Sexual dysfunction following rectal cancer surgery

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Running Title: Sexual dysfunction in rectal cancer

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ABSTRACT

Sexual and urological problems after surgery for rectal cancer are common, multifactorial, inadequately discussed, and untreated.

The urogenital function is dependent on dual autonomic sympathetic and parasympathetic innervation and four key danger zones exist that are at risk of nerve damage during colorectal surgery: one of these sites is in the abdomen and three are in pelvis. Many studies have demonstrated that the identification and preservation of autonomic pelvic nerves can reduce the incidence of sexual dysfunction. Intraoperative neuromonitoring can aid sparing of the autonomic nerves but indications are not yet standardized.

This review article systematically assesses the epidemiology of sexual dysfunction following rectal cancer surgery, describing the anatomical basis of autonomic nerve preserving techniques and exploring the scientific evidence available to support the laparoscopic or robotic approach over open surgery.

INTRODUCTION

Background:

Conventionally, outcome assessments in colorectal cancer include mortality, morbidity, disease recurrence, and long-term survival. However, patient-reported outcomes (e.g., quality of life) are now also regarded as key measurements in assessing outcomes of intervention.

Sexual problems after surgery for rectal cancer are common, multifactorial, inadequately discussed, and untreated [1].

Patients feel that sexual function is relevant and needs to be discussed [2-3] and they also consider a physician's responsibility to initiate discussions about sexual function both before and after surgery [4].

More than 50% of patients do not perceive they receive satisfactory preoperative information [5] and in female patients sexual dysfunction following rectal cancer surgery is reported to be discussed in only 9% of the cases [1]. Surprisingly, less than 10% of the patients were referred to a specialist following development of sexual dysfunction [6].

Aim of this review is to systematically assess the epidemiology of sexual dysfunction following rectal cancer surgery, to describe the anatomical basis of autonomic nerve preserving techniques and to explore the scientific evidence available to support the laparoscopic or robotic approach over open surgery.

Definitions:

Male Sexual dysfunction is defined as inability to achieve a satisfactory sexual relationship which may involve inadequacy of erection or problems with ejaculation [7].

Erectile dysfunction or impotence is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [8].

In women sexual dysfunction has been reported as dyspareunia, decreased lubrication, or inability to achieve orgasm. A clinical definition of Female Sexual Dysfunction is "the persistent/recurring decrease in sexual desire, the difficulty/inability to achieve an orgasm, and/or feeling of pain during sexual intercourse [9].

Anatomical basis:

Understanding the causes of sexual dysfunction following rectal surgery requires an understanding of the complex anatomy of the pelvic nervous system. Nerve injury can occur via direct injury or via vascular damage to the vasa nervosa. The blood supply to the nerves enters laterally and can be disrupted with traction or devascularization.

Sexual and urinary functions are dependent on dual autonomic (sympathetic and parasympathetic) innervation. The sympathetic component arises from the thoracolumbar trunk (T12 to L2) to the superior hypogastric plexus that lies in front of the aortic bifurcation. The sympathetic fibers enter the pelvis as a pair of hypogastric nerves running 1 to 2 cm medial and parallel to the ureters along the posterior and superior parts of the mesorectum before reaching the inferior hypogastric plexus. The parasympathetic fibers of the ventral sacral nerve branches (S2 to S5) run together with the pelvic splanchnic nerves to the inferior hypogastric plexus, where they converge with a small segment of the autonomic fibers from genitourinary organs. Damage of the superior hypogastric plexus and the hypogastric nerves causes bladder instability (loss of relaxation) and retrograde ejaculation or loss of ejaculation, whereas damage of the inferior hypogastric plexus and sacral branches leads to difficulties in bladder emptying (loss of contraction) and impotence. In women, the increased blood flow to the vagina and vulva, causing vaginal lubrication and swelling of the labia and clitoris, is also under the predominant control of these parasympathetic nerves. The sympathetic nerves are responsible for emission and the rhythmic contractions of the genital ducts and organs during orgasm.

METHODS

Data sources and search strategy:

After the development of a review protocol in compliance with the PRISMA guidelines for reporting systematic reviews and meta-analysis of observational studies [10], a comprehensive literature search of Medline, Scopus, Web of Science, Embase and the Cochrane Central Register of controlled trials was performed with no language, publication date or publication status restrictions.

An extensive search was conducted using the search terms: “nerve sparing”, “autonomic nerve preserving”, “*rectal surgery”, “proctectomy”, “rectal cancer”, “total mesorectal excision”, “sexual

dysfunction", "impotence", "urogenital dysfunction". The last search was run on October 12th, 2016.

The reference list of the retrieved articles was searched to identify additional eligible studies.

Eligibility criteria and study selection:

Inclusion criteria were as follows: (1) studies evaluating sexual function in patients undergoing rectal resection for cancer; (2) studies reporting the indication for surgery and type of surgical approach; (3) total mesorectal excision performed according to standardized technique, (4) sexual and urinary dysfunction reported separately (5) postoperative follow-up of 12 months minimum, (6) complete follow-up data and losses clearly reported.

Reviews were only checked to find further relevant studies, and when the same author and institution published the same case series in different articles, only the most recent paper was evaluated.

Two reviewers independently assessed the reports for eligibility at title and abstract level. In case of discrepancies, a third author was consulted and agreement was reached by consensus.

Data extraction and methodological quality appraisal:

Two authors independently retrieved the data from each included study filling an electronic database. For studies that reported insufficient data, the corresponding authors were contacted for further information, if no response was obtained after two reminders the study was excluded from the review.

The quality of the included studies was evaluated by the Newcastle-Ottawa Scale (NOS) [11]: on a scale of 9, a greater score was considered to be an indicator of better quality.

Statistical analysis:

Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary measures for dichotomous outcomes while Weighted Mean Difference (WMD) and 95% CI were used for continuous outcomes. They were calculated with the fixed effects Mantel-Hænzel model

Statistical analysis was performed using STATA 12 statistical software (STATA Corp, College Station, Texas, USA).

RESULTS:

An increasing number of studies assessed the incidence and prevalence of sexual dysfunction over the last 30 years, as demonstrated in Figure 1. Several diagnostic tools are available to diagnose and monitor urogenital dysfunction following rectal cancer surgery; these are summarized in table 1.

Epidemiology:

The prevalence of sexual dysfunction is high following rectal cancer surgery.

The majority of the studies published on the topic unfortunately concentrated on the prevalence of male sexual dysfunction (Figure 2) [1, 6, 12-37], without recognizing that the disorder can be already present in a significant number of patients before surgery. Significant heterogeneity in the prevalence of sexual dysfunction following surgery for rectal cancer is reported in the literature, with rates between 5 and 90%.

Several studies have prospectively evaluated the incidence of sexual dysfunction after surgical treatment for rectal cancer and the figures are shown in Figure 3 [5, 6, 38-49].

Female sexual dysfunction prevalence ranges from 65 to 80% in recent observational studies [50 45].

Four key zones at risk of nerve injury during rectal surgery:

Four danger zones exist that are sites ‘at risk’ of nerve damage during colorectal surgery. One of these sites is in the abdomen and three are in pelvis: these have been comprehensively described by Lindsey et al [51].

1. Origin of the inferior mesenteric artery: the purely sympathetic nerves of the superior hypogastric plexus are vulnerable to injury at this zone. The risk occurs when the inferior mesentery artery pedicle is ligated flush with the aorta. It is advised to control the artery 1 to 2 cm from the aortic origin.

2. Posterior mobilization of the rectum: the damage is purely sympathetic at this level, as the nerve erigentes have not yet joined the bundle. Anatomic dissection of the rectum is carried out in the loose areolar connective tissue immediately outside the fascia propria of the rectum, and the nerves

lie just outside this “holy” plane. Injury can occur if the correct plane is not entered; the dissection is not carefully performed under direct vision, or if blunt dissection is used or bleeding occurs.

3. Lateral dissection of the rectum: the second pelvic zone at risk of autonomic nerve damage is the lateral plane of rectal dissection. Dissection performed away from the mesorectal plane may injure the pelvic plexuses, especially if excess traction is placed on the rectum, tenting the plexus superiorly and medially.

4. Anterior dissection of the rectum: the third pelvic danger zone is encountered during the anterior part of the dissection. This is a very narrow space between the rectum and the prostate and seminal vesicles. During deep dissection of the anterior extra-peritoneal rectum away from the prostate and seminal vesicles, or during haemostasis in this difficult-to-access area, the cavernous nerves are at risk. This is probably where most parasympathetic nerve damage occurs, and may explain why impotence is more common the deeper the pelvic dissection goes.

The pelvic dissection, particularly during the anterior and lateral mobilization of the rectum, is where the damage to the autonomic nerves is most likely to occur, and it is where new techniques and devices are more likely to impact on functional results [52]. The technique of transanal total mesorectal excision (TaTME) holds interesting premises, but follow-up data are awaited. Surgeons need to be aware of the potential damage of collateral heat spread to the nerves [53]; however, no evidence exists to date, to support the selective use of any integrated energy device for rectal dissection.

Disagreement still exists on the need to resect Denonvilliers’ Fascia with the specimen in rectal cancer surgery [54]. Some authors prefer to leave it intact on the prostate in order to minimize the risk of damage to the neurovascular bundles [55], however other surgeons routinely remove this fascia together with the specimen for oncological reasons [56]. The authors’ practice is to leave Denonvilliers’ Fascia intact on the prostate only in early posterior tumors. Adequate removal of the tumor is the first priority of surgery, and the pelvic nerves should be sacrificed if necessary.

Laparoscopic Vs Open Surgery:

The magnified view offered by laparoscopic surgery could lead to improve sexual function outcomes helping the surgeon in an easier detection of pelvic nerves, even if adequate experience is mandatory. The available data are limited, but suggest that neither form of surgical approach demonstrates superiority in preservation of sexual and bladder function [57].

Despite increasing evidence for the clinical benefits of laparoscopic rectal surgery, the dissemination of this technique has been slow; with main technical constraints for a swift uptake being a prolonged learning curve [58] and a high conversion rate [59].

Three systematic reviews have concluded that there is no significant difference in male and female sexual dysfunction between laparoscopic and open groups [60-62] and comparative studies are summarized in table 2 [20, 39, 42, 46, 62-65].

Laparoscopic Vs Robotic Surgery:

Only few studies have compared the incidence of sexual dysfunction in patients undergoing laparoscopic and robotic surgery. The available studies are shown in table 3 [30, 36, 66-68]. No preferred approach exists to date and further studies are needed with long-term follow-up.

The role of Radiotherapy:

The effect of neoadjuvant radiotherapy on sexual dysfunction following multimodality treatment for rectal cancer has been investigated by several studies (table 4) [34, 69, 25, 19, 70, 45, 43, 71]. Radiotherapy increases the rate of sexual dysfunction but can rarely be considered the only causative factor. Interesting developments on the role of radiotherapy on sexual dysfunction are expected from the long term follow up of patients undergoing watch and wait management after complete response following radiotherapy.

No difference in the incidence of postoperative of sexual dysfunction between short course and long course radiotherapy regimen has been demonstrated in two randomized trials [72-73].

Intraoperative neuromonitoring:

Many studies have demonstrated that the identification and preservation of autonomic pelvic nerves can reduce the incidence of sexual dysfunction but not cut out the risk. Indications and techniques for autonomic nerve preservation are not yet standardized. New technological devices can help the surgeons in intraoperative nerves identification, but they cannot guarantee the 100% success [74].

Intraoperative neurostimulation demonstrated a higher sensitivity in detecting the nerve structures than visual assessment by the surgeon (82 vs 46%) [75].

Intraoperative neuromonitoring during open TME can be performed with a novel neuromonitoring system enabling bipolar electric stimulation of pelvic autonomic nerves under continuous electromyography of the internal anal sphincter and manometry of the urinary bladder. For electromyography, bipolar needle electrodes are inserted under endosonographic guidance.

The combined assessment of cystomanometry and electromyography predicted postoperative sexual function with a sensitivity of 80%, specificity of 93 % in a recent series by Kneist et al [76-77].

CONCLUSIONS:

The incidence of sexual dysfunction is high after multimodality treatment for rectal cancer. Injury to the autonomic pelvic nerves is one of the most important causes, and should be avoided, considering the well-known relationship between them and the pelvic organs.

There is evidence to support routine use of standardized diagnostic tools and need for standardized documentation of the extent of the nerve sparing technique and anterior plane of dissection used.

There is no evidence to date in favor of any surgical approach (Open Vs Laparoscopic Vs Robotic).

Results of long term follow-up are awaited in patients undergoing transanal total mesorectal excision, and in complete responders following radiotherapy.

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FIGURES AND TABLES:

Figure 1. Studies on sexual dysfunction following rectal surgery published between 1986-2016.

Figure 2. Prevalence of sexual dysfunction at 12 months after rectal cancer surgery [1, 6, 12-37],

Figure 3. Incidence of sexual dysfunction [5, 6, 38-49].

Table 1. Tools for diagnosis and monitoring of urogenital dysfunction.

Table 2. Incidence of sexual dysfunction: Laparoscopic Vs Open Surgery [20, 39, 42, 46, 62-65].

Legend: NOS Newcastle-Ottawa Score.

Table 3. Incidence of sexual dysfunction: Laparoscopic Vs Robotic Surgery [30, 36, 66-68].
Legend: NOS Newcastle-Ottawa Score.

Table 4. Role of Neoadjuvant Radiotherapy [34, 69, 25, 19, 70, 45, 43, 71].

Legend: NOS Newcastle-Ottawa Score; RT Radiotherapy.