesterone), 65% have no recurrence in 5 years; if patients have their SO in the first half of their menstrual cycles by history and with confirmation showing low progesterone blood levels, 72% will have no recurrence in 5 years. This increased level of benefit from appropriately timed SO, suggests that timed SO+T is more effective than GnRH + tamoxifen, and equivalently effective or better than GnRH + aromatase inhibitor"[2].

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Further discussion is warranted. The adjuvant therapy primary analysis results are definitive that patients in historical luteal phase are extremely unlikely to have better outcomes than patients in historical follicular phase[5]. The data presentation in the primary publication, while reporting the one exploratory analysis finding of better DFS in confirmed luteal versus unconfirmed luteal patients, was conservative in combining all patients in the trial, randomized and non-randomized. Because for unexplained reasons the nonrandomized patients enjoyed better-than-expected survival, the striking finding in the randomized patients reported here above, was not found. Differences in outcomes in non-randomized versus randomized groups of patients have been repeatedly observed, explained by selection bias, so these findings are not unusual, and are the basis for the current report emphasizing the clear explicatory findings for the primary trial result, and their consistency with the results of the metastatic trial[6, 7].

b) *The hypothesis-generating study data and their interpretation*

The previous hypothesis-generating study also deserves comment[4]. The discussed adjuvant study was designed to test the hypothesis that surgery during historical luteal phase (L^H) of the menstrual cycle had superior efficacy [5]. This design followed from secondary exploratory analyses of an adjuvant study of surgical oophorectomy plus tamoxifen, which strongly suggested that L^H was superior [4]. How can the findings from these 3 studies be reconciled [4, 5, 6]? The hypothesis-generating study categorized patients as being F^H or L^H based on reported "day one' of their menstrual cycle at the time of their breast and surgical oophorectomy surgeries (done under the same anesthesia on the same days) [4]. Without careful discussion of this time point, we assumed that day one of the menstrual cycle according to the Vietnamese women was the day they began their menstrual bleeding. In discussions with Vietnamese, now American immigrant women, who had resided in Vietnam during the same period the study was conducted and who were in the same age range as the study subjects, these women indicated that their definition of day one of their menstrual cycle when they were in Vietnam, was the day they had no further menstrual bleeding. In exploring this possibility with the 3 Vietnamese investigating physicians, they agreed that this misunderstanding was very plausible. If we assume that this alternative definition was operative in the study for at least some of the women and their reported LMP dates, then the classifications made in the reported secondary analyses were wrong and the conclusion that L^H oophorectomy surgery gives better outcomes was grounded in mis-classifications[4]. If the conclusions from the new adjuvant (reported here) and metastatic studies are correct and represent 'truth', given this different definition, theoretically the original study might be expected to show the same result. This is because if we make the assumption that day of surgery in the menstrual cycle is always $F^H + 6$, and $L^H + 6$, new L^H defined patients will all be beyond day 21 in their cycles and more likely to be in hormonally-confirmable luteal phase (which patients in the new adjuvant and metastatic studies did well), and new F^H patients will include true F patients, and prolonged F patients (or "L^H unconfirmed"), the latter sub-group of whom did badly in the new studies as discussed above [5, 6]. Thus, conceivably the original study could in fact, with appropriate definitions of day one of the cycle, give the same L^H (very likely confirmable) better result than in a combined group of F^H (likely confirmable) and F^H (prolonged) (=L^H unconfirmed). When re-analyses were done under these new definitions, no DFS and OS differences were seen between the two redefined L^H and F^H groups. Given the now-likely poor and mixed patient and physician definitions quality of the menstrual cycle history data in this study, this revised result is not surprising [4].

c) *Menstrual cycle hormonal biology which may explain the new surgical oophorectomy timing findings*

What biological explanation is consistent with the summarized data that prolonged follicular phase patients derive minimal benefit from surgical oophorectomy plus tamoxifen treatments? To begin, it is important to note that typical human levels of progesterone are < 1 nanogram (ng) to about 20 ng/ml, while levels of estradiol are 50-200 picograms (pg)/ml. Thus, a typical luteal phase level of progesterone of 10 ng/ml is 50-fold greater than a typical estradiol level of 200pg/ml. When ovulation is delayed, there are sustained high estradiol levels for as many as 14 days or more. Indeed, in our data, the mean estradiol levels on the day of surgery were higher in the prolonged follicular phase (or L^H unconfirmed) group of patients than in the confirmed follicular patients. In the surgical oophorectomy situation, no progesterone "rescue" follows. In normal follicular phase, estradiol exposure is short, and in normal luteal phase exposure to some duration of progesterone "rescue' occurs before the oophorectomies. In anovulatory patients, the high and prolonged estradiol levels stimulate growth of micro-metastases as the last hormonal signal that these lesions receive. When it is done during the follicular phase of a cycle, oophorectomy appears to send a strong anti-growth signal. A flare of the metastatic disease is often seen about 7-10 days after starting the treatment. This kind of flaremay be what is occurring with follicular phase oophorectomy. In a normal luteal phase, oophorectomy may have relatively small acute effects because of the last signals, which are high progesterone level-mediated.

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The data from our two trials collectively are showing extraordinarily limited effects (in the sense of limited/no benefit from oophorectomies plus tamoxifen) in designated prolonged follicular phase-low progesterone patients from limited-time hormonal differences, while showing strong effects when this surgery is done in usual follicular or high progesterone luteal phases.

d) Other data which bear on the new hypothesis/ interpretations

There are five observations which validate our findings because they are consistent with our observation of limited benefit from prolonged follicular phase patient-surgical oophorectomy. First, there are immediate and severe vasomotor symptoms in women following surgical oophorectomy. Second, men with metastatic prostate cancer have immediate responses with decreases in bone pain following orchiectomy. Third, Badwe et al. found that short-term adjuvant, parenteral peri-operative progesterone, which was associated with better outcomes in axillary node positive patients [8]. These results are consistent with our observation of absence of benefit with low-progesterone prolonged follicular phase patients. Four, the peaks of hazards for recurrence of breast cancer at 2-3 years post diagnosis and treatment have most strongly been related to peri-operative changes. Baum et al. suggested that minor peri-operative changes can lead to major long-term effects [9, 10]. Finally, other peri-operative conditions of limited duration have been suggested to have major longer-term impacts[11].

V. Conclusions

The potential greater efficacy with timing in the menstrual cycle of the surgical oophorectomy would make this treatment combined with tamoxifen, already the first global option adjuvant treatment based on efficacy, practicality and cost-efficacy, an even more compelling therapy [2, 3]. A practical interpretation is that acting on this observation and performing surgical oophorectomies whenever possible in hormonally confirmed follicular or luteal phases appears very unlikely to be harmful in terms of efficacy. Were surgical oophorectomy plus tamoxifen adjuvant therapy widely promoted and applied across the world, a reasonable estimate is that 100,000 women a year would be saved, women who otherwise would get little or no effective adjuvant treatment (12). Were timed surgical oophorectomy widely promoted and applied as host-personalized therapy, an additional 20,000 women per year might be saved.

If a conservative position is taken with regard to these timing data, that the case that women in prolonged follicular phase with low progesterone levels benefit little from oophorectomy done at this time, has but limited support, then the rational approach is to do a clinical trial of timed SO+T (excluding prolonged follicular phase confirmed women) vs. GnRH/LHRH +T (or aromatase inhibitor). With provision of the drugs, this would not be a difficult trial to do, certainly with low- and middle-income county participation.

Declarations

Ethics approval and consent to participate

The data reported in this manuscript have come from previously approved clinical trials. The approvals have been both in the home countries of the patients and in the United States.

Consent for publication

With this submission the sole author implicitly provides consent to publish.

Availability of data and material

The primary study data and files are available. ClinicalTrials.govnumbers, NCT 00201851 and NCT00293540

Competing interests

The author reports no conflicts of interest.

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Authors' contributions

The sole author is responsible for all parts of this report.

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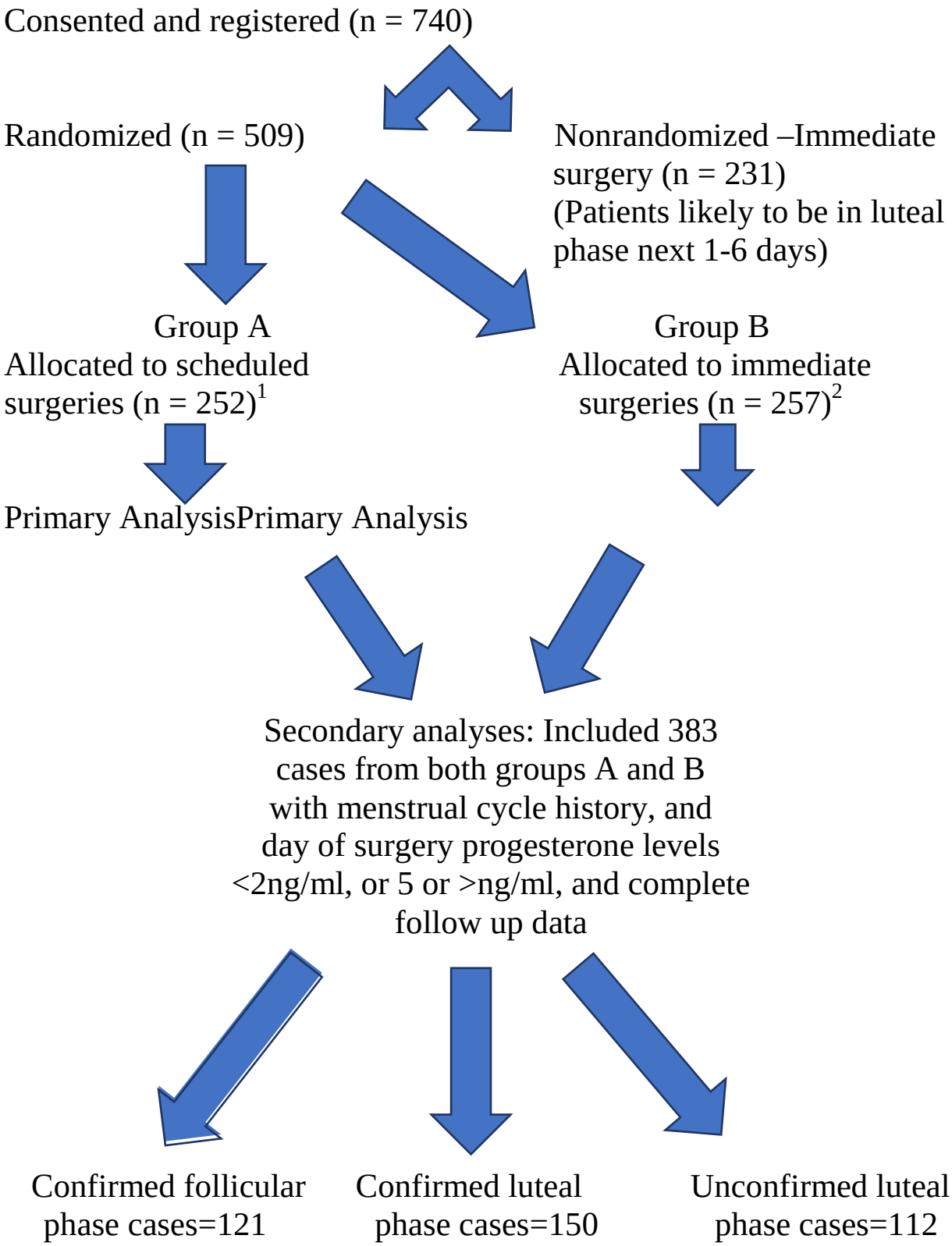


Figure 1: CONSORT diagram for the trial.

[1]Scheduled surgeries were assigned to be in mid-luteal phase by history. For these patients, by history, 96% of surgeries were done in luteal phase.

[2]For these patients, 66% had surgeries by history in follicular phase

These percentages make clear the rationale for the secondary analyses based on the better menstrual cycle phase status of study patients using day of surgery progesterone levels.

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Alternatively, you can download our basic template from https://globaljournals.org/Template

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Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

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- Submitting a manuscript with pages out of sequence.
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- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
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References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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