

Iatrogenic effects of radical cancer surgery on male fertility

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Iatrogenic causes of male infertility can include medications, chemotherapy, radiation, and surgery. In this review, we discuss commonly performed urologic cancer surgeries and nonurologic surgeries that harbor a high risk of iatrogenic infertility. These include radical prostatectomy, radical cystectomy, retroperitoneal lymph node dissection, pelvic colon surgery, and anterior spine surgery. In addition, we review the anatomy and surgical strategies that help to reduce the risks of infertility. With an increase in life expectancy and improvements in fertility preservation, it is important to properly counsel patients about the risks of infertility and provide options for fertility preservation before surgery. (Fertil Steril® 2021;116:625–9. ©2021 by American Society for Reproductive Medicine.)

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The impact of cancer treatments on fertility is increasingly significant as cancer-related mortality continues to decline in the United States. In a survey regarding patients' experiences of cancer-related infertility, only 60% of men were counseled about infertility as a side effect of cancer treatments, and only 51% were offered sperm banking (1). The lack of information was noted to be the most common reason for failing to bank sperm. The 2018 American Society of Clinical Oncology update on fertility preservation recommended that healthcare providers address the possibility of infertility as early as possible before starting cancer treatments and should refer patients who are interested in fertility preservation to reproductive specialists (2). It is significant for healthcare providers to be aware of iatrogenic effects of cancer treatments on fertility and provide an early and informed discussion with the patient.

In the management of solid organ cancers, surgical resection remains the cornerstone for primary treatment. However, iatrogenic effects of surgeries

on male fertility are common. For example, radical prostatectomy irreversibly alters the anatomy of the ejaculatory system and causes obstructive azoospermia. Sperm banking can be the most significant and reliable option to preserve fertility in patients before surgical management. Informed counseling can help patients preserve fertility and improve quality of life in cancer survivorship. In this review, we discuss the common iatrogenic causes of infertility related to surgeries performed for cancer, including radical prostatectomy, radical cystectomy, retroperitoneal lymph node dissection (RPLND), pelvic colon surgery, and anterior spine surgery.

RADICAL PROSTATECTOMY/ CYSTECTOMY: OBSTRUCTIVE AZOOSPERMIA

Radical prostatectomy and radical cystectomy are major potentially morbid operations that have been known to result in a significant impact on a patient's quality of life (3, 4). The preser-

vation of sexual function and fertility is an important consideration, especially in younger patients. Forty percent of patients diagnosed with prostate cancer and 25% of patients diagnosed with bladder cancer are under the age of 64 years (5). One major side effect of standard radical prostatectomy and cystoprostatectomy on fertility is obstructive azoospermia which occurs during transection of the vasa deferentia and removal of the seminal vesicles (6). Presurgical sperm banking provides a reliable option. When surveyed, one out of five patients with prostate cancer would consider sperm banking before surgery (7). Physicians should inquire about a patient's wish to preserve fertility and provide fertility counseling to all patients of childbearing age (8). For men who did not have presurgical sperm cryopreservation, other options include after treatment testicular sperm extraction for use with in vitro fertilization and intracytoplasmic sperm injection.

Fertility-preserving surgical techniques have been reported with promising functional outcomes. Spitz et al. (9) first described a sexual function- and fertility-preserving radical cystectomy. The dissection plane is performed between the anterior surface of the vas deferens and the posterior surface of the bladder and continued to the

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prostatic base. The prostatic stroma is then incised anteriorly to the level of the urethra and then posteriorly proximal to the ejaculatory ducts. The bladder and prostatic cuff can then be removed en bloc. The vas deferens, seminal vesicles, posterior prostate, and neurovascular bundles are spared, and the erectile and ejaculatory function can be preserved. Spitz et al. (9) adopted this technique for 4 men with a median age of 26 years old who presented with nonurothelial bladder pathology requiring a cystectomy. All patients had normal erectile function after surgery with antegrade ejaculation preserved in three patients. This technique was subsequently modified and replicated in several other series (10–13). Colombo et al. (10) performed seminal sparing cystectomy in eight young patients with non-muscle-invasive high-risk bladder cancer with 18-month mean follow-up. The original technique was modified by first performing a transurethral resection of the prostate. All urothelium and glandular prostatic tissue from the bladder neck to the verumontanum were removed and proven to be disease-free. All patients had good erectile function postoperatively. Antegrade ejaculation was preserved in 50% of patients, while the remaining had retrograde ejaculation secondary to transurethral resection.

While prostate- and seminal vesicle-sparing cystectomy offers promising functional outcomes, it has the potential to compromise oncologic outcomes. Vallancien et al. (14) investigated a large cohort of 100 patients with bladder transitional cell carcinoma who underwent prostate-sparing cystectomy with a mean follow-up of 38 months. The 5-year cancer-specific survival rates were as 90% for PT0-T1, 73% for PT2, and 63% for PT3 disease. Judicious patient selection is obligatory to achieve appropriate cancer control.

Salem (15) proposed an innovative approach that minimizes the risk of local cancer recurrences. Four patients with muscle invasive urothelial carcinoma of the bladder underwent nerve-sparing radical cystectomy with removal of the bladder, whole prostate with the prostatic urethra, regional lymph nodes, and seminal vesicles, yet the vas deferens was preserved and anastomosed to the bulbar urethra in the perineum. All patients were able to maintain normal erections after the surgery, and two patients maintained antegrade ejaculation with a mean spermatozoa number of 2.5 million/mL. Oncologic outcomes were promising with all patients being cancer-free at a mean follow-up of 35.5 months.

While traditional radical surgeries to manage cancer of the bladder and prostate result in obstructive azoospermia, modified techniques have been described to maintain reproductive tract continuity in select patients. Regardless, patients undergoing these surgeries should be counseled regarding the expectation that obstructive azoospermia will be the result of the treatment, and before treatment cryopreservation of sperm should be offered.

RETROPERITONEAL LYMPH NODE DISSECTION: ANEJACULATION/RETROGRADE EJACULATION

Retroperitoneal lymph node dissection plays an integral role in the management of testicular cancer. Historically, a complete RPLND template included an extensive bilateral dissec-

tion of nodal tissues surrounding the aorta and vena cava, which includes the suprahilar and interiliac regions (16). It was later recognized that this procedure came with significant morbidity, including a loss of ejaculatory function because of the disruption of bilateral retroperitoneal efferent sympathetic nerve fibers. The postganglionic sympathetic fibers arise from posterior to the vena cava on the right side and from posterior to the aorta on the left and travel anteriorly along the aorta. They join to form the hypogastric plexus that provides sympathetic innervation to the pelvic organs. The disruption of the sympathetic efferent signals leads to the loss of seminal emission and bladder neck closure (17). With an evolving understanding of the distribution of retroperitoneal metastases and increasing effectiveness and utilization of chemotherapy, attention was then turned to modified dissection templates. Modified templates were introduced to minimize complications, including its negative impact on fertility among a population of predominantly young patients, while maintaining adequate cancer control (16, 18). A unilateral modified templated dissection template was introduced in selected patients with early-stage disease and clinically negative lymph nodes. This strategy allowed for the preservation of antegrade ejaculation in 75%–89% of patients by sparing the contralateral sympathetic nerves (17, 19, 20). Additionally, prospective identification and preservation of bilateral lumbar postganglionic nerve fibers has shown higher antegrade ejaculation rates ranging between 88% and 100% (17, 20, 21). Donohue et al. (17) reviewed his cohort of 244 patients with clinical stage 1 nonseminomatous germ cell tumor (NSGCT) who underwent primary RPLND. A total of 167 patients underwent a modified unilateral lymph node dissection along with prospective bilateral nerve sparing, and the remaining underwent a unilateral dissection without prospective nerve sparing. Seventy-five percent of those with modified unilateral template and 98% of those with bilateral nerve sparing had preserved antegrade ejaculation. In a more contemporary cohort, 89% of patients with modified unilateral dissection and 99% of patients with prospective bilateral nerve sparing had maintenance of antegrade ejaculation (20). Despite initial concerns regarding oncologic efficacy, excellent cancer-specific survival has been reported in most series, with >99% at a median follow-up ranging between 13 and 48 months with less than 1% of infield retroperitoneal recurrence (16, 17, 21).

In addition, the preservation of ejaculatory function is possible in the postchemotherapy setting for metastatic NSGCT. Bilateral nerve sparing in postchemotherapy RPLND has been reported with success rates ranging between 25% and 79% depending on a variety of factors, including the surgeon's preferences, extent of dissection, and tumor burden (22–24). Beck et al. (25) and Cho et al. (26) investigated the long-term oncologic and functional outcomes of unilateral template dissection that spares the contralateral nerve fibers among 100 patients with low-volume residual retroperitoneal tumor (<5 cm) after cisplatin-based chemotherapy (25, 26). At a median follow-up of 125 months, the 10-year disease-free survival was 92%, and the total recurrence rate was 7% with no recurrence within the full bilateral dissection template. Antegrade ejaculation was preserved in 98% of

patients. It appeared that in appropriately selected patients, unilateral modified templates can be safely performed in the postchemotherapy setting without compromising long-term oncologic outcomes. However, Carver et al. (27) reviewed over 500 patients with metastatic NSGCT who underwent postchemotherapy RPLND and discovered that the incidence of retroperitoneal disease outside of unilateral templates remained high, ranging between 7% and 32% (27). It remains controversial to what extent the dissection template can be modified in the postchemotherapy setting to minimize functional complications.

PELVIC COLON SURGERY: ANEJACULATION/RETROGRADE EJACULATION

Colorectal surgeries can be associated with a high rate of postoperative complications (28). Functional complications with changes in sexual and urinary function can significantly impact a patient's postoperative quality of life. Damage to the sympathetic nerve branches during pelvic dissection can result in retrograde ejaculation or anejaculation. As previously described, the sympathetic nerves travel anteriorly along the aorta. Moving caudally, the hypogastric plexus courses medial to the ureter between the endopelvic fascia and pelvic peritoneum (29). The hypogastric nerves eventually connect with the nervi erigentes and join the sacral parasympathetic fibers to supply numerous branches to innervate the pelvic organs. Several locations have been identified in which damage is most likely to occur (29). First, during high ligation of the inferior mesenteric artery, disruption of the preaortic hypogastric plexus may occur. Second, during posterior dissection of the rectum, nerves immediately posterior to a smooth layer of the fascia propria surrounding the rectum can be easily injured during blunt dissection. Furthermore, lateral dissection around the rectum may injure the adjacent pelvic plexus. Finally, during anterior rectal dissection, the neurovascular bundles located posterolateral to the apex and the base of the prostate near the lateral edge of the Denovilliers' fascia are at risk of injury (29).

The importance of autonomic nerve preservation has been widely recognized in colorectal surgeries to decrease functional complications. However, it remains technically challenging to identify and preserve the pelvic autonomic nerves and neurovascular bundles in a deep and narrow pelvis. The published rates of ejaculatory function preservation range between 10% and 87% (30–33). With the development of advanced laparoscopic techniques in the past three decades, attention has turned to laparoscopic approaches, which provide a magnified view of the dissection. Despite the advances in technology and deeper understanding regarding the anatomy, published data demonstrate mixed efficacy. In a few single-center retrospective studies, a laparoscopic approach with pelvic autonomic nerve preservation has been reported with good functional outcomes with the preservation of ejaculation in 90%–96% of patients (34, 35). However, two randomized trials comparing laparoscopic vs. open resection found no difference in the preservation of sexual function (36, 37). It is likely that the surgeon's experience and a long learning

curve are required to optimize the outcomes of laparoscopic pelvic resection. Robotic assisted laparoscopic surgery, while long a mainstay of pelvic urologic surgery, is increasingly being adopted for treating colorectal cancer (38). Several studies have reported similar preoperative and postoperative sexual function using the robotic assisted technique (39, 40). In a randomized controlled trial comparing outcomes between robotic and laparoscopic surgeries for patients with rectal cancer, sexual function scores measured by a colorectal cancer-specific quality of life questionnaire at 12 months postoperatively were better in the robotic assisted group than in the laparoscopic group (35 vs. 23, $P = .03$) (41, 42). There appears to be a trend toward better sexual function preservation with robotic approaches. The magnified view and improved ergonomics of the robot have been proposed to facilitate the identification and preservation of pelvic autonomic nerves. Unfortunately, the study did not collect specific data for sexual function, such as rates of ejaculation preservation. Larger and multi-institutional trials with data on functional outcomes are needed.

ANTERIOR LUMBAR SPINE SURGERY: ANEJACULATION/RETROGRADE EJACULATION

Anterior spine surgery is performed for benign as well as malignant spinal pathologies (43). The advantage of an anterior approach allows for direct access to the anterior vertebral column while avoiding any of the posterior spinal stabilization structures and minimizing the risk of perineural fibrosis and epidural scarring (43). However, retrograde ejaculation is a common complication after anterior spinal surgeries, occurring at a rate of 2.7% (44). This is because of the proximity of the hypogastric plexus that travels anteriorly along the aorta. Injury to the nerves can occur during dissection, excess traction, or accidental ligation. Anterior spine surgery was originally performed via an invasive transperitoneal approach. The procedure has since evolved to a minimally invasive retroperitoneal approach, with a significantly lower rate of iatrogenic infertility (44). In a prospective multicenter study by Sasso et al. (45), 146 patients underwent a single-level anterior lumbar interbody fusion via either a transperitoneal or retroperitoneal surgical approach. At 2-year follow-up, 10% of patients who underwent transperitoneal surgical exposure vs. 0.86% of patients in the retroperitoneal approach group had persistent retrograde ejaculation. In a meta-analysis reviewing complications after anterior spine surgery, the transperitoneal approach was found to be associated with a significantly higher rate of retrograde ejaculation compared with the retroperitoneal approach (44).

Interestingly, another risk factor for developing retrograde ejaculation after anterior spine surgery is the use of recombinant human bone morphogenetic protein-2 (rhBMP-2). Recombinant human bone morphogenetic protein-2 is an osteogenic growth factor approved by the US Food and Drug Administration for use in anterior lumbar fusion (46). The use of rhBMP-2 has been reported with improved fusion rates, decreased blood loss, and shorter hospital stay (47). However, concerns were raised regarding its known side

effects, including increased local inflammation, ectopic boney growth, and increased neuroinflammation (48). It was suggested that the exposure of the hypogastric plexus to rhBMP-2 leads to increased local inflammation and damage to the neuroplexus. Multiple studies have demonstrated an association between rhBMP-2 and retrograde ejaculation (49–51). In a randomized controlled trial by Burkus et al. (51), the use of rhBMP-2 was found to be associated with a two times higher incidence of retrograde ejaculation. Comer et al. (50) noted a similar finding in a cohort-controlled study. Among patients who underwent anterior lumbar interbody fusion, those who were exposed to BMP-2 had a statistically significantly higher rate of retrograde ejaculation (6.3% vs. 0.9%). On the other hand, a prospective study by Tepper et al. (52) and a retrospective cohort by Lindley et al. (53) both reported no statistically significant difference in the rates of retrograde ejaculation between patients who received rhBMP-2 and those who did not. It is important to note that these studies were performed in small study populations.

In conclusion, several cancer surgeries carry the risk of impairing fertility. For men who are to receive cancer treatment, adequate informed counseling should be provided, and sperm cryopreservation should be offered. With the development of new technologies and innovations in surgical technique, autonomic nerve-sparing surgeries are feasible with reasonably improved functional outcomes. However, careful patient selection is paramount, and adequate oncologic source control should not be compromised.

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