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Title: Surgical strategies for lymphocele prevention in minimally-invasive radical prostatectomy and lymph-node dissection: a systematic review

Running title: lymphocele prevention during prostatectomy

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Abstract:

Purpose: Pelvic lymph node dissection (PLND) is an important step during robotic radical prostatectomy (RARP). The collection of lymphatic fluid (lymphocele) is the most common complication with potentially severe impact; therefore different strategies have been proposed to reduce its incidence.

Material and methods: In this systematic review EMBASE, MEDLINE, Cochrane Library and NIH Registry of Clinical Trials were searched for papers including the following interventions: transperitoneal vs extraperitoneal approach, any reconfiguration of the peritoneum, the use of pelvic drains and the use of different sealing techniques and sealing agents. The outcome evaluated was the incidence of symptomatic lymphocele. Both randomized and non-randomized and/or retrospective studies.

Results: Twelve studies were included (including one ongoing RCT). Due to the heterogeneity of included studies no meta-analysis was performed. No significant impact was reported by different sealing techniques and agents or by surgical approach. Three retrospective, non-randomized studies showed a potential benefit of peritoneal reconfiguration in order to maximize the peritoneal surface of reabsorption.

Conclusion: Lymphocele formation is a multi-step and multifactorial event, high quality literature analyzing risk factors and preventive measures is rather scarce. Peritoneal reconfiguration could represent a reasonable option that deserves further evaluation; no other preventive measure is supported by current evidence.

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Background

Extended pelvic lymph node dissection (PLND) at time of radical prostatectomy is a procedure with controversial survival benefit but with pivotal role in providing staging and prognostic information [1]. European Urology Association (EAU) guidelines recommend performing an extended pelvic lymph node dissection (intended as removing lymphatic tissue covering the external iliac vessels, in the obturator fossa and both medially and laterally to the internal iliac artery) when the estimate risk of lymph node metastasis is at least 5%[2].

Description of the condition

Lymphocele can be defined as a collection of lymphatic fluid without an epithelial lining [3]. It is usually a surgical complication following the disruption of lymphatic vessels. Although lymphocele after radical prostatectomy seems directly attributable to pelvic lymph node dissection [4] its true incidence is difficult to estimate because most lymphoceles occur asymptomatically and there is no standard screening procedure after prostatectomy. When considering symptomatic lymphocele, incidence has been reported between 0 to 8% [5].

A lymphocele can become symptomatic because of superinfection of the lymphatic fluid (causing pain, fever and/or sepsis) or because of the compression on adjacent structures; the latter event can result in abdominal discomfort or venous drainage impairment leading to lower limb edema, deep venous thrombosis and/or pulmonary embolism. Lymphocele, even when asymptomatic, might also affect radiation therapy planning [6].

Lymphocele is the most frequent complication following radical prostatectomy[5] and many potential risk factors have already been reviewed by Lee and colleagues[7]: many of them are indeed non-modifiable elements such as patient age[8], comorbidities[9], surgeon experience[10] and lymph node involvement [11,12].

The current literature strongly supports the idea that the extent of PLND should not be guided by the aim of preventing lymphocele formation but rather by the purpose of

improving oncologic outcomes. Additionally, studies comparing lymphocele incidence in extended vs standard templates showed controversial results regarding the theoretical increasing risk of lymphocele with extended dissection [8,4,13].

Similar considerations can be made regarding the role of prophylactic anticoagulation (LMWH, low molecular weight heparin) where guidelines already defined its role in the setting of minimally invasive radical prostatectomy[14] and the expected benefits in TVP/PE reduction should outweigh the potential increased risk of lymphocele [15-17].

In this systematic review we aim to analyze intraoperative strategies that can be applied at time of minimally-invasive surgery to reduce the risk of symptomatic lymphocele.

Description of the interventions

Transperitoneal vs Extraperitoneal approach

Experiences from open radical prostatectomy suggest that there could be a benefit from transperitoneal approach because of the wider surface for lymphatic fluid reabsorption offered by the peritoneum [18,12]. Porpiglia and Chung found lower incidences of symptomatic lymphocele in the transperitoneal approach compared to the extraperitoneal, although methodological considerations impaired the inclusion of these studies in our analysis [19,20]. The rationale and benefit of peritoneal fenestration is confirmed also in a recent meta-analysis in the setting of kidney transplantation [21].

Peritoneum Reconfiguration

With the same rationale noted above, it was observed that even when the transperitoneal approach is used, the incidence of lymphoceles is still significant [5] and this is thought to be caused by the early adherence of the perivescical fat to the lymph node dissection bed when the pneumoperitoneum is released, thus jeopardizing the potential advantages originating from the peritoneum opening [22]. Some authors have then investigated the efficacy of interventions aimed to delay the spontaneous closure of the peritoneal wall.

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Pelvic Drains

Pelvic drains are used to ensure drainage of blood, urine and lymph from the surgical bed. With the diffusion of minimally invasive techniques, where magnification of the image facilitates accurate suturing and detection of urine and blood spillage, there is a debate on whether drainage can be safely omitted [23,24] but other studies show that in the setting of RRP, higher lymphocele rates were found when drains were removed early or completely omitted compared to 7 days of drainage [12]. A large retrospective series of patients undergoing PLND at the time of either RRP or LRP reported in the multivariate analysis that symptomatic lymphocele was associated with the number of nodes removed and use of LMWH, but not with the number drains placed (1 vs 2) [17].

A Cochrane review updated in 2014 found that drainage of surgical field after PLND performed for gynecological cancer was not effective in preventing lymphocele and in particular, when the peritoneum was left open, the presence of drain was even associated to an increased risk [25].

Ligation Techniques and Hemostatic Agents

It is intuitive that meticulous dissection and ligation of lymphatic vessels is mandatory to reduce the risk of lymphocele. Various agents and techniques to facilitate this aim are available and currently used at surgeon's discretion. Fibrin sealants are widely used to maximize hemostasis based on their interaction on coagulation cascade. Some of these agents have been investigated in order to assess their ability to prevent lymphocele formation with a mechanism thought to be due to the mechanical compression with a lymphostatic effect or a direct effect of the presence of coagulation cascade components in the lymphatic fluid. A meta-analysis of randomized controlled trials including patients who underwent lymph node dissection for gynecological malignancies found no differences in overall and symptomatic lymphocele rates in groups where fibrin collagen agents were used vs standard technique (OR 0.61 95% CI 0.36 to 1.05 p = 0.08 and OR 0.59 95% CI 0.26 to 1.35 p = 0.22, respectively) but showed a decreased duration and volume of lymphatic drainage[26]. Inguinal lymph node dissection is a procedure known by urologists for penile cancer but it is also performed for melanoma: in this setting a recent meta-

analysis showed no improvement in terms of duration of drain placement, total drained volume and wound related complication with the use of tissue sealants [27].

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Methods

Methods and results of the current review are presented following the PRISMA guidelines[28].

RCTs, cohort studies and case control studies were considered. Cross-sectional studies and case reports were excluded because of their statistical inadequacy for an accurate statistical assessment of risk factors and outcomes. Participants were patients who underwent pelvic lymphadenectomy with any template as part of their surgical treatment for prostate cancer performed with a robot-assisted or laparoscopic technique. At least seven postoperative days of follow-up were considered reasonable for detecting lymphocele. Authors evaluated all the interventions that can be performed at time of surgery to prevent lymphocele formation including the extraperitoneal vs transperitoneal approach, any reconfiguration of the peritoneum, the use of pelvic drains or the use of any ligation technique or hemostatic agent. Outcomes evaluated were the incidence of significant lymphocele intended as any lymphocele of diameter 3cm or greater or any symptomatic lymphocele. Expecting different definitions for symptomatic lymphocele, inclusion criteria were met when the study methodology clearly described abdominal or pelvic symptoms related to lymphocele or DVT-related symptoms (including Clavien-Dino grade I or greater) or any required intervention, including antibiotic treatment, surgical or percutaneous drainage.

A comprehensive search of terms (prostate cancer, prostatectomy, lymphocele, pelvic lymphadenectomy, complications) in EMBASE, MEDLINE, Cochrane Library and NIH Registry of Clinical Trials from 1980 up to January 31th 2019 was performed. All languages were included in the primary selection. Other sources of literature were not considered in this study.

Two authors (GM and AM) undertook the study selection screening the titles and abstracts of articles found in the search and discarding those which did not meet the eligibility criteria. Full-text copies of the eligible articles were obtained. Both review authors

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independently assessed whether the studies met the inclusion criteria, with disagreements resolved by discussion. For each included study, information regarding the location of the study, methods of the study, the participants (age range, eligibility criteria), the nature of the interventions and data relating to the outcomes specified above were collected.

Risk of bias for randomized clinical trials was assessed through the Cochrane Collaboration tools [29] and summarized in Table 2. For non-randomized study bias was assessed through the Newcastle-Ottawa Scale [30] and summarized in Table 3.

Extracted data were judged by authors to be inappropriate for pooled analysis due to the low quality and heterogeneity of the studies, thus no meta-analysis was performed.

Results

After removing duplicates, 220 studies were evaluated and after screening of abstracts and titles 56 full text articles were obtained; 44 of them did not meet the inclusion criteria leaving 12 studies (including 1 ongoing randomized trial) in the final analysis.

The study selection process is summarized in Figure 1 showing the PRISMA flow chart.

Characteristics of included studies are shown in Table 1.

Effects of the interventions

Transperitoneal vs Extraperitoneal

A large (n=671 pairs), propensity-matched approach and prospectively maintained cohort of patients undergoing robotic PLND either with extraperitoneal (eRARP) or transperitoneal (tRARP) approach were compared in terms of rates of symptomatic lymphocele[31]; patients on the tRARP group had higher T stage (p=0.0015), higher incidence of N+ disease (p=0.0002) and number of LN removed (p<0.0001). No differences in symptomatic lymphocele were found between the groups [e-RARP 19/671 (2.83%) vs t-RARP 10/671 (1.49%), p = 0.09]. Notably the tRARP group had more LNs removed and incidence of pN1 disease. When controlling for N stage and LN removed, logistic regression showed a non-significant trend for higher lymphocele rates in eRARP when controlling for

LN count (p = 0.071), pathological N stage (p = 0.111), or both combined (p = 0.085) on symptomatic lymphocele rates.

Peritoneum Reconfiguration

Stolzenburg and colleagues in 2008 performed bilateral peritoneal fenestration at the end of extraperitoneal radical prostatectomy with lymphadenectomy in 50 patients and compared them to 50 patients where the peritoneum was left intact, looking at lymphocele detection at 8 and 30 days on US examination. Significant differences ($p<0.001$) were found in the fenestration group (3 lymphocele found, all of them asymptomatic) and 16 were found in the control group (7 out of 16 were symptomatic). No differences in terms of pain, inflammation and bowel function were reported [32].

Three studies report peritoneal reconstruction as an intervention to prevent lymphocele formation during transperitoneal RARP:

- Lebeis and colleagues analyzed the rates of lymphocele detection on 77 consecutive patients who underwent a peritoneal interposition flap ("created by rotating and advancing the peritoneum around the lateral surface of the ipsilateral bladder to the dependent portion of the pelvis and fixing it to the bladder itself"). They were compared retrospectively to 77 patients who underwent standard procedure without this reconfiguration. Authors reported no lymphocele in the group with peritoneal flap and 9 (11.6%) lymphoceles in the comparison group (p=0.0033) with a mean detection time of 30.4 days (range 6-72). Every patients with lymphocele experienced symptoms[22].
- Dal Moro and colleagues performed a variation of the aforementioned technique (P.L.E.A.T. - preventing lymphocele ensuring absorption transperitoneally – figure 2) on 176 patients and compared the rates of symptomatic lymphocele to 195 patients who underwent no peritoneal reconfiguration. Results showed significant higher rates (p=0.039) of symptomatic lymphocele in the control group (9/195 - 4.1%) vs the "P.L.E.A.T" group (1/176 - 0.6%) with calculated median detection time of 32 days (range 11-145); the P.L.E.A.T. cohort was characterized by higher pathologic staging and higher number of lymph nodes removed[33].

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- Stolzenburg and colleagues in 2018 evaluated US diagnosis of both symptomatic and asymptomatic lymphocele at 8, 28 and 90 days in 193 patients who underwent a reconfiguration with a four point peritoneal flap fixation (4PPFF) compared to matched controls where no reconfiguration was performed. They reported a significant difference in the incidence of symptomatic lymphocele: two patients (1.03%) in the 4PPFF group versus nine patients (4.6%) without 4PPFF (p = 0.0322). Asymptomatic lymphocele incidence was also lower in the 4PPFF group (p = 0.0058) [34].

Results from the undergoing triple blind randomized clinical trial using a "Peritoneal Iliac Flap" are eagerly awaited (NCT03567525) in order to provide higher quality evidence on this topic.

Pelvic Drains

A single-center randomized non-inferiority trial (non-inferiority margin set at 10%) was performed by Chenam et al. in 2018. Patients were assigned to pelvic drainage (PD) or non-drainage after RARP. Five patients were excluded because of anastomotic leakage or inadequate hemostasis. The study did not reach the target accrual number, however after adjustment for the type I error level authors found no statistically significant differences in 90-day complication rate and symptomatic lymphocele rate (2/92 (2.2%) in the non-drainage cohort and 3/97 (4.1%) in the PD cohort, p=0.7) [35].

Sealing Techniques and Sealing Agents

In the setting of LRP different instruments can be used to achieve efficient hemostasis and facilitate lymph node dissection. Yasumizu et al. evaluated one of them looking at lymphocele rates in patients undergoing limited LND during e-LRP with conventional technique (ultrasonic cutting and coagulating system - SonoSurg) or using a vessel sealing device (EnSeal). At 90 days CT scan detected lymphocele in 35/60 patients in the conventional technique groups compared to 28/60 (p=0.201), only one lymphocele was symptomatic from the first group. In this study authors calculated a mean size of 1335mm², when the presence of a collection >1500mm² was established as an outcome,

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the use of vessel sealing device was the only outcome predictor on the multivariate analysis ($p<0.01$)[36]. A RCT performed by Grande and colleagues evaluated the rate lymphocele detection and symptomatic lymphocele at 10 and 90 days after RARP and PNLD in 110 patients in whom titanium clips were used during LND and 110 patients in whom LND was performed with bipolar energy only. Results showed no difference between groups in terms of symptomatic lymphocele (6/110 in the titanium clips groups vs 5/110 in the bipolar energy group; $p=0.7$). Similarly, no difference was found in lymphocele detection rates ($p=0.9$)[37].

In the setting of laparoscopic extraperitoneal LND for prostate cancer, Waldert evaluated in a small cohort bilateral application of 2.5cc Floseal ® *(Baxter Healthcare, Deerfield, IL: an hemostatic matrix containing human derivated thrombin)* after LND and 1/32 (3.1%) symptomatic lymphoceles were detected in the Floseal group compared to 16/110 (14.5%) in the control group ($p=0.149$). In this study timing of imaging was defined by patient symptoms and was not reported [38], the small numbers probably limited the statistical validity of the study.

A randomized trial evaluated the impact of the use of Arista AH™ *(Davol Inc.: hemostatic powder that acts through Microporous Polysaccharide Hemospheres)* applied only on one side of the PLND bed compared to the other side in 88 patients undergoing RARP. A CT scan at 3 months was performed in every patient and fluid collections of 3cm or greater were considered lymphocele. Five of them (5.7%) occurred on the Arista AH side and nine (10.2%) on the untreated side ($p = 0.248$). None of the lymphocele was symptomatic and no statistical difference was found in average lymphocele size ($p = 0.441$) [39].

More recently, a randomized controlled trial by Buelens and colleagues evaluated lymphocele formation and volume at 1 week, 1 and 3 months after surgery in patients undergoing transperitoneal robot assisted extended PNLD for staging before external beam radiation therapy (n=50) or during RP (n=50). Twenty-five patients were randomized to bilateral placement of TachoSil *(Nycomed-Takeda Austria GmbH: hemostatic sponge made of horse collagen and human thrombin)* above the external iliac vessels. Symptomatic lymphoceles were evaluated as a secondary endpoint. Patient undergoing

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PNLD only were older, had a worse ASA score and a more advanced clinical T stage; their procedures, other than shorter operative time and blood loss, included higher number of lymph node removed and higher N+ stage. Symptomatic lymphoceles were detected in 13 patients (26%) in both TachoSil and control group (p=0.85) without differences regarding the surgical procedure (p=0.39) [40].

Discussion

The overall incidence of symptomatic lymphocele in the included studies is consistent to other reports [5] and, even if relatively low, should be taken in account as it can lead to relevant complications that make efforts and costs of these procedures vain.

Only one study evaluating t-RARP vs e-RARP met the inclusion criteria and was included in our review, reporting no significant differences between the two techniques [31]. Notably the raw incidence of lymphocele was almost twice in the eRARP group, with higher number nodes removed and positive nodes in the tRARP group. These results should then be taken cautiously; in fact PLND in e-RARP may be more technically challenging and in this study it was performed in patients with lower risk of nodal disease, by a single experienced surgeon. Given the increasing need of performing extended PLNDs the most promising, low-quality, evidence comes from techniques that enhance the peritoneal surface of reabsorption. The techniques described in the setting of extraperitoneal [32] or transperitoneal [33,22,34] approaches are cheap, safe and quick, however, evidence from randomized clinical trials is awaited to confirm these results.

The rationale for drain placement goes further than preventing lymphocele and although the well conducted study by Chenam [35] suggests that pelvic drains can be safely omitted, this conclusion may not be used to make any recommendation or generalized to larger cohort of patients and different surgical experiences. In particular this study is limited to a single-center experience, designed to detect overall complications and results are based on an interim analysis due to poor accrual. Overall, in most of the studies analyzed drains were left in place until drainage volume was less than <100cc/24h and this usually happens in the first postoperative days; this strategy can be helpful in detecting rare but severe

events like anastomotic disruption and hemorrhage probably without affecting morbidity but may not be sufficient to control lymphatic leakage [12].

None of the included studies was able to show improvement in lymphocele prevention with any of the techniques described, some trends towards improvement were shown by Gilbert[39] and Waldert [38] but none of them reached significant levels, mainly with concerns related to the small sample size in relation to the incidence of the disease. In general the use of hemostatic agents or clips remains questionable particularly when considering costs implicated with it.

Reported results must be read in light of the risk of bias present in the studies. Six of the included studies are retrospective and non-randomized. Direct comparison between studies results is difficult because of potential confounding interventions in the same group (for example different extent of PLND) and many other potential confounders that were not reported in the papers. The outcome of symptomatic lymphocele was assessed at different times and with different techniques. The only group of comparable interventions was that of peritoneal reconfiguration, but due to the retrospective nature of the study and the lack of information on potential confounder was not judged to be amenable to meta-analysis. All studies in this setting show some benefit in peritoneal reconfiguration but results are to be read in light of the high risk of bias and thus prospective and randomized studies are eagerly awaited.

Despite the reported limitations the current review provides a summary of the most updated available evidence that could help the surgeon in its intraoperative evaluations and guide future research.

Conclusion

Symptomatic lymphocele is the most common complication after RARP. Maximizing peritoneal surface of reabsorption could help preventing its formation and, even though supported only by non-randomized data, could be a quick and inexpensive option and deserves further evaluation in prospective randomized setting. Current literature does not support the use of particular sealing techniques or agents. Further evidence is needed to draw meaningful conclusions about other approaches for lymphocele prevention.

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Authors' contribution:

G. Motterle: Project development, data collection, data analysis, manuscript writing

A. Morlacco: Project development, data collection, data analysis, manuscript writing

N. Zanovello: manuscript editing and critical revision

M. Ahmed: manuscript editing and critical revision

F. Zattoni: Critical revision of the manuscript for important intellectual content, supervision

RJ. Karnes: Critical revision of the manuscript for important intellectual content, supervision

F. Dal Moro: Critical revision of the manuscript for important intellectual content, supervision

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List of abbreviations used:

e-RARP/LRP: extraperitoneal robotic/laparoscopic radical prostatectomy

LN: lymph node

LND: lymph node dissection

LRP: laparoscopic radical prostatectomy

PLND: pelvic lymph node dissection

RARP: robotic radical prostatectomy

RCT: randomized clinical trial

RRP: retropubic radical prostatectomy

t-RARP/LRP: transperitoneal robotic/laparoscopic radical prostatectomy

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Table 1: Characteristics of Included Studies

Author	Study Period	Methods	N Participants (pairs in matched design)	Surgical Technique	Extent of LND	LMWH prophilaxis	Drain	Peritoneum reconfiguration	Ligation Techniques	Other agents	Primary outcome
Buelens	2013-2016	RCT	100	Robotic, transperitoneal	Extended	Yes	Yes	n.d.	Metallic clips	Tachosil*	Lymphocele volume on 1w, 1mo, 3 mo
Chenam	2012-2016	RCT	189	Robotic, transperitoneal	Limited or Extended	None	Yes vs No*	n.d.	Weck clips	None	Complications at 90days
DalMoro	n.d.	Cohort	371	Robotic, transperitoneal	Limited or Extended	Yes	Yes	yes*	n.d.	n.d.	Symptomatic Lymphocele
Gilbert	n.d.	RCT	88	Robotic, transperitonea	Limited or	Yes	No	not closed	Hem-o-Lock	AristaAH	Lymphocele detection at 3

				l	Extended					*	months
Grande	2012-2015	RCT	220	Robotic, approach n.d.	Extended	n.d.	n.d.	n.d.	Clips vs bipolar *	n.d.	Lymphocele at 10 and 30d
Horovitz	2003-2016	Cohort, propensity matched	671	Robotic, transperitoneal vs extraperitoneal *	Extended	Yes	n.d.	n.d.	Hem-o-Lock	n.d.	Symptomatic Lymphocele
Lebeis	n.d.	Cohort	154	Robotic, transperitoneal	Limited or Extended	Yes	Yes	yes*	Hem-o-Lock	n.d.	Symptomatic Lymphocele
Stolzenburg	2006-2007	Cohort	100	Laparoscopic, extraperitoneal	Extended	n.d.	n.d.	yes*	n.d.	n.d.	Complications up to 90days

Journal of Endourology

Stolzenburg	2010-2017	Cohort	193	Laparoscopic or robotic, transperitoneal	Extended	n.d.	Yes	Yes*	Clips	n.d.	Symptomatic and asymptomatic lyphocele up to 90d
Waldert	2008-2009	Cohort	142	Laparoscopic, extraperitoneal	Limited	Yes	Yes	n.d.	n.d.	FloSeal*	Symptomatic Lymphocele
Yasumizu	2010-2011	RCT	120	Laparoscopic, extraperitoneal	Limited	n.d.	Yes	n.d.	VSD*	n.d.	Lymphocele detection at 1 month

* Intervention investigated in the study; n.d.= no information available

Table 2: Risk of Bias Assessment for Randomized Studies

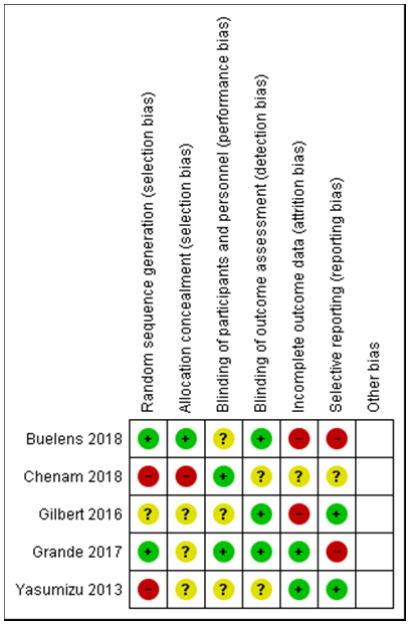

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Table 3: Risk of Bias Assessment for Non-Randomized Studies

Author	Selection	Comparability	Outcome
Dal Moro	****		**
Horovitz	****	**	***
Lebeis	****		**
Stolzenburg (2008)	***		**
Stolzenburg (2018)	***	**	**
Waldert	****		**

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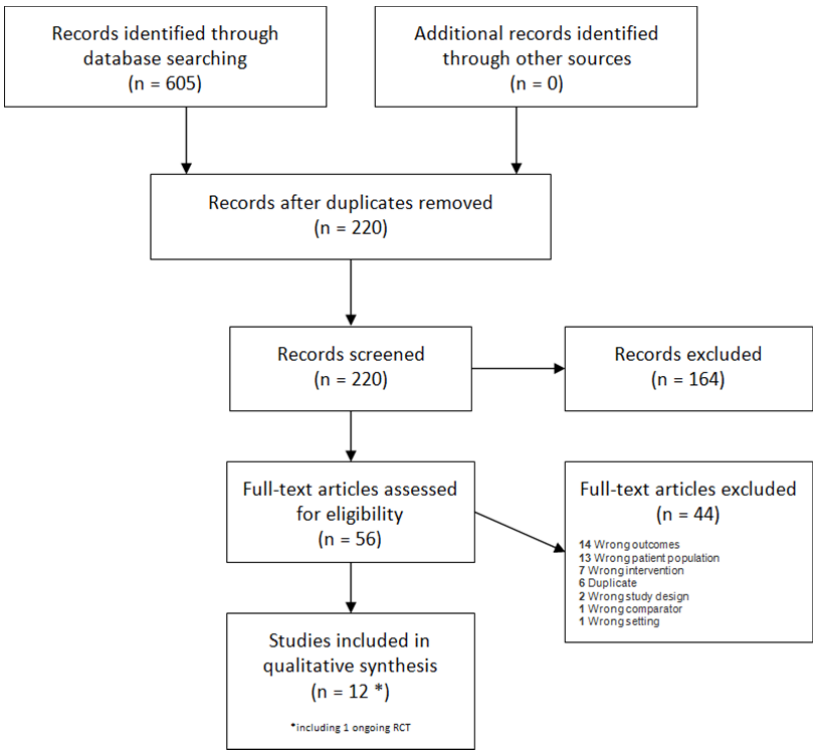
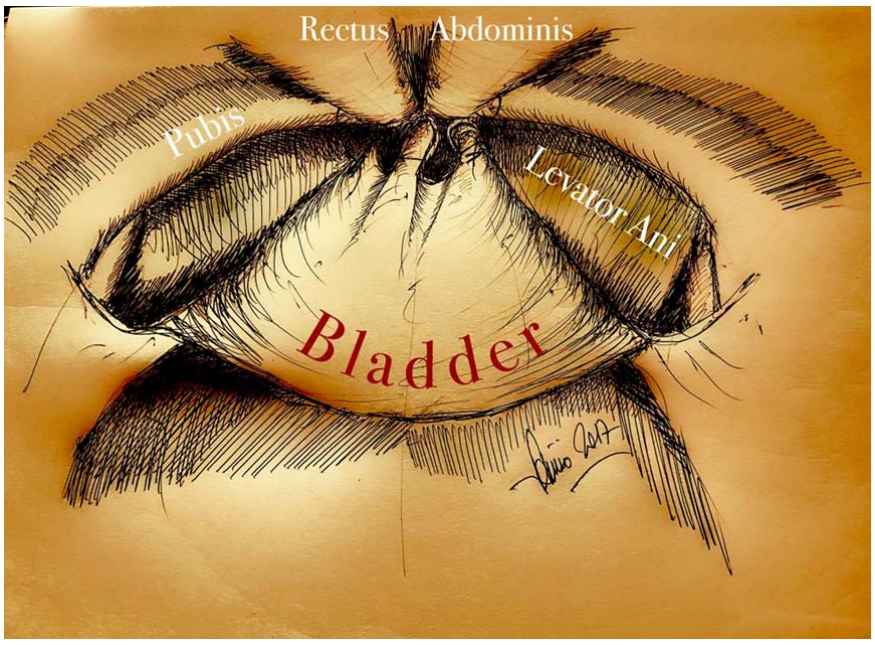


PRISMA flowchart of study selection



P.L.E.A.T. reconfiguration (original drawing by the author)

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