



Methods of Preservation of Sexual Function Besides Prevention of Male Infertility Subsequent to Radical Surgery for Cancer - A Mini Review

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Abstract

Earlier we had highlighted with regards to what can be the future options for fertility preservation with regards to the patients in whom a diagnosis cancer has been made at a young age, besides stand to lose fertility subsequently to the initiation of chemotherapy or secondary to surgery in case of a primary malignancy of testis or adjacent organs. Here we have tried to emphasize besides the other iatrogenic etiologies of male infertility like chemotherapy, radiation therapy, in addition to other medications on the part of the usually carried out surgeries for urologic, besides non-urologic cancer surgeries which possess, a great capacity of resulting in iatrogenic infertility. They are inclusive of Radical prostatectomy, radical cystectomy, Retroperitoneal Lymph Node Dissection (RPLND), pelvic colon rectal surgery, along with anterior lumbar spine surgery. Apart from that we summarize the anatomical in addition to surgical approaches which aid in reduction of the chances of generation of infertility. With the escalation of life span in addition to enhancement in fertility preservation, it becomes of significance that appropriate counseling of the patients with regards to infertility is done besides offering options.

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Introduction

The influence of cancer therapy on fertility is escalatingly becoming significant in view of cancer associated mortality is on the reduction in US in addition to all over the world. A survey performed with regards to the patients experiences of cancer associated infertility, just 60% of men received counseling with regards to infertility being an adverse action in addition to just 50% were given a choice of semen banking [1]. The absence of any knowledge was an observation for being the commonest explanation for failure of sperm cryopreservation. In 2018, the American Society of Clinical Oncology update with regards to fertility preservation advocated that health care providers account for the probability of infertility as fast as feasible prior to initiation of cancer therapy in addition to their requirements is to refer the patients that are interested with regards to fertility preservation to reproductive endocrinologists [2]. The awareness of the health care providers is important with regards to the iatrogenic actions of cancer therapy on fertility as well as gives an informed detailing to the patient.

During the management of solid organ cancers, surgical removal continuing to be the primary treatment. Nevertheless, iatrogenic actions pointed to the action of surgical treatment on male fertility are usual. Like in case of radical prostatectomy, irreversible alterations of the anatomy, of the ejaculatory system as well as resulting in obstructive azoospermia. Sperm banking can be the most important besides its reliability is maximum with regards to fertility preservation in patients that need surgical management. Hence informed, counseling can aid patients to ensure fertility preservation, besides, enhancement of Quality of Life (QOL). Earlier we had highlighted with regards to what can be the future options for fertility preservation with regards to the patients in whom a diagnosis cancer has been made at a young age, besides stand to lose fertility subsequently to the initiation of chemotherapy or secondary to surgery in case of a primary malignancy of testis [3-7]. Herein this mini-review we detail the usual iatrogenic actions of surgical management that are

associated with cancer surgeries inclusive of, radical prostatectomy, radical cystectomy, Retroperitoneal, Lymph Node Dissection (RPLND), pelvic colon surgery as well as anterior spinal surgery.

Materials and Methods

Thus here we conducted a systematic review utilizing search engine Pubmed, Google scholar and others utilizing the MeSH terms like; cancer treatment; male infertility; Radical prostatectomy; radical cystectomy; Retroperitoneal Lymph Node Dissection (RPLND); pelvic colon rectal surgery, along with ;anterior lumbar spine surgery; an ejaculation; obstructive azoospermia; fertility preservation; semen cryopreservation; retrograde ejaculation from 1990 till date In 2021.

Results

We found a total of 105 articles out of which we selected 46 articles for this mini -review. No meta-analysis was done.

Obstructive azoospermia association with radical prostatectomy/cystectomy

Radical prostatectomy in addition to radical cystectomy represent the most potentially deleterious surgeries that are correlated with, an important influence on the patients Quality of Life (QOL) [8,9]. It is significant to preserve sexual function, besides fertility preservation particular in younger patients inclusive of the prepubertal boys. 40% of the patients manifestation is with prostate cancer in addition to 25% of patients having a diagnosis of bladder cancer are below the age of 64 years [10]. One of the significant adverse actions of radical prostatectomy along with cystoprostatectomy on fertility, is obstructive azoospermia, that took place at the time of the vasa deferentia cutting in addition to the seminal vesicles, getting removed [11]. Sperm banking conducted prior to surgery is dependent methods. On a survey that was done, one of 5 patients, with prostate cancer would think of sperm banking prior to surgery [12]. The requirements of clinicians is to find out from the patients with regards to their willingness for fertility preservation as well as give counseling to all patients that belong to the child bearing age [13]. In case of men not having undergone sperm cryopreservation, the other methods available, subsequent to treatment are Testicular Epididymal Sperm Extraction (TESE) for the utilization of *In Vitro* Fertilization (IVF) as well as Intracytoplasmic Sperm Injection (ICSI).

The fertility preservation, strategies, with regards to surgical processes has got documented that possess advantageous functional results. Spitz et al. [14] initially detailed how to preserve sexual function besides fertility preserving radical cystectomy. The dissection is made among the anterior surface of the vas deferens as well as the posterior surface the bladder that is continued towards the base of prostate. Furthermore the prostatic stroma gets incised anteriorly to the urethral level as well as then posteriorly proximal to the ejaculatory ducts. The bladder in addition to prostatic cuff can then get resected en bloc. The vas deferentia, seminal vesicles, posterior prostate, along with neurovascular bundles get spared, thus erection in addition to ejaculatory function get conserved. Spitz et al. [14] made the utilization of this technique in case of 4 men possessing a median age of 26 years whose manifestation, was with non-urothelial bladder pathology that needs a cystectomy. All patients had a normal erectile function subsequent to surgery with anterograde ejaculation getting conserved in 3 patients. Following that a modification was carried out in certain series [15,16]. Colombo et al. [15] carried out a seminal sparing cystectomy in 8 young patients, with non-muscle invasive high risk bladder cancer with 18 months mean follow up.

The originating method got modification by initially conduction of a transurethral removal of the prostate. All urothelium in addition to glandular prostatic tissue from the bladder neck till the verumontnum were resected besides evidenced to be free of the disease. Good erectile function was existent postoperatively in all patients, whereas the rest had retrograde ejaculation subsequent to transurethral removal.

Whereas, prostate as well as seminal vesicles –sparing cystectomy gives advantageous functional, results, it carries probability of compromising oncologic results. A big cohort of 100 patients with bladder transitional cell carcinoma was evaluated by Vallancien et al. [17], who went via a prostate sparing cystectomy with a mean functional, follow up of 38 months. The 5 year cancer particular survival rates were high up to 90% for PT0 to T1, 73% for PT2 as well as 63% for PT3 disease. Hence patient selection is of utmost significance for attainment of proper cancer regulation.

Salem et al. [18] posited a novel strategy which aids in the reduction of the chances of local cancer recurrence to the least. Four subjects with urothelium carcinoma of bladder that was invading muscle went via nerve sparing radical cystectomy with resection of the bladder, whole prostate, in addition to prostatic urethra, regional lymph nodes, as well as seminal vesicles, nevertheless preservation of vas deferens was attained in addition to its anastomosis to the bulbar urethra in the perineum. All the patients possess the capacity of sustenance of normal erections subsequent to surgery, with 2 patients maintaining antegrade ejaculation possessing an average spermatozoa concentration of 2.5 million/ml. Oncological results were good will all the subjects cancer free at an average follow up of 35.5 months.

Whereas, classical radical surgeries for the management of bladder as well as prostate cancer cause obstructive azoospermia, alteration of surgical procedures have been detailed for sustenance of the continuity of the reproductive tract in particular subjects. Irrespective of that, patients going via these surgical procedures need counseling with regards to anticipation of obstructive azoospermia, would be the final result, hence prior to treatment initially cryopreservation of sperm is offered in addition to carried out.

Anejaculation/Retrograde ejaculation association with retroperitoneal lymph node dissection

Retroperitoneal Lymph Node Dissection (RPLND) has a significant impact in the testicular cancer management. As per the historical aspects a total RPLND template was inclusive of an exhaustive bilateral dissection of lymph node tissue which was surrounding the aorta in addition to inferior vena cava that was inclusive of suprahilal, besides interiliac areas [19]. Later the observation was that this event was correlated with significant morbidity that was inclusive of, ejaculation getting impaired in view of the discontinuation of bilateral retroperitoneal efferent sympathetic nerve fibers. The post ganglionic sympathetic nerve fibers originating from posterior to vena cava on the right side in addition to the aorta on the left as well as travel anteriorly along the aorta. They join to generate the hypogastric plexus which yield sympathetic innervation of the pelvic organs. On disrupting this sympathetic efferent signals result in deletion of seminal emission in addition to bladder neck closure [20]. With greater insight obtained with regards to the distribution of retroperitoneal metastasis, besides escalation of efficacy besides the chemotherapy utility, further focus was then shifted to introduction of the modification of templates for attainment of minimal complications, that was inclusive of the negative impact on fertility in a population comprised of young

patients basically, whereas sustenance, of proper cancer regulation [19,21]. A unilateral manipulation of template dissection template got introduction in case of relative early disease in selection of patients that were correlated with clinically absent lymph nodes. This approach aided in preservation, of antegrade ejaculation in case of 75% to 89% of patients, by sparing of the contralateral lymph nodes [17,19,20]. Furthermore, a prospective isolation, besides preservation of bilateral lumbar post ganglionic nerve fibers has demonstrated greater antegrade ejaculation rates varying among 88% to 100% [20,22]. Donohue et al. [20], evaluated his cohort of 244 patients, with clinical stage in non-Seminomatous Germ Cell Tumor (NSGCT) that went *via* primary RPLND. A total amount of 167 patients had a modification of unilateral, lymph nodes dissection in addition to prospective bilateral prospective nerve sparing, whereas the rest had a unilateral dissection without prospective nerve sparing. 75% of the ones with modification of unilateral template in addition to 98% with those with bilateral prospective nerve sparing possessed capacity of antegrade ejaculation [22]. Although initially, there was botheration of oncologic effectiveness, wonderful cancer particular survival got documented, in maximum series, with over 99% at a median follow up varying among 13 to 48 months with <1% of infield retroperitoneal recurrence [19,20,22].

Additionally, the preservation of ejaculation is not feasible in the post chemotherapy setting in case of metastatic NSGCT. The bilateral nerve sparing post chemotherapy RPLND has got documented with variable success rates, varying among 25% to 79%, based on a lot of factors that were inclusive of what the surgeon preferred, degree of dissection, besides, burden of the tumor [23]. Beck et al. [24] as well as Cho et al. [25], evaluated the long term oncologic in addition to functional results of unilateral template dissection which is contralateral nerve fibers sparing in case of 100 patients, manifestation was low volume residual retroperitoneal tumor (<5 m) subsequent to cisplatin dependent chemotherapy [24,25]. At a median follow up of 125 months, the 10 years disease free period of survival was 92% in addition to the full recurrence rate being 7% with no recurrence in case of total bilateral dissection template. Antegrade ejaculation preservation was existent in 98% of patients. It seemed that in proper selection of patients unilateral modification of template can get attained with safety without any compromise of long term results. Nevertheless, Carver et al. [26], evaluated greater than 500 patients with metastatic NSGCT who had gone *via* post chemotherapy RPLND in addition to their observation being that the incidence of retroperitoneal disease outside of the unilateral template continued to be on the greater side with a range among 7% to 32% [27]. At present controversy exists with regards to what degree the dissection template modification with regards the template in the post chemotherapy setting with the idea of ensuring minimal complications as far as functional results are concerned.

Anejaculation/Retrograde ejaculation association with pelvic colon surgery

Colon rectal surgery can possess a great correlation with the postoperative complications [27]. Functional complications correlated with these surgical procedures are the alterations in sexual in addition to urinary function significantly influence the patients postoperative quality of life. Injury to the sympathetic nerves branches at the time of pelvic dissection can cause Anejaculation/Retrograde ejaculation. The way earlier detailed the sympathetic nerves traverse anteriorly along the aorta. Caudally, the hypogastric plexus travels medial to the ureter among the end pelvic fascia along with peritoneum [28]. The

hypogastric nerves ultimately join the nervierigentis besides making a connection with the sacral parasympathetic nerves fibers to innervate the pelvic organs *via* a lot of branches. Various sites have got isolated, where maximum chances of injury occurrence lies [28]. Initially at the time of the high ligation of the inferior mesenteric artery, interference with the preaortic hypogastric plexus can take place. Subsequently at the time of posterior, dissection of the rectum, nerves just posterior to the smooth layer of the fascia propria that is surrounding the rectum carries the maximum likelihood of proneness to injury at the time of the blunt dissection. Moreover, lateral dissection next to rectum might damage the pelvic plexus lying just next to it. Lastly, at the time of the anterior rectal dissection, the neurovascular bundles that are existent posterolateral to the apex as well as the base of the prostate adjacent to the lateral border of the Denovillier's fascia possess the capacity of getting damaged [28].

The significance of autonomic nerves conservation has got broadly accepted in case of colorectal surgeries for the reduction of functional complications. Nevertheless, from the open technical point it continues to be a problem with regards to the isolation in addition to preservation of the pelvic autonomic nerves besides the neurovascular bundles in case of pelvis that is small besides, in such depth. The rates of ejaculatory functions getting preserved has got documented varying about 10 as well as 87% [29]. Once advancement of laparoscopic procedures, have taken place in the last 30 years, concentration has shifted to the laparoscopic strategies. With greater, insight besides the technical advancement that gives a magnification with regards to the anatomy the data, demonstrated mixed effectiveness. In case of some single center retrospective studies, a laparoscopic strategy with pelvic autonomic nerves conservation has got documented with good functional results with 90% to 95% conservation of ejaculation in such patients [30]. Nevertheless, 2 randomized trials where they contrasted laparoscopic *vs.* open resection observed no variation with regards to the conservation of sexual function [31,32]. Probability exists that both surgeon's experience in addition to longer learning time that is the need for maximization of the results of laparoscopic pelvic resection. Robotic-aided laparoscopic procedure, whereas the major surgical strategy in case of pelvic urologic surgery is escalatingly being utilized for the management of colorectal cancer [33]. Variety of studies has documented akin pre as well as postoperative sexual function with the utilization of robotic-aided laparoscopic procedure [34]. At the time of a Randomized Controlled Trial (RCT), that contrasted the results among robotic as well as laparoscopic procedure in case of rectal cancer, sexual function scores as estimated by a colorectal particular quality of life questionnaire at 12 months postoperatively were of advantage in case of the robotic-aided laparoscopic procedure in contrast to the laparoscopic group (35 *vis a vis* 23, p=0.3) [35]. It seems that a tendency towards more advantageous sexual function preservation exists with the robotic technology. The magnifications of view in addition to ergonomics of the robot have got posited to promote the isolation in addition to conservation of the pelvic autonomic nerve. To our misfortune, the study did not accumulate particular data with regards to sexual function, like the rates of ejaculation conservation. Studies that are larger in addition to multi-institutional, trials with data with regards to functional result are the requirements.

An ejaculation/Retrograde ejaculation association with anterior lumbar spine surgery

Anterior lumbar spine surgery gets conducted for the benign in

addition to malignant spinal pathologies [36]. Why anterior strategy is better, is that it aids in direct access of anterior vertebral column whereas prevention of any of the posterior spinal stabilization structures with reduction of risk of perineural fibrosis besides epidural scarring [36]. Nevertheless, retrograde ejaculation is a usual complication subsequent to anterior spine surgeries that takes place at a rate of 2.7% [37]. This is secondary to the nearness of the hypogastric plexus which traverses anteriorly along the aorta. Damage to the nerve can take place at the time of dissection in addition to too much traction, or ligation by accident. Initially, anterior spine surgery was done with the utilization of invasive transperitoneal strategy. Subsequently, lot of evolution has taken place with regards to the least invasive retroperitoneal surgical technique with a significantly lesser rate of iatrogenic infertility [37]. In case of a prospective multicenter study that was carried out by Sasso et al. [38], 146 patients, went *via* a single level anterior lumbar interbody fusion through either utilization of transperitoneal or retroperitoneal surgical strategy. At 2 year follow up, 10% of patients who had gone *via* transperitoneal surgical strategy *vs.* 0.86% of retroperitoneal surgical strategy, evaluation documented had constant retrograde ejaculation. During a meta-analysis where the subsequent to anterior spine surgeries, a significantly greater rate of retrograde ejaculation was the observation that correlated with transperitoneal surgical strategy in contrast to the retroperitoneal surgical strategy [37].

Intriguingly, one more risk factor for the generation of retrograde ejaculation, following anterior spine surgeries was the utilization of recombinant human Bone Morphogenetic Protein (rhBMP-2). rhBMP-2 is an osteogenic growth factor which has received approval from the USFDA for its utilization in anterior lumbar fusion [39]. The utilization of rhBMP-2 has got documented to cause escalation of fusion rates, reduction in blood loss in addition to reduction in hospital stay [40]. Nevertheless, worries were raised with regards to its known actions, inclusive of escalation of local inflammation, ectopic bony growth as well as enhancement of neuroinflammation [41]. It got pointed that the exposure of hypogastric plexus to rhBMP-2 resulted in escalation of local inflammation, in addition to injury to the Neuro Plexus. A lot of studies illustrated a correlation with rhBMP-2 as well as retrograde ejaculation [42-44]. A Randomized Controlled Trial (RCT) conducted by Bruckus et al. [44], the utilization of rhBMP-2 was observed to be correlated with a twofold greater incidence of retrograde ejaculation. Comer et al. [43], observed an akin observation in a cohort controlled study. Of the patients who had an anterior lumbar inter body fusion, the ones who had received BMP-2 possessed a statistically significant greater incidence of retrograde ejaculation (6.3% *vs.* 0.9%). Alternatively, a prospective study conducted by Temper et al. [45], in addition to a retrospective cohort by Lindley et al. [46], both documented no statistically significant variation incidence of retrograde ejaculation in the incidence of retrograde ejaculation. What is significant that these were conducted in a small study population?

Conclusion

Various cancer surgeries possess the capacity of resulting in impairment of fertility. For men who have to obtain cancer treatment, enough counseling needs to be given in addition to sperm cryopreservation has to be offered. With the generation of innovative techniques, besides advancements of surgical procedures, autonomic nerves sparing surgeries become possible with adequate enhancement of functional results. Nevertheless, appropriate patient selection with

care is of significance, with enough oncologic source regulation is of importance with no compromise to be tolerated.

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