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Planejamento Virtual com Imagens Tridimensionais para a Ressecção de Nódulos em Órgãos Sólidos: Revisão Sistemática e Meta-Análise

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Planejamento Virtual com Imagens Tridimensionais para a Ressecção de Nódulos em Órgãos Sólidos: Revisão Sistemática e Meta-Análise

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Orientador: Dr. Bruno Hochhegger

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Resumo da Dissertação

Introdução: Cirurgias guiadas por imagem têm apresentado melhorias em desfechos clínicos, como segurança do paciente, tempo operatório (OT), sangramento intraoperatório (EBL), tempo de internação pós-operatório (POHS) e prevalência de eventos pós-operatórios (POE). **Objetivos**: Revisar sistematicamente os efeitos do planejamento virtual com imagens 3D para a ressecção de nódulos nos seguintes órgãos sólidos: pulmão, fígado e rim. **Métodos**: Bases eletrônicas foram pesquisadas até dezembro de 2020 para incluir estudos randomizados e não-randomizados que comparassem os resultados da ressecção cirúrgica de nódulos pulmonares, hepáticos ou renais com e sem o planejamento virtual a partir de imagens 3D de tomografia computadorizada. De cada artigo foram extraídas as seguintes variáveis: OT, EBL, a média do POHS e o número de POE. O tamanho do efeito (ES) do planejamento virtual 3D vs. planejamento não-3D foi obtido individualmente por estudo para cada variável contínua (OT, EBL, POHS), sendo calculado também o ES geral a partir de todos os estudos para OT, EBL, POHS. Os dados foram agrupados usando um modelo de efeitos aleatórios. **Resultados**: Dentre 2397 estudos identificados, 10 foram incluídos, totalizando 897 pacientes. Houve uma diferença significativa no OT entre os grupos com um ES moderado favorecendo o grupo 3D (ES, -0,42; IC 95%: -0,56, -0,29; $I^2 = 83,1\%$; $p<0,001$). Em relação ao EBL, houve uma diferença significativa entre 3D e não 3D com um pequeno ES favorecendo o planejamento virtual (ES, -0,15; IC 95%: -0,28, -0,02; $I^2 = 22,5\%$; $p=0,0236$). Não houve diferença entre os grupos 3D e não 3D para POHS (POHS ES, -0,01; IC 95%: -0,19,0,17; $I^2 = 0,0\%$; $p=0,925$) e POE (POE OR, 0,80; IC 95%: 0,54,1,19; $I^2 = 0,0\%$; $p=0,267$). **Conclusões**: O planejamento virtual com imagens 3D de TC para ressecção cirúrgica de nódulos de pulmão, rim e fígado pode reduzir OT e EBL sem efeitos sobre POHS e POE imediatos.

Palavras-chave: imagens tridimensionais de tomografia computadorizada; cirurgia guiada por imagem; nódulo; pulmão; fígado; rim

Abstract

Introduction: image-guided surgery has been associated with improvements on clinical outcomes, such as patient safety, operation time (OT), intraoperative estimated blood loss (EBL), postoperative hospital stay (POHS), and prevalence of postoperative events (POE). **Aim of study:** To systematically review the effects of 3D-imaging virtual planning for nodule resection in the following solid organs: lung, liver, and kidney. **Materials and methods:** electronic databases were searched through December 2020 to include randomized and non-randomized studies that compared outcomes of surgical resection of lung, liver, or kidney nodules with and without 3D virtual planning with computed tomography. We extracted from each article the mean OT, mean EBL, mean POHS, and the number of POE. The effect size (ES) of 3D virtual planning vs. non-3D planning was extracted from each study to calculate the pooled measurements for continuous variables (OT, EBL, POHS). Data were pooled using a random-effects model. **Results:** The literature search yielded 2397 studies and 10 met the inclusion criteria with a total of 897 patients. There was a significant difference in OT between groups with a moderate ES favoring the 3D group (ES, -0.42; 95%CI: -0.56,-0.29; I^2=83.1%; p<.001). Regarding EBL, there was a significant difference between 3D and non-3D with a small ES favoring IGS (ES, -0.15; 95%CI: -0.28,-0.02; I^2 = 22.5%; p=.0236). There was no difference between the 3D and non-3D groups for both POHS (POHS ES, -0.01; 95%CI: -0.19,0.17; I^2 = 0.0%; p=.925) and POE (POE OR, 0.80; 95%CI: 0.54,1.19; I^2 = 0.0%; p=.267). **Conclusions**: 3D-imaging planning for surgical resection of lung, kidney, and liver nodules could reduce OT and EBL with no

effects on immediate POHS and POE. Such changes in these perioperative variables could improve medium and long-term postoperative clinical outcomes.

Keywords: Three-dimensional CT imaging; image-guided surgery; lung; liver; kidney

Lista de abreviaturas

3D	three-dimensional
3DVP	3D-imaging virtual planning
EBL	estimated blood loss
ES	effect size
IGS	image-guided surgery
IQR	interquartile range
MINORS	methodological index for non-randomized studies
OT	operation time
OR	odds ratio
POE	postoperative events
POHS	postoperative hospital stay
SMD	standardized mean difference
VATS	video-assisted thoracoscopic
LPN	laparoscopic partial nephrectomy

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SUMÁRIO

1. REFERENCIAL TEÓRICO

A prática cirúrgica segura e eficaz exige um conhecimento profundo de anatomia. Dominar extensamente cada detalhe anatômico de cada paciente permite aos cirurgiões uma abordagem individualizada a cada organismo, permitindo maior êxito nos procedimentos e tratamento dos pacientes. Com avanços tecnológicos no desenvolvimento de exames de imagem, tem se permitido cada vez mais um detalhamento anatômico maior de cada paciente de maneira não invasiva[1].

1.1. Definição de cirurgia guiada por imagem

A integração desses avanços na radiologia, com novos software de processamento dos exames de imagem, levou à possibilidade do desenvolvimento de sistemas de cirurgia guiada por imagem (CGI). O termo CGI define genericamente qualquer terapia invasiva realizada usando como auxílio ou guia imagens do órgão abordado no procedimento[1]. Tais imagens podem ser derivadas de qualquer exame radiológico, como endoscopias, fluoroscopias, ultrassonografias, tomografia computadorizada (TC), ressonância nuclear magnética (RNM) ou até mesmo métodos híbridos de imagem[2].

1.2. Aplicações dos sistemas de cirurgia guiada por imagem

Com o desenvolvimento de novas tecnologias de pós-processamento de exames de imagem, têm crescido as possibilidades de uso de sistemas de CGI pré e intraoperatórias. Os sistemas CGI mais utilizados são aqueles que fornecem informações adicionais pré-operatórias usando como guia modelos virtuais tridimensionais (3D), obtidos através de exames de imagem comumente utilizados na avaliação pré-operatória, como TC ou RNM[3,4]. Através desses modelos 3D, é possível a segmentação de estruturas de maior risco ou a demarcação de lesões (Figura 1)[3].

Figura 1. Imagens de reconstruções tridimensionais a partir de tomografia computadorizada de tórax de um paciente com câncer de pulmão demonstram a capacidade de segmentação das estruturas torácicas e de destaque da lesão alvo na avaliação pré-operatória. Arquivo pessoal dos autores.

São inúmeras também as aplicações de sistemas de CGI no intraoperatório. A grande maioria dos sistemas de CGI fornece suporte ao procedimento com informações adicionais, como exibição da distância entre estruturas, fornecimento de alertas de proximidade quando o cirurgião chega muito próximo de estruturas delicadas, que se lesadas, podem resultar em danos permanentes ao paciente, ampliação do volume de estruturas ou lesões ou até mesmo como guia virtual por imagens 3D[5-8]. Além dessa classe de sistemas de CGI que fornece informações no intraoperatório, há também a modalidade de sistemas de CGI que também interfere no processo de tomada de decisões durante o procedimento, como reduzindo a velocidade do instrumento cirúrgico quando muito próximo de estruturas de risco, ou até mesmo restringindo movimentos do cirurgião quando conectados a braços robóticos[9,10].

1.3. Efeitos do uso de cirurgia guiada por imagem

Múltiplos trabalhos na literatura têm mostrado que os sistemas de CGI podem melhorar a orientação intraoperatória, a identificação e a localização das estruturas anatômicas e suas variações em cada paciente, diminuindo, assim, a carga de trabalho do cirurgião e contribuindo na melhora no desempenho[11-15]. Por outro lado, alguns trabalhos também têm interrogado a possibilidade de efeitos adversos negativos com o uso de sistemas CGI, como o aumento do tempo cirúrgico até o domínio da técnica de CGI, maior pressão e sobrecarga de trabalho, erros devido à dependência excessiva da assistência do computador e possível interferência no desenvolvimento de habilidades cirúrgicas[3].

O uso de sistemas de CGI tem apresentado na literatura melhoras em diversos desfechos clínicos, como segurança do paciente, tempo cirúrgico (tCx), sangramento estimado intraoperatório (sCx), tempo de internação pós-operatória (tPO) e prevalência de eventos pós-operatórios (EPO)[16-19]. Tais aperfeiçoamentos nestas variáveis transoperatórias poderiam influenciar os desfechos clínicos pós-operatórios (PO) no médio e longo prazo[20-26]. Dados de estudos prévios mostraram que o tCx prolongado foi associado a um aumento do risco infecção da ferida operatória[20.] Em uma meta-análise anterior, cada 10 min, 15 min, 30 min e 60 min adicionais de cirurgia aumentava a probabilidade de infecção do sítio cirúrgico em 5%, 13%, 17% e 37%, respectivamente[20]. Além disso, dados na literatura também descrevem piores resultados no PO associados a maiores sCx, especialmente em cirurgias renais, hepáticas e pulmonares[27-34].

Em uma meta-análise anterior sobre cirurgia endoscópica em seios da face guiada por imagem, o uso de sistemas CGI foi associado a uma redução de 52% no número de complicações PO significativas e de 34% no número total de complicações PO[11]. Em uma outra metanálise sobre o uso de CGI para cirurgias de coluna, houve uma redução de 61% no risco de perfuração pedicular com navegação guiada por imagem[35]. No entanto, os dados para outros tipos de cirurgia ainda são escassos, limitando-se geralmente a séries de casos ou estudos não randomizados. Em relação a órgãos sólidos, há apenas alguns estudos sobre o uso de orientação 3D para cirurgias pulmonares, hepáticas e renais, porém, até o presente momento, não há nenhuma revisão sistemática ou meta-análise sobre o efeito de CGI nesses órgãos sólidos[36-45].

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3. OBJETIVOS

GERAL:

Realizar uma revisão sistemática e meta-análise sobre o uso do planejamento virtual com imagens tridimensionais de tomografia computadorizada para a ressecção cirúrgica de nódulos pulmonares, hepáticos e renais.

ESPECÍFICOS:

a) Determinar o efeito do planejamento virtual tridimensional no tempo cirúrgico da ressecção de nódulos pulmonares, hepáticos e renais.
b) Determinar o efeito do planejamento virtual tridimensional no sangramento intraoperatório da ressecção de nódulos pulmonares, hepáticos e renais.
c) Determinar o efeito do planejamento virtual tridimensional na duração média de internação pós-operatória da ressecção de nódulos pulmonares, hepáticos e renais.
d) Determinar o efeito do planejamento virtual tridimensional no número de eventos pós-operatórios da ressecção de nódulos pulmonares, hepáticos e renais.

4. ARTIGO CIENTÍFICO REDIGIDO EM INGLÊS

Three-dimensional virtual planning for nodule resection in solid organs: a systematic review and meta-analysis

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4.1. TITLE PAGE

Three-dimensional virtual planning for nodule resection in solid organs: a systematic review and meta-analysis

Brief title: 3D virtual planning for nodule resection

Manuscript type: meta-analysis

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4.2. ABSTRACT

Objectives: To systematically review the effects of 3D-imaging virtual planning for nodule resection in the following solid organs: lung, liver, and kidney.

Methods: MEDLINE, EMBASE, and Cochrane Library were searched through December 2020 to include randomized and non-randomized studies that compared outcomes of surgical resection of lung, liver, or kidney nodule resection with and without 3D virtual planning with computed tomography. We extracted from each article the mean operation time (OT), mean estimated blood loss (EBL), mean postoperative hospital stay (POHS), and the number of postoperative events (POE). The effect size (ES) of 3D virtual planning vs. non-3D planning was extracted from each study to calculate the pooled measurements for continuous variables (OT, EBL, POHS). The odds ratio (OR) was extracted from each study to combine the pooled number of POE. Data were pooled using a random-effects model.

Results: The literature search yielded 2397 studies and 10 met the inclusion criteria with a total of 897 patients. There was a significant difference in OT between groups with a moderate ES favoring the 3D group (ES,-0.42;95%CI:-0.56,-0.29;I^2=83.1%;p<.001). Regarding EBL, there was a significant difference between 3D and non-3D with a small ES favoring IGS (ES,-0.15;95%CI:-0.28,-0.02;I^2=22.5%;p=.0236). There was no difference between the 3D and non-3D groups for both POHS (POHS ES,-0.01;95%CI:-0.19,0.17;I^2=0.0%;p=.925) and POE (POE OR,0.80;95%CI:0.54,1.19;I^2=0.0%;p=.267).

Conclusions: 3D-imaging planning for surgical resection of lung, kidney, and liver nodules could reduce OT and EBL with no effects on immediate POHS and POE. Such changes in these perioperative variables could improve medium and

long-term postoperative outcomes.

Keywords

Three-dimensional CT imaging; image-guided surgery; nodule resection; solid organs

4.3. INTRODUCTION

With the development of new post-processing technologies, there has been an increase in the use of image-guided surgery (IGS) systems to assist surgeons during challenging operations (1, 2). Several preoperative and intraoperative applications of IGS systems are currently available. The most used IGS systems are those that provide preoperative information support, such as segmentation of risk structures or targets by three-dimensional (3D) virtual guidance. IGS systems can also offer intraoperative information support, such as distance visualization, proximity warnings when close to important structures, and augmentation of risk structures or targets (1, 2).

IGS systems could improve intraoperative orientation, identification, and location of anatomical structures and their variations, decreasing surgeons' workload and contributing to performance enhancement (1, 3-7). On the other hand, adverse side effects could also arise from the use of IGS systems, such as increased perceived time, pressure and mental demands, errors due to overreliance on the computer assistance, and possible interference on the development of surgical skills (2).

Clinical outcomes, such as patient safety, operation time (OT), intraoperative estimated blood loss (EBL), postoperative hospital stay (POHS), and prevalence of postoperative events (POE) have been reported to improve with the use of IGS systems (1, 8-11). Previous systematic reviews and meta-analyses have reported positive effects of IGS on clinical outcomes of maxillofacial surgery, neurosurgery, and spinal surgery (3-5). Until now, there are only a few state-of-the-art reviews about the use of 3D-guidance for operations of the lung (12-14), liver (15-17), and kidney (18-21), but no systematic reviews or meta-analyses on the effect of IGS on these solid organs were performed. This meta-analysis aimed to assess the effects of 3D-imaging virtual planning (3DVP) for surgical resection of lung, liver, and kidney nodules.

4.4. METHODS

4.4.1. Search strategy

This study was reported following Enhancing the Quality and Transparency of Health Research Reporting Guidelines, including the Preferred Reporting Items for Systematic Reviews and Meta-analysis Of Observational Studies in Epidemiology guidelines. We searched all available literature published in the PubMed-MEDLINE, EMBASE, and Cochrane databases through 31 December 2020. The databases were comprehensibly searched using the equivalent terms included in Appendix E1.

4.4.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if the following criteria were present: (1) comparison of surgical outcomes of lung, liver, or kidney nodule resection surgery with and without image guidance; (2) report of the 3DVP effects on at least one of the following clinical outcomes: operation time, intraoperative bleeding, postoperative hospital stay, or postoperative events; (3) use of preoperative or intraoperative 3D reconstruction from computed tomography (CT) or magnetic resonance images; and (4) design of the study as randomized and non-randomized controlled trials.

Exclusion criteria were the following: (1) studies that used image guidance for biopsy, radiotherapy, or robotic-assisted surgery; (2) studies that used other types of IGS, not the 3D reconstruction, such as augmented reality; (3) case reports, letters to editor, reviews, or meta-analysis; (4) studies not published in English; (5) studies with animals, corpses, or phantoms.

4.4.3. Study quality assessment

Two reviewers assessed the quality of all eligible studies with the methodological index for non-randomized studies (MINORS) (22). This tool is composed of 12 items that assess the methodological quality of non-randomized surgical studies. Each of these items is scored from 0 to 2, where 0 indicates that the issue was not reported in the evaluated study, 1 corresponding to items reported inadequately, and 2 correspond to items reported adequately (22).

4.4.4. Data extraction

Three reviewers independently reviewed all included articles to collect all the primary data (e.g., study design, country of recruitment, type of surgery, nodule site). From each article, the mean operation time (OT), mean estimated blood loss (EBL), mean postoperative hospital stay (POHS), and the number of postoperative events (POE) were extracted. Any disagreements were resolved by consensus.

4.4.5. Statistical analysis

The effect size (ES) (standardized mean difference, SMD) of 3DVP versus non-3DVP was extracted from each study to calculate the pooled measurements for continuous variables (OT, EBL, POHS). The magnitude of effect for SMD was considered as “small” if equal to 0.2, “medium” if 0.5, and large if 0.8 (23). The odds ratio (OR) were extracted from each study to combine the pooled results regarding the number of POE. In studies were the standard deviation was not reported, it was estimated based on sample size, median and interquartile range (24). Data were pooled using a random-effects model.

Heterogeneity between studies was tested with the Q test (25). The I2 index was used to quantify the extent of heterogeneity. Publication bias was estimated using the funnel plot and the Egger's and Begg's tests (26, 27). Sensitivity analyses that excluded each of the individual articles were conducted to evaluate whether any specific study significantly influenced the overall pooled results. All P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata version 15.0 (StataCorp LP, College Station, Texas, USA).

4.5. RESULTS

4.5.1. Study characteristics

The initial search yielded 2397 studies, from which 86 were reviewed, and 10 met the inclusion criteria (8-11, 28-33) (Figure 1). The median MINORS score was 17 (interquartile range (IQR), 15.25-17.25). Only one study had a MINORS score lower than 15 (MINORS score = 5) (28). A total of 897 patients were included, of which 469 (52.3%) subjects had undergone 3DVP, and 428 (47.7%) were non-3DPV controls (Table 1). Lung was the main surgical site in two studies that performed video-assisted thoracoscopic (VATS) segmentectomy, lobectomy, and bilobectomy (8, 28). Three studies approached liver nodule resection using 3DVP, performing hemihepatectomy, extended hepatectomy, segmentectomy, sectionectomy, or partial resection (9, 29, 30). Five studies used image-guided kidney surgery using laparoscopic partial nephrectomy (LPN), robot-assisted partial nephrectomy, or minimum incision endoscopic nephrectomy (10, 11, 31-33).

4.5.2. Operation time

All studies were included in the pooled OT analysis (8-11, 28-33) (Figure 2). Six studies described a significant shorter OT for IGS (8-11, 29, 30). In the remaining, there was no significant difference in the OT between IGS and non-IGS (28, 31-33). Pooled analysis revealed a significant difference on OT between the groups with a moderate ES favoring the IGS group and a significantly high heterogeneity between studies (SMD, -0.56; 95%CI: -0.91, -0.22; $I^2 = 83.1\%$; $p = .000$). Visual analysis of the forest plot (Figure 2) revealed that the article by Xue et al. was the greater contributor to the high heterogeneity between studies. Therefore, we performed a sensitivity analysis with removal of such study, which resulted in a lower but still significant heterogeneity ($I^2 = 52.8\%$; $p = .031$), and a slightly lower effect size (SMD, -0.36; 95%CI: -0.58, -0.15) (Figure 3).

Nakayama et al. also performed a subgroup analysis of the OT and found that IGS impact was more significant for patients with repeated hepatectomy, as the 3D group presented a 130 minutes shorter median OT compared to the group without 3D ($p = .03$) (9). Among the types of hepatic resections, segmentectomy was the only that presented a statistically significant shorter OT for the 3D group (MD, -43.5 minutes) ($p = .03$) (9).

Although Wang et al. did not find a significant difference in the mean OT between 3D-guided and non-3D-guided LPN, the authors found a significant shorter OT (MD = -28.1 minutes; $p = .018$) for patients with medium-high complexity renal lesions that had a 3D virtual-surgery planning (i.e., R.E.N.A.L. score ≥ 8) (31). Likewise, when controlling for case complexity and other covariates, Shirk et al. also found that patients whose surgical planning involved 3-D VR models showed differences in OT (OR, 1.00; 95%CI, 0.37-2.70; estimated OR, 2.47).

4.5.3. Estimated blood loss

All studies were included in the pooled EBL analysis (8-11, 26-31). Only two studies found a significantly lower EBL for 3DVP (10, 11). There was a significant difference between 3DVP and non-3DVP with a small ES favoring IGS and a non-significant heterogeneity between studies (SMD, -0.18; 95%CI: -0.33, -0.02; $I^2 = 22.5\%$; $p = .236$) (Figure 4).

Wang et al. reported a mean EBL of 148.1 (range, 85 - 290) ml for 3D-guided LPN vs. a mean EBL of 176.1 (range, 80 - 225) ml for non-3D-guided LPN ($p < 0.001$) (11). However, in our pooled analysis, the SMD between the groups in this study was not significant (SMD, -0.56; 95%CI: -1.25, 0.13).

Although Shirk et al. did not find significant differences in EBL between the control and intervention groups, patients without 3D VR-assisted surgical planning were more likely to have EBL greater than 200 mL (OR, 1.98; 95%CI, 1.04-3.78) (33). In addition, when controlling for case complexity and other covariates, the non-IGS group was more likely to have higher EBL (OR, 1.98; 95%CI, 1.04-3.78; estimated OR, 4.56) (33).

4.5.4. Postoperative hospital stay and postoperative events

Five studies reported the POHS (8, 9, 11, 28, 30), and six studies reported POE (8, 9, 29-32). None of the studies reported a statistically significant difference in the length of POHS or the number of POE between 3DVP and non-3DVP. The pooled analyses failed to demonstrate any difference between the 3DVP and non-3DVP groups for both POHS (SMD, -0.15; 95%CI: -0.39, 0.10; $I^2 = 37.0\%$; p = .174) (Figure 5) and POE (OR, 0.80; 95%CI: 0.54, 1.19; $I^2 = 0.0\%$; p = .0973) (Figure 6).

For lung surgery, PO complications occurred at similar rates for 3D-guided (n = 6; 17%) and non-3D-guided VATS-segmentectomy (n = 5; 16%) in the study by Xue et al. (8). These included atrial fibrillation, air leakage, pneumonia, and atelectasis. Xue et al. also reported a similar chest tube duration (3D-VATS-segmentectomy, 4.1 ± 1.8 days; vs. non-3D-VATS-segmentectomy, 4.1 ± 2.2 days; p = .93) (8).

Nakayama et al. only defined POE as complications of grade IIIa or higher by the Clavien-Dindo classification (9, 34). Although Fang et al. did not find any significant difference for POE between the groups, non-3D-guided liver resections had significantly more Clavien-Dindo complications of grades III and IV (n = 8; 14.3%; vs. n = 2; 3.3%; p = .048) (30). Patients that underwent 3D-guided liver resection also had less PO ascites (n = 2; 3.3%; vs. n = 8; 14.3%; p = .048), lower serum total bilirubin (23.2 ± 16.1 g/L; vs. 31.1 ± 24.1 g/L; p = .032), and higher serum albumin (29.3 ± 5.2 g/L; vs 27.8 ± 7.9 g/L; p = .0330) (30).

Two studies on renal nodule resection reported a lower rate of opening of the collecting system and urinary leakage in the 3D-guided nephrectomy groups (31, 32). Wang et al. reported significantly more cases of urinary leakage for patients with medium-high complexity renal lesions (i.e., R.E.N.A.L. score ≥ 8) that underwent non-3D-guided nephrectomy (4 vs. 0; p = .033) (31). None of the studies reported significant differences between the IGS and non-IGS groups on renal function, such as a significant increase in serum creatinine level or decrease in ipsilateral glomerular filtration rate postoperatively (31, 32). Although Shirk et al. did not report median POHS for the control and intervention groups, the authors found that patients without 3D VR-assisted surgical planning were more likely to have a length of hospital stay longer than two days (OR, 2.86; 95%CI, 1.59-5.14) (33). Further, when controlling for case complexity and other covariates, patients whose surgical planning involved 3-D VR models showed differences in clamp time (OR, 1.60; 95%CI, 0.79-3.23; estimated OR, 11.22), and length of hospital stay (OR, 2.86; 95%CI, 1.59-5.14; estimated OR, 5.43) (33).

4.6. DISCUSSION

In this meta-analysis, we found that IGS resulted in significantly lower OT and EBL but had no significant impact on POHS and POE. These results demonstrate that 3D-imaging virtual planning could improve some perioperative surgical variables. Although this meta-analysis could not find significant differences in the immediate postoperative clinical outcomes (POHS and POE), improvements in perioperative variables such as OT and EBL could influence medium and long-term clinical outcomes (35-41).

Previous data have shown that prolonged OT was associated with increased risk of infection at the surgical site. In a previous meta-analysis, every additional 10 min, 15 min, 30 min, and 60 min of surgery increased the likelihood of surgical site infection in 5%, 13%, 17%, and 37%, respectively (35). Also, previous studies have reported worse outcomes associated with higher blood losses during surgery, especially in the kidney (42), liver (43-46), and lung (47-49).

The use of IGS systems was linked to a reduction of 52% in the number of significant complications and 34% of total complications in a previous meta-analysis on image-guided endoscopic sinus surgery (3). In another meta-analysis of pedicle screw insertion in spine surgery, the use of IGS systems was associated with a reduction of 61% in the risk of pedicle perforation (50). However, data for other types of surgery are scarce. To our knowledge, this is the first meta-analysis evaluating only solid organs.

Our study has some limitations. First, our pooled analysis demonstrated significantly high heterogeneity for the OT (I^2 = 83.1%; p = .000) that was reduced in a complementary analysis without the study by Xue et al. (I^2 = 52.8%; p = .031) without the loss of the favoring effect towards IGS. Such findings could be attributed to several factors, including the comparison of different organ surgeries, types of surgery, sample sizes, surgeons' experience, software used for reconstruction, and different levels of surgery complexity. However, secondary subgroup analysis to try to identify the sources of heterogeneity, including those mentioned above, could not be performed due to the limited number of studies included in the meta-analysis. However, by using standardized mean differences, we tried to minimize the influence of some of these variables in our analysis. Second, we only included three solid organs that are among the most common sites of resection surgery of nodular lesions. Future studies using other organs could help to validate the benefits of IGS systems further. Third, there were limitations inherent to any meta-analyses, such as selection bias, publication bias, missing information from studies. Finally, most of the included studies were not prospective randomized clinical trials comparing IGS vs. non-IGS.

In summary, our data demonstrated that 3D-imaging virtual planning for resection of lung, kidney, and liver nodules could reduce operation time and estimated blood loss with no effects on immediate postoperative hospital stay and postoperative events.

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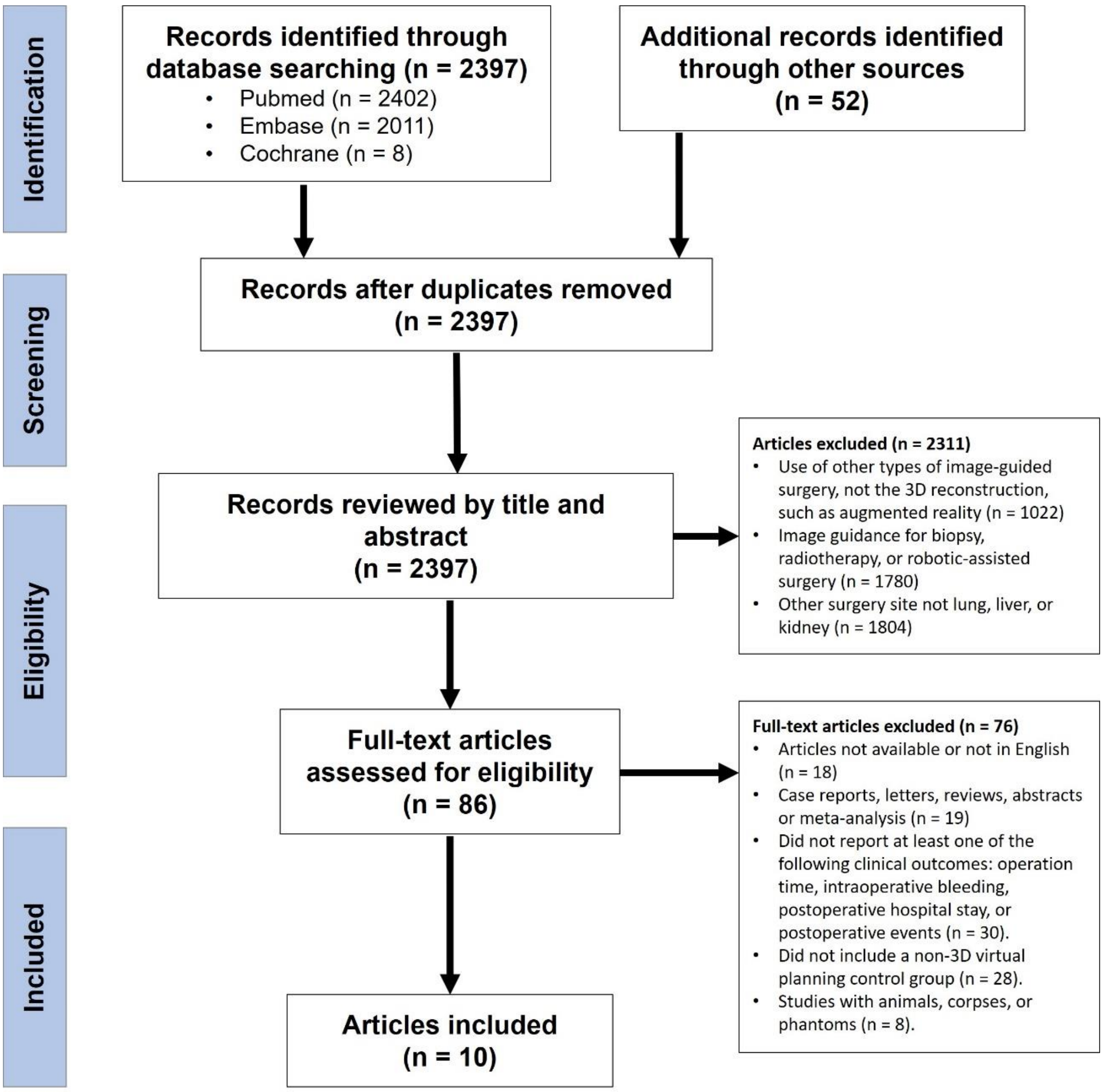
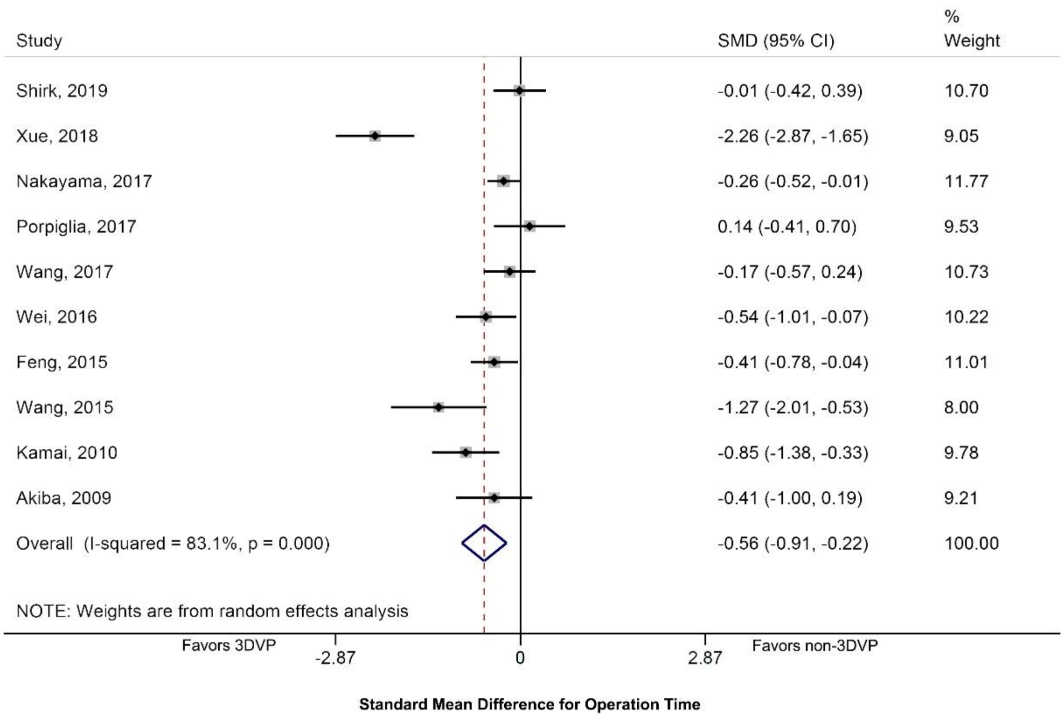
4.8. FIGURES

4.8.1. Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

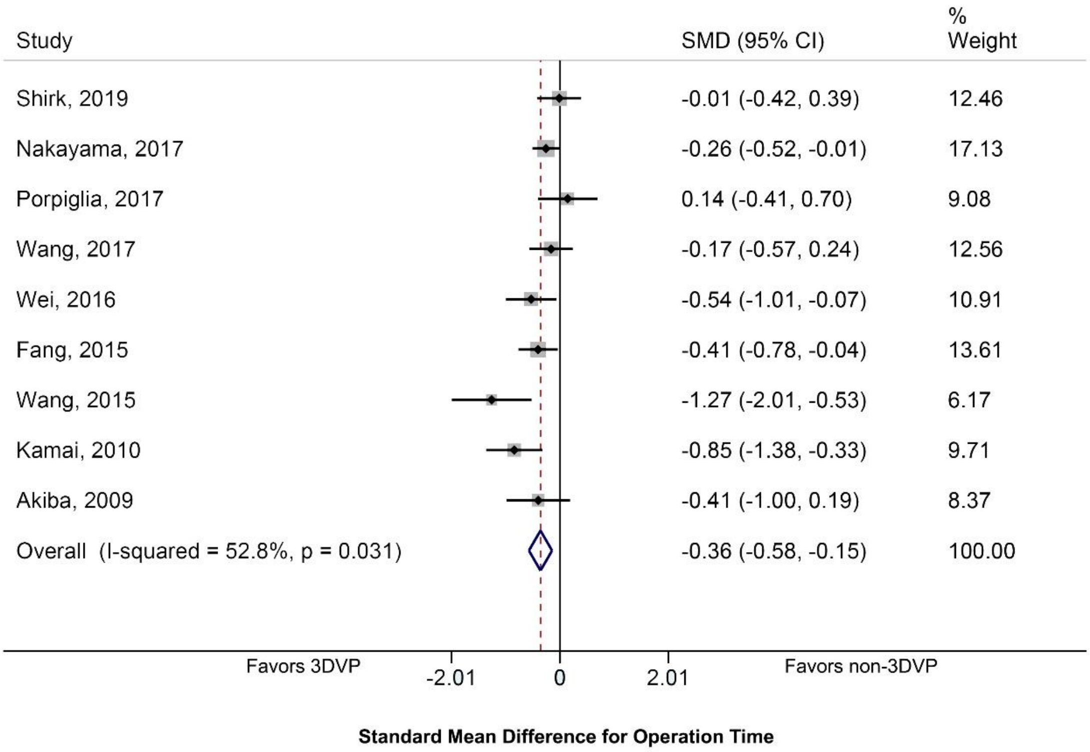


* Note. - The same study could be excluded for multiple reasons.

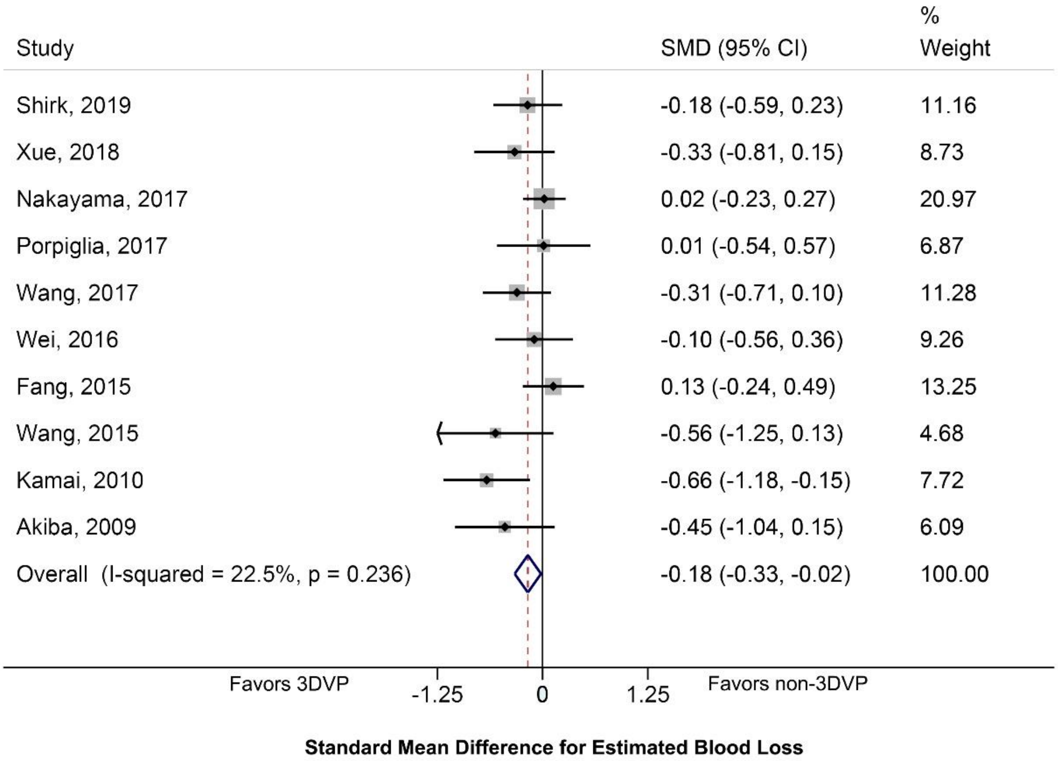
4.8.2. Figure 2 Forest plot of standard mean difference for operation time



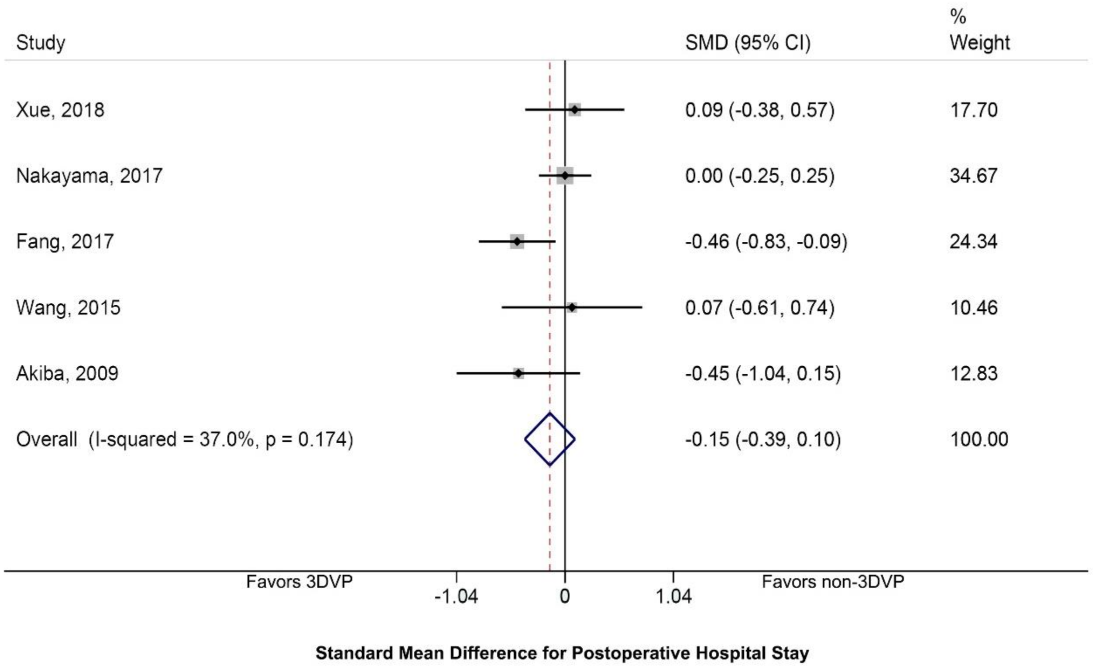
4.8.3. Figure 3 Sensitivity analysis of standard mean difference for operation time



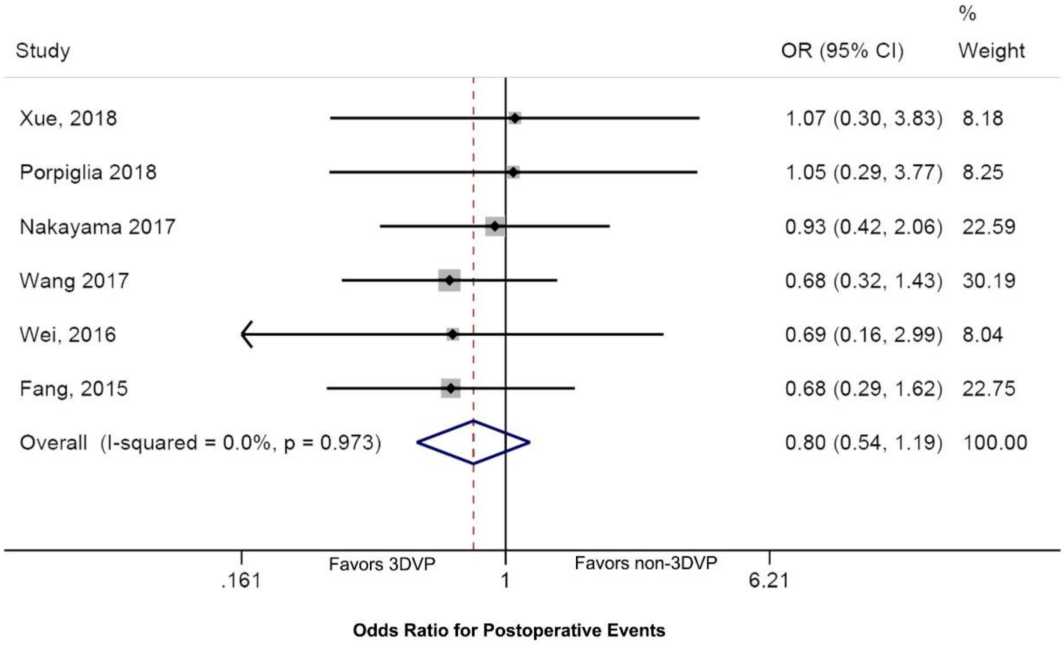
4.8.4. Figure 4 Forest plot of standard mean difference for estimated blood loss



4.8.5. Figure 5 Forest plots of standard mean difference for postoperative hospital stay



4.8.6. Figure 6 Forest plots of the odds ratio for postoperative events



4.9. TABLES

Table 1. Characteristics of included studies for meta-analysis.

Study	Year	Country	Study Design	n	Nodule Site	Surgery	MINORS score	Software for 3D-reconstruction	Open-source software	No. of patients in IGS group	No. of patients in non-IGS group	Outcomes
Xue	2018	China	R	68	Lung	VATS segmentectomy	16	3D Slicer, v.4	Y	36	32	OT, EBL, POHS, POE
Akiba	2009	Japan	NA	27	Lung	VATS segmentectomy, lobectomy, bilobectomy	5	NA	NA	27	19	OT, EBL, POHS
Nakayama	2017	Japan	R	240	Liver	Hemihepatectomy, Sectionectomy, Segmentectomy, Partial resection	17	SYNAPSE VINCENT, FUJIFILM Medical Co.	N	120	120	OT, EBL, POHS, POE
Wei	2016	China	P	74	Liver	En-bloc resection, Hepatectomy + thrombectomy	19	(3D Plus Body Visible System, Yorktal Medical	N	31	43	OT, EBL,
Fang	2015	China	R	116	Liver	Hemihepatectomy, extended hepatectomy, partial resection, mesohepatectomy	17	Medical Image Three-Dimensional Visualization System (MI-3DVS)	N	60	56	OT, EBL, POHS, POE
Wang	2015	China	R	35	Kidney	LPN	18	NA	NA	21	14	OT, EBL, POHS

Wang	2017	China	R	94	Kidney	LPN	15	Medical Imaging Three Divisional Visualization System, Yorktal, Inc.	N	49	45	OT, EBL, POE
Porpiglia	2018	Italy	P	52	Kidney	RAPN	17	M3DICS, Medics Srl	N	21	31	OT, EBL, POE
Kamai	2010	Japan	NA	80	Kidney	MIES nephrectomy	15	Leonardo InSpace, Siemens Healthcare	N	60	20	OT, EBL
Shirk	2019	USA	P	92	Kidney	RAPN	21	Reveal software versions 2.1-2.3; Ceevra	N	44	48	OT, EBL, POHS, POE

Note. - 3D = three-dimensional, EBL = estimated blood loss, MIES = minimum incision endoscopic surgery, NA = not available, OT = operation time, P = prospective, POE = postoperative events, POHS = postoperative hospital stay, R = retrospective, VATS = video-assisted thoracoscopic, LPN = laparoscopic partial nephrectomy, RAPN = robot-assisted partial nephrectomy

4.10. LIST OF SUPPLEMENTARY CONTENT

4.10.1 - Search strategy

(Image-guid*[tw] OR “image guidance”[tw] OR “image guided”[tw] OR three-dimensional[tw] OR 3D[tw] OR computer-aided[tw] OR “computer assistance”[tw] OR “computer navigated”[tw] OR augment*[tw]) AND (surger*[tw] OR surgeon*[tw] OR intervention*[tw] OR procedure*[tw]) AND (thorax*[tw] OR thoracic*[tw] OR chest*[tw] OR lung*[tw] OR airway*[tw] OR kidney*[tw] OR renal*[tw] OR urolog*[tw] OR liver*[tw] OR hepatic*[tw]) AND ((Bibliography[ptyp] OR pubmed books[filter] OR Classical Article[ptyp] OR Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Overall[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR systematic[sb] OR Validation Studies[ptyp]) AND "loattrfull text"[sb] AND English[lang]

5. CONCLUSÕES

Em resumo, os dados do trabalho demonstraram que o planejamento virtual com imagens tridimensionais de tomografia computadorizada para a ressecção de nódulos pulmonares, renais e hepáticos pode reduzir o tempo cirúrgico e o sangramento intraoperatório sem efeitos imediatos no tempo de internação hospitalar pós-operatória e no número de eventos pós-operatórios imediatos. Tais mudanças nessas variáveis perioperatórias podem melhorar os resultados pós-operatórios no médio e longo prazo para ressecções nodulares no pulmão, fígado e rim.

6. CONSIDERAÇÕES FINAIS

O presente estudo faz parte de um projeto maior intitulado “Simulação de Imagem Cirúrgica no Câncer de Pulmão: Preview Trial**”,** aprovado pelo Comitê de Ética em Pesquisa (CEP) da Irmandade Santa Casa de Misericordia de Porto Alegre (ISCMPA) (Parecer N° 3.265.012). O desenvolvimento desta revisão sistemática e meta-análise possibilitou um embasamento mais robusto e crítico para a realização do projeto acima. A partir dele será desenvolvido um estudo prospectivo, analítico, randomizado a ser realizado com 50 pacientes atendidos na ISCMPA em que serão analisados resultados referentes a segurança cirúrgica entre pacientes submetidos à reconstrução de imagens 3D pela tomografia computadorizada para visualização anatômica pulmonar pré-operatória e de pacientes sem a reconstrução. Os grupos serão divididos de forma randomizada. Serão comparados os dois grupos e avaliado os desfechos de tempo cirúrgico e perda sanguínea relacionada ao procedimento.

7. BIOGRAFIA

Durante o Mestrado em Patologia na UFCSPA, foram publicados 13 artigos em revistas internacionais indexadas ao PubMed junto ao orientador Dr. Bruno Hochhegger:

1. Basso Dias A, **Zanon M**, Altmayer S, Sartori Pacini G, Henz Concatto N, Watte G, Garcez A, Mohammed TL, Verma N, Medeiros T, Marchiori E, Irion K, **Hochhegger B**. Fluorine 18–FDG PET/CT and diffusion-weighted MRI for malignant versus benign pulmonary lesions: a meta-analysis. Radiology. 2019 Feb;290(2):525-34.

   Citações (Até 16/02/2021): 14 Fator impacto (2019): 7.931

2. Altmayer S, Zanon M, Pacini GS, Watte G, Barros MC, Mohammed TL, Verma N, Marchiori E, Hochhegger B. Comparison of the computed tomography findings in COVID-19 and other viral pneumonia in immunocompetent adults: a systematic review and meta-analysis. European radiology. 2020 Dec;30(12):6485-96.

   Citações (Até 16/02/2021): 18 Fator impacto (2019): 4,101

3. Machado Medeiros T, Altmayer S, Watte G, **Zanon M**, Basso Dias A, Henz Concatto N, Hoefel Paes J, Mattiello R, de Souza Santos F, Mohammed TL, Verma N, **Hochhegger B**. 18F-FDG PET/CT and whole-body MRI diagnostic performance in M staging for non–small cell lung cancer: a systematic review and meta-analysis. European Radiology. 2020 Jul;30(7):3641-9.

   Citações (Até 16/02/2021): 3 Fator impacto (2019): 4,101

4. Altmayer S, **Zanon M**, Sprinz C, Watte G, **Hochhegger B**. Is the effect of hyperglycemia on liver 18 F-FDG standardized uptake value really clinically significant?. European journal of nuclear medicine and molecular imaging. 2019 Jun;46(6):1216-7.

   Citações (Até 16/02/2021): 0 Fator impacto (2019): 7,081

5. Giacomelli IL, Barros M, Pacini GS, Altmayer S, **Zanon M**, Dias AB, Nin CS, Rodrigues RP, Marchiori E, Watte G, **Hochhegger, B**. Multiple cavitary lung lesions on CT: imaging findings to differentiate between malignant and benign etiologies. Jornal Brasileiro de Pneumologia (Online), v. 46, p. e20190024-e20190024, 2020.

   Citações (Até 16/02/2021): 4 Fator impacto (2019): 1,870

6. **Hochhegger, B; Zanon, M**; Altmayer S, Mandelli NS, Stüker G, Mohammed TL, Verma N, Meirelles GS, Marchiori E. COVID-19 mimics on chest CT: a pictorial review and radiologic guide. The British journal of radiology. 2021 Feb 1;94(1118):20200703.

Citações (Até 16/02/2021): 0 **Fator impacto (2019): 2,196**

7. da Silva TK, **Zanon M**, Altmayer S, Pacini GS, Watte G, Stein R, Pitrez PM, **Hochhegger B**. High-resolution CT pulmonary findings in children with severe asthma. Jornal de pediatria. 2021 Jan 1;97(1):37-43.

   Citações (Até 16/02/2021): 0 **Fator impacto (2019): 2,029**

8. Verma N, Pacini GS, Torrada JP, Oliveira DM, **Zanon M**, Marchiori E, Mohammed TL, **Hochhegger B**. Subspecialized radiology reporting: productivity and impact on the turnaround times for radiology reports in a middle-income country. Radiologia Brasileira. 2020 Aug;53(4):236-40.

   Citações (Até 16/02/2021): 0 **Fator impacto (2019): 1,4734**

9. **Hochhegger B**, Marchiori E, **Zanon M,** Rubin AS, Fragomeni R, Altmayer S, Carvalho CR, Baldi BG. Imaging in idiopathic pulmonary fibrosis: diagnosis and mimics. Clinics. 2019;74.

   Citações (Até 16/02/2021): 8 **Fator impacto (2019): 1,435**

10. Moraes MO, Roman DH, Copetti J, Santos FD, Agra A, Noronha JA, Carvalhal G, Neto EJ, **Zanon M**, Baldisserotto M, **Hochhegger B**. Effects of the addition of quantitative apparent diffusion coefficient data on the diagnostic performance of the PI-RADS v2 scoring system to detect clinically significant prostate cancer. World journal of urology. 2020 Apr;38(4):981-91.

    Citações (Até 16/02/2021): 4 **Fator impacto (2019): 3,217**

11. Lonzetti L, **Zanon M**, Pacini GS, Altmayer S, de Oliveira DM, Rubin AS, Gazzoni FF, Barros MC, **Hochhegger B**. Magnetic resonance imaging of interstitial lung diseases: a state-of-the-art review. Respiratory medicine. 2019 Aug 1;155:79-85.

    Citações (Até 16/02/2021): 8 **Fator impacto (2019): 3,095**

12. Zampieri JF, Pacini GS, **Zanon M**, Altmayer SPL, Watte G, Barros M, Durayski E, Meirelles GSP, Guimarães MD, Marchiori E, Souza Junior AS, **Hochhegger B**. Thoracic calcifications on magnetic resonance imaging: correlations with computed tomography. Jornal Brasileiro de Pneumologia. 2019;45(4).

    Citações (Até 16/02/2021): 0 **Fator impacto (2019): 1,870**

7. APÊNDICES

7.1. Prêmios e distinções acadêmicas

Prêmio Presidente da Academia Nacional de Medicina 2019

Academia Nacional de Medicina

Diploma

Conferido ao Dr. Matheus Zanon, Vencedor do ***Prêmio Presidente da Academia Nacional de Medicina/2019 – Carlos Pinto Seidl – Secção de Ciências Aplicadas à Medicina,*** *como Co-autor Colaborador do Trabalho: "Ressonância magnética de nódulos pulmonares: acurácia em região endêmica de doença granulomatosa".*

Rio de Janeiro, 02 de julho de 2019

Acadêmico Jorge Alberto Costa e Silva
Presidente

Acadêmico José Galvão-Alves
Secretário Geral

Acadêmico Milton Ary Meier
Tesoureiro

Academia
Nacional de
Medicina

8. ANEXOS

8.1. Parecer do Comitê de Ética da ISCMPA

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: SIMULAÇÃO DE IMAGEM CIRÚRGICA NO CÂNCER DE PULMÃO: PREVIEW TRIAL
Pesquisador: Bruno Hochhegger
Área Temática:
Versão: 1
CAAE: 09695919.1.0000.5335
Instituição Proponente: Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.265.012

Apresentação do Projeto:
Estudo prospectivo, analítico, randomizado a ser realizado com 50 pacientes atendidos na Santa Casa, em que serão analisados resultados referentes a segurança cirúrgica entre pacientes submetidos à reconstrução de imagens 3D pela tomografia computadorizada para visualização anatômica pulmonar pré-operatória e de pacientes sem a reconstrução. Os grupos serão divididos de forma randomizada. Serão comparados os dois grupos e avaliado os desfechos de tempo cirúrgico e perda sanguínea relacionada ao procedimento.

Objetivo da Pesquisa:
O pesquisador declara sobre:
- Objetivo Primário: demonstrar a influência do simulador de imagem cirúrgico produzido pela TC-3D na cirurgia torácica vídeo-assistida no que se refere ao tempo cirúrgico e ao volume de perda sanguínea perioperatória.
- Objetivo Secundário: correlacionar as estruturas anatômicas pulmonares (arterial, venoso, fissuras e ressecção brônquica) desenvolvidas pelo simulador com as mesmas
durante o transoperatório.

Avaliação dos Riscos e Benefícios:
O pesquisador declara sobre:
- Riscos: A confidencialidade dos pacientes está assegurada, pois as imagens e todas as descrições no texto do estudo não terão qualquer identificação nominal. O presente estudo não

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proporcionará nenhum risco extra aos pacientes, uma vez que os mesmos serão submetidos à exame de imagem tomográfico conforme indicação clínica e serão submetidos ao procedimento invasivo conforme indicação da equipe cirúrgica assistente. A reconstrução 3D não acarretará nenhum malefício aos sujeitos da pesquisa. Existe sempre o mínimo risco de quebra de confidencialidade dos
sujeitos participantes, contudo, os pesquisados buscam zelar pelo sigilo dos indivíduos participantes da maneira mais idônea.
- Benefícios: Com os dados do estudo e se comprovando os benefícios da utilização de imagens em reconstrução 3D para avaliação anatômica pulmonar, pacientes futuros poderão também se beneficiar dessa técnica como forma de aumentar a segurança do procedimento.

Comentários e Considerações sobre a Pesquisa:
O pesquisador declara sobre: Critério de Inclusão:
- Critérios de inclusão: pacientes apresentando nódulo pulmonar semissólido com progressão (3 cm), pacientes com tumores sólidos estádios I e II, pacientes com tumores sólidos de pequeno tamanho, todos esses definidos como ressecáveis por ressecção em cunha conforme indicação do cirurgião responsável pelo tratamento. Para serem elegíveis, os pacientes deverão ter sido submetidos à TC de tórax na instituição no intervalo máximo de 1 mês antes da realização do VATS.
- Critério de Exclusão:
Pacientes que possuam registro incompleto no sistema de prontuário eletrônico da instituição (Tasy);
Pacientes com lesões com extensão além de um lobo pulmonar único;
Pacientes impróprios para anestesia geral ou para o procedimento cirúrgico;
Pacientes que não concordarem em assinar o termo de consentimento livre e esclarecido (TCLE);
Pacientes que apresentem imagem torácica por TC com mais do que 1 mês entre aquisição de imagem e realização de procedimento cirúrgico, e
Pacientes com contraindicação ao uso de contraste para realização da tomografia computadorizada.

Considerações sobre os Termos de apresentação obrigatória:
Os seguintes documentos foram anexados e estão adequados: Folha de Rosto para Pesquisa envolvendo seres humanos, Formulário de Inscrição de projetos de Pesquisa – CEP da ISCMPA, Orçamento, Declaração de Confidencialidade no Estudo, Declaração de Autorização da Chefia

responsável, Declaração de isenção de ônus à Instituição, TCLE, Declaração de utilização de dados de prontuário e uso de publicação.

Conclusões ou Pendências e Lista de Inadequações:

A pesquisa encontra-se de acordo com a Norma vigente Resolução 466/12 para pesquisa em seres humanos.

Considerações Finais a critério do CEP:

Após avaliação do protocolo acima descrito, o presente comitê não encontrou óbices quanto ao desenvolvimento do estudo em nossa Instituição e poderá ser iniciado a partir da data deste parecer.

Obs.: 1 - O pesquisador responsável deve encaminhar à este CEP, Relatórios de Andamento dos Projetos desenvolvidos na ISCMPA. Relatórios Parciais (pesquisas com duração superior à 6 meses), Relatórios Finais (ao término da pesquisa) e os Resultados Obtidos (cópia da publicação).

2 – Para o início do projeto de pesquisa, o investigador deverá apresentar a chefia do serviço (onde será realizada a pesquisa), o Parecer Consubstanciado de aprovação do protocolo pelo Comitê de Ética.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1285783.pdf	15/03/2019 18:04:43		Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	15/03/2019 18:04:25	Bruno Hochhegger	Aceito
Folha de Rosto	Folha_Rosto.pdf	01/03/2019 17:43:24	Bruno Hochhegger	Aceito
Outros	Formulario_Inscricao.pdf	12/02/2019 22:35:28	Bruno Hochhegger	Aceito
Outros	Declaracao_AutorizacaoChefia.pdf	12/02/2019 22:35:02	Bruno Hochhegger	Aceito
Outros	DeclaracaoUsoDados.pdf	12/02/2019 22:34:21	Bruno Hochhegger	Aceito
Outros	Declaracao_IsencaoOnus.pdf	12/02/2019 22:33:54	Bruno Hochhegger	Aceito

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IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

Continuação do Parecer: 3.265.012

Outros	Declaracao_Confidencialidade.pdf	12/02/2019 22:33:23	Bruno Hochhegger	Aceito
Orçamento	Orcamento.pdf	12/02/2019 22:33:02	Bruno Hochhegger	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	16/01/2019 15:11:46	Bruno Hochhegger	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 15 de Abril de 2019

Assinado por:
Claudio Marcel Berdún Stadñik
(Coordenador(a))

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8.2. Resumo do artigo publicado na Surgical Oncology.

Surgical Oncology 38 (2021) 101598

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journal homepage: www.elsevier.com/locate/suronc

ELSEVIER

Three-dimensional virtual planning for nodule resection in solid organs: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Three-dimensional
Image-guided surgery
Lung
Liver
Kidney

ABSTRACT

Objectives: To systematically review the effects of 3D-imaging virtual planning for nodule resection in the following solid organs: lung, liver, and kidney.
Methods: MEDLINE, EMBASE, and Cochrane Library were searched through September 31, 2020 to include randomized and non-randomized controlled studies that compared outcomes of surgical resection of lung, liver, or kidney nodule resection with and without 3D virtual planning with computed tomography. From each article, the mean operation time (OT), mean estimated blood loss (EBL), mean postoperative hospital stay (POHS), and the number of postoperative events (POE) were extracted. The effect size (ES) of 3D virtual planning vs. non-3D planning was extracted from each study to calculate the pooled measurements for continuous variables (OT, EBL, POHS). Data were pooled using a random-effects model.
Results: The literature search yielded 2397 studies and 10 met the inclusion criteria with a total of 897 patients. There was a significant difference in OT between groups with a moderate ES favoring the 3D group (ES,-0.56; 95%CI: 0.91,-0.29; $I^2 = 83.1\%$; $p < .001$). Regarding EBL, there was a significant difference between 3D and non-3D with a small ES favoring IGS (ES,-0.18; 95%CI: 0.33,-0.02; $I^2 = 22.5\%$; $p = .0236$). There was no difference between the 3D and non-3D groups for both POHS (POHS ES,-0.15; 95%CI: 0.39,0.10; $I^2 = 37.0\%$; $p = .174$) and POE (POE odds ratio (OR),0.80; 95%CI:0.54,1.19; $I^2 = 0.0\%$; $p = .0.973$).
Conclusions: 3D-imaging planning for surgical resection of lung, kidney, and liver nodules could reduce OT and EBL with no effects on immediate POHS and POE. Improvements in these perioperative variables could improve medium and long-term postoperative clinical outcomes.

1. Introduction

With the development of new post-processing technologies, there has been an increase in the use of image-guided surgery (IGS) systems to assist surgeons during challenging operations [1,2]. Several preoperative and intraoperative applications of IGS systems are currently available. The most used IGS systems are those that provide preoperative information support, such as segmentation of risk structures or targets by three-dimensional (3D) virtual guidance. IGS systems can also offer intraoperative information support, such as distance visualization, proximity warnings when close to important structures, and augmentation of risk structures or targets [1,2].

IGS systems could improve intraoperative orientation, identification, and location of anatomical structures and their variations, decreasing

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Available online 30 April 2021

surgeons' workload and contributing to performance enhancement [1, 3–7]. On the other hand, adverse side effects could also arise from the use of IGS systems, such as increased perceived time, pressure and mental demands, errors due to overreliance on the computer assistance, and possible interference on the development of surgical skills [2].

Clinical outcomes, such as patient safety, operation time (OT), intraoperative estimated blood loss (EBL), postoperative hospital stay (POHS), and prevalence of postoperative events (POE) have been reported to improve with the use of IGS systems [1,8–11]. Previous systematic reviews and meta-analyses have reported positive effects of IGS on clinical outcomes of maxillofacial surgery, neurosurgery, and spinal surgery [3–5]. Until now, there are only a few state-of-the-art reviews about the use of 3D-guidance for operations of the lung [12–14], liver [15–17], and kidney [18–21], but no systematic reviews or meta-analyses on the effect of IGS on these solid organs were performed. This meta-analysis aimed to assess the effects of 3D-imaging virtual planning (3DVP) for surgical resection of lung, liver, and kidney nodules.

2. Methods

2.1. Search strategy

This study was reported following Enhancing the Quality and Transparency of Health Research Reporting Guidelines, including the Preferred Reporting Items for Systematic Reviews and Meta-analysis Of Observational Studies in Epidemiology guidelines. We searched all available literature published in the PubMed-MEDLINE, EMBASE, and Cochrane databases through September 31, 2020. The databases were comprehensibly searched using the equivalent terms included in Appendix E1.

2.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if the following criteria were present [1]: comparison of surgical outcomes of lung, liver, or kidney nodule resection surgery with and without image guidance [2]; report of the 3DVP effects on at least one of the following clinical outcomes: operation time, intraoperative bleeding, postoperative hospital stay, or postoperative events [3]; use of preoperative or intraoperative 3D reconstruction from computed tomography (CT) or magnetic resonance images; and [4] design of the study as randomized and non-randomized controlled trials.

Exclusion criteria were the following [1]: studies that used image guidance for biopsy, radiotherapy, or robotic-assisted surgery [2]; studies that used other types of IGS, not the 3D reconstruction, such as augmented reality [3]; case reports, letters to editor, reviews, or meta-analysis [4]; studies not published in English [5]; studies with animals, corpses, or phantoms.

2.3. Study quality assessment

Two reviewers assessed the quality of all eligible studies with the methodological index for non-randomized studies (MINORS) [22]. This tool is composed of 12 items that assess the methodological quality of non-randomized surgical studies. Each of these items is scored from 0 to 2, where 0 indicates that the issue was not reported in the evaluated study, 1 corresponding to items reported inadequately, and 2 correspond to items reported adequately [22].

2.4. Data extraction

Three reviewers independently reviewed all included articles to collect all the primary data (e.g., study design, country of recruitment, type of surgery, nodule site). From each article, the mean operation time (OT), mean estimated blood loss (EBL), mean postoperative hospital stay (POHS), and the number of postoperative events (POE) were extracted. Any disagreements were resolved by consensus.

2.5. Statistical analysis

The effect size (ES) (standardized mean difference, SMD) of 3DVP versus non-3DVP was extracted from each study to calculate the pooled measurements for continuous variables (OT, EBL, POHS). The magnitude of effect for SMD was considered as "small" if equal to 0.2, "medium" if 0.5, and large if 0.8 [23]. The odds ratio (OR) were extracted from each study to combine the pooled results regarding the number of POE. In studies were the standard deviation was not reported, it was estimated based on sample size, median and interquartile range [24]. Data were pooled using a random-effects model.

Heterogeneity between studies was tested with the Q test [25]. The I^2 index was used to quantify the extent of heterogeneity. Publication bias was estimated using the funnel plot and the Egger's and Begg's tests [26, 27]. Sensitivity analyses that excluded each of the individual articles were conducted to evaluate whether any specific study significantly influenced the overall pooled results. All P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata version 15.0 (StataCorp LP, College Station, Texas, USA).

3. Results

3.1. Study characteristics

The initial search yielded 2397 studies, from which 86 were reviewed, and 10 met the inclusion criteria [8–11,28–33] (Fig. 1). The median MINORS score was 17 (interquartile range (IQR), 15.25–17.25). Only one study had a MINORS score lower than 15 (MINORS score = 5) [28].

A total of 897 patients were included, of which 469 (52.3%) subjects had undergone 3DVP, and 428 (47.7%) were non-3DPV controls (eTable 1). Lung was the main surgical site in two studies that performed video-assisted thoracoscopic (VATS) segmentectomy, lobectomy, and bilobectomy [8,28]. Three studies approached liver nodule resection using 3DVP, performing hemihepatectomy, extended hepatectomy, segmentectomy, sectionectomy, or partial resection [9,29,30]. Five studies used image-guided kidney surgery using laparoscopic partial nephrectomy (LPN), robot-assisted partial nephrectomy, or minimum incision endoscopic nephrectomy [10,11,31–33].

3.2. Operation time

All studies were included in the pooled OT analysis [8–11,28–33] (Fig. 2). Six studies described a significant shorter OT for IGS [8–11,29, 30]. In the remaining, there was no significant difference in the OT between IGS and non-IGS [28,31–33]. Pooled analysis revealed a significant difference on OT between the groups with a moderate ES favoring the IGS group and a significantly high heterogeneity between studies (SMD, −0.56; 95%CI: −0.91, −0.22; $I^2 = 83.1\%$; $p < .001$). Visual analysis of the forest plot (Fig. 2) revealed that the article by Xue et al. was the greater contributor to the high heterogeneity between studies. Therefore, we performed a sensitivity analysis with removal of such study, which resulted in a lower but still significant heterogeneity ($I^2 = 52.8\%$; $p = .031$), and a slightly lower effect size (SMD, −0.36; 95%CI: −0.58, −0.15) (Fig. 3).

Nakayama et al. also performed a subgroup analysis of the OT and found that IGS impact was more significant for patients with repeated hepatectomy, as the 3D group presented a 130 min shorter median OT compared to the group without 3D ($p = .03$) [9]. Among the types of hepatic resections, segmentectomy was the only that presented a statistically significant shorter OT for the 3D group (MD, −43.5 min) ($p = .03$) [9].

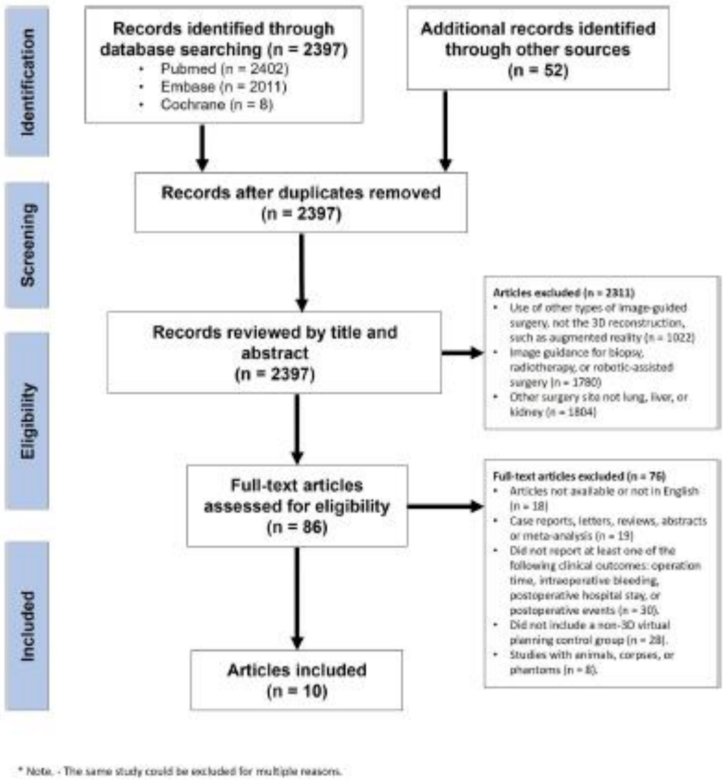

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

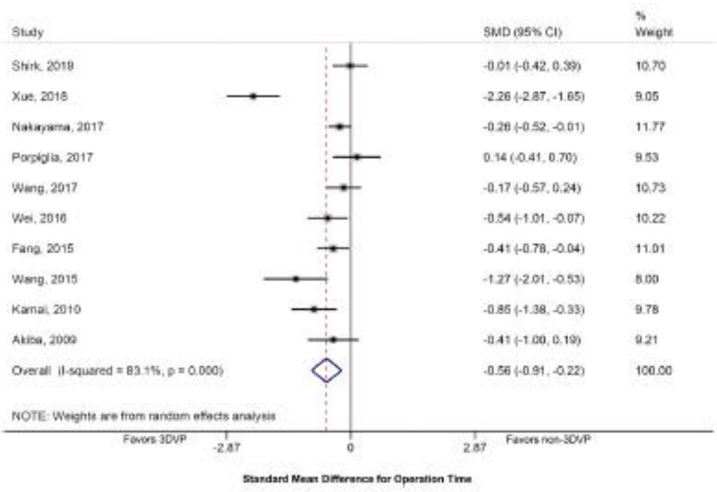

Fig. 2. Forest plot of standard mean difference for operation time.

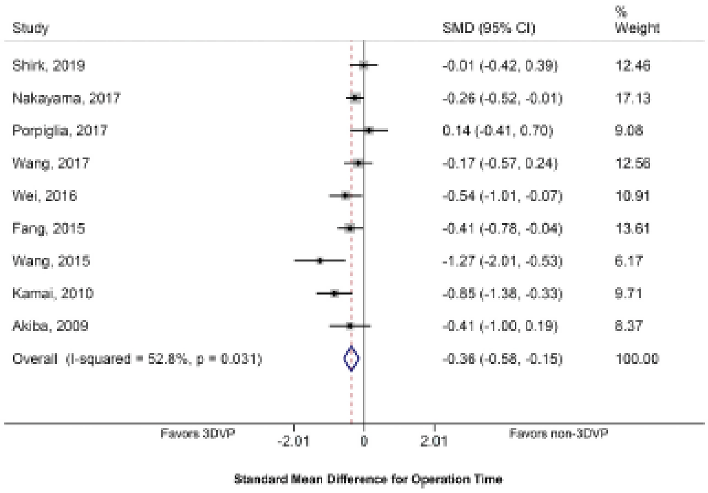

Fig. 3. Sensitivity analysis of standard mean difference for operation time.

Although Wang et al. did not find a significant difference in the mean OT between 3D-guided and non-3D-guided LPN, the authors found a significant shorter OT (MD = −28.1 min; p = .018) for patients with medium-high complexity renal lesions that had a 3D virtual-surgery planning (i.e., R.E.N.A.L. score ≥8) [31]. Likewise, when controlling for case complexity and other covariates, Shirk et al. also found that patients whose surgical planning involved 3-D VR models showed differences in OT (OR, 1.00; 95%CI, 0.37–2.70; estimated OR, 2.47).

3.3. Estimated blood loss

All studies were included in the pooled EBL analysis [8–11,28–33]. Only two studies found a significantly lower EBL for 3DVP [10,11]. There was a significant difference between 3DVP and non-3DVP with a small ES favoring IGS and a non-significant heterogeneity between studies (SMD, −0.18; 95%CI: −0.33, −0.02; I^2 = 22.5%; p = .236) (Fig. 4).

Wang et al. reported a mean EBL of 148.1 (range, 85–290) mL for 3D-guided LPN vs. a mean EBL of 176.1 (range, 80–225) mL for non-3D-guided LPN (p < .001) [11]. However, in our pooled analysis, the SMD between the groups in this study was not significant (SMD, −0.56; 95%CI: −1.25, 0.13).

Although Shirk et al. did not find significant differences in EBL between the control and intervention groups, patients without 3D VR-assisted surgical planning were more likely to have EBL greater than 200 mL (OR, 1.98; 95%CI, 1.04–3.78) [33]. In addition, when controlling for case complexity and other covariates, the non-IGS group was more likely to have higher EBL (OR, 1.98; 95%CI, 1.04–3.78; estimated

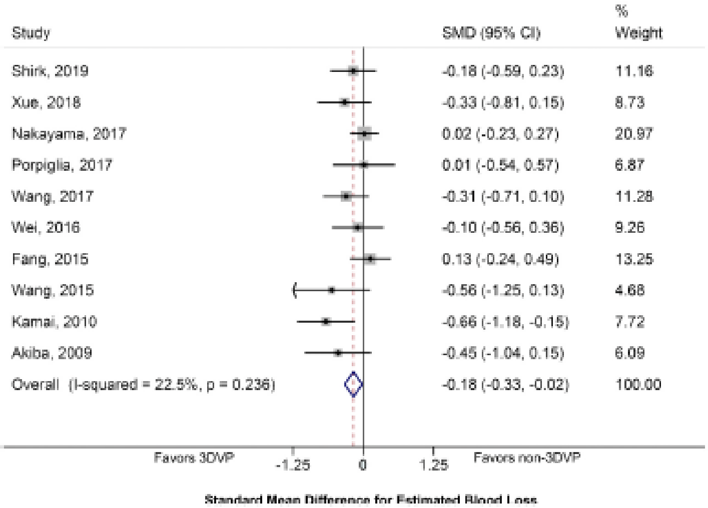

Fig. 4. Forest plot of standard mean difference for estimated blood loss.

OR, 4.56) [33].

3.4. Postoperative hospital stay and postoperative events

Five studies reported the POHS [8,9,11,28,30], and six studies reported POE [8,9,29–32]. None of the studies reported a statistically significant difference in the length of POHS or the number of POE between 3DVP and non-3DVP. The pooled analyses failed to demonstrate any difference between the 3DVP and non-3DVP groups for both POHS (SMD, −0.15; 95%CI: −0.39, 0.10; $I^2 = 37.0\%$; p = .174) (Fig. 5) and POE (OR, 0.80; 95%CI: 0.54, 1.19; $I^2 = 0.0\%$; p = .0973) (Fig. 5).

For lung surgery, PO complications occurred at similar rates for 3D-guided (n = 6; 17%) and non-3D-guided VATS-segmentectomy (n = 5; 16%) in the study by Xue et al. [8]. These included atrial fibrillation, air leakage, pneumonia, and atelectasis. Xue et al. also reported a similar chest tube duration (3D-VATS-segmentectomy, 4.1 ± 1.8 days; vs. non-3D-VATS-segmentectomy, 4.1 ± 2.2 days; p = .93) [8].

Nakayama et al. only defined POE as complications of grade IIIa or higher by the Clavien-Dindo classification [9,34]. Although Fang et al. did not find any significant difference for POE between the groups, non-3D-guided liver resections had significantly more Clavien-Dindo complications of grades III and IV (n = 8; 14.3%; vs. n = 2; 3.3%; p = .048) [30]. Patients that underwent 3D-guided liver resection also had less PO ascites (n = 2; 3.3%; vs. n = 8; 14.3%; p = .048), lower serum total bilirubin (23.2 ± 16.1 g/L; vs. 31.1 ± 24.1 g/L; p = .032), and higher serum albumin (29.3 ± 5.2 g/L; vs 27.8 ± 7.9 g/L; p = .0330) [30].

Two studies on renal nodule resection reported a lower rate of opening of the collecting system and urinary leakage in the 3D-guided nephrectomy groups [31,32]. Wang et al. reported significantly more cases of urinary leakage for patients with medium-high complexity renal lesions (i.e., R.E.N.A.L. score ≥8) that underwent non-3D-guided nephrectomy (4 vs. 0; p = .033) [31]. None of the studies reported significant differences between the IGS and non-IGS groups on renal function, such as a significant increase in serum creatinine level or decrease in ipsilateral glomerular filtration rate postoperatively [31,32]. Although Shirk et al. did not report median POHS for the control and intervention groups, the authors found that patients without 3D VR-assisted surgical planning were more likely to have a length of hospital stay longer than two days (OR, 2.86; 95%CI, 1.59–5.14) [33].

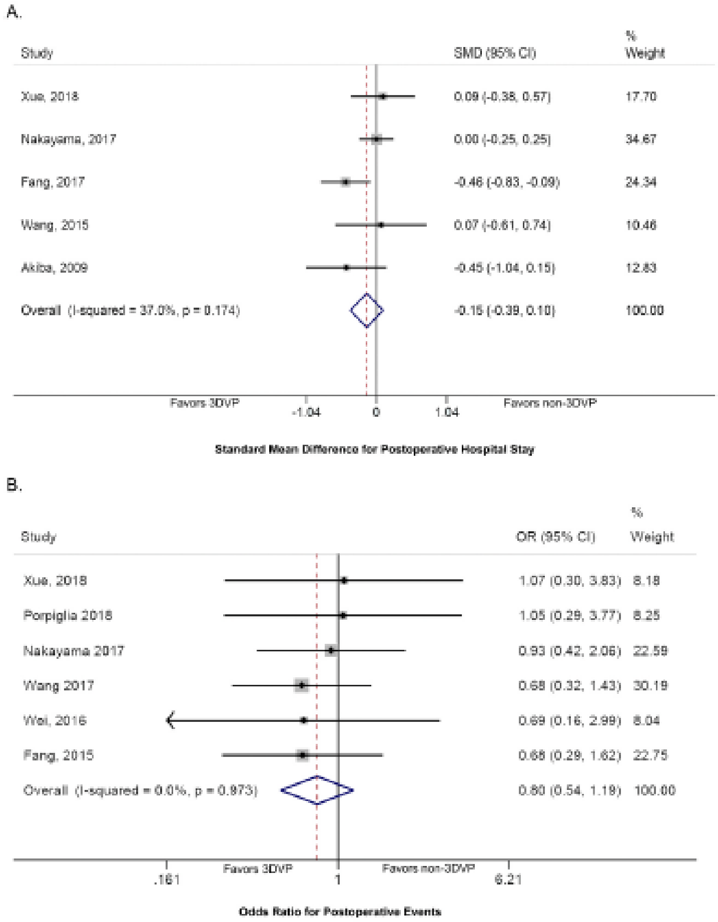

Fig. 5. Forest plots of (A) standard mean difference for postoperative hospital stay and (B) odds ratio for postoperative events.

Further, when controlling for case complexity and other covariates, patients whose surgical planning involved 3-D VR models showed differences in clamp time (OR, 1.60; 95%CI, 0.79–3.23; estimated OR, 11.22), and length of hospital stay (OR, 2.86; 95%CI, 1.59–5.14; estimated OR, 5.43) [33].

4. Discussion

In this meta-analysis, we found that IGS resulted in significantly lower OT and EBL but had no significant impact on POHS and POE. These results demonstrate that 3D-imaging virtual planning could improve some perioperative surgical variables. Although this meta-analysis could not find significant differences in the immediate postoperative clinical outcomes (POHS and POE), improvements in perioperative variables such as OT and EBL could influence medium and long-term clinical outcomes [35–42].

Previous data have shown that prolonged OT was associated with increased risk of the surgical site. In a previous meta-analysis, every additional 10 min, 15 min, 30 min, and 60 min of surgery increased the likelihood of surgical site infection in 5%, 13%, 17%, and 37%, respectively [35]. In another study including over 76,000 patients who underwent laparoscopic procedures, increasing operation time was independently linked with increased odds of complication in several elective procedures, such as colectomy, cholecystectomy, and gastric bypass ([42]).

Also, previous studies have reported worse outcomes associated with higher blood losses during surgery, especially in the kidney [43], liver [44–47], and lung [48–50]. In one series evaluating partial nephrectomy, operative blood loss higher than 250 mL and 1000 mL were associated with 60% and 1150% increased risk of hemorrhagic complications, respectively ([43]). For laparoscopic liver resection, EBL >250 mL has been described to correlate with higher conversion rates to open surgery and overall complications, including liver and kidney failure and postoperative mortality ([44]). In another series including resection of hepatocellular carcinoma, higher blood losses were associated with tumor recurrence and survival ([47]). In our study, we found a small but significant effect size on the use of 3DVP towards minimising bleeding during surgery. Although this effect was small, techniques that minimise blood losses may benefit nodule resection surgery, reducing complications and postoperative mortality. As 3DVP allows a throughout preoperative evaluation of blood supply and anatomy variations, large blood losses could be prevented, enhancing patient safety.

The use of IGS systems was linked to a reduction of 52% in the number of significant complications and 34% of total complications in a previous meta-analysis on image-guided endoscopic sinus surgery [3]. In another meta-analysis of pedicle screw insertion in spine surgery, the use of IGS systems was associated with a reduction of 61% in the risk of pedicle perforation [51]. However, data for other types of surgery are scarce. To our knowledge, this is the first meta-analysis evaluating only solid organs.

Some concerns have been raised related with the use of IGS systems, as workload increase and impairment on the learning of new surgical skills. For image-guided endoscopic sinus surgery, the previous meta-analysis could not find any significant difference between image-guided and standard surgeries, even when the included studies objectively assessed cardiovascular and endocrine indicators of workload and stress [3]. Also, 3D reconstructions have been shown to impact positively on the surgical education in some papers [52,53]. In our meta-analysis, we did not assess the 3DVP impact on surgeons, but future studies should try to include such analysis.

Our study has some limitations. First, our pooled analysis demonstrated significantly high heterogeneity for the OT ($I^2 = 83.1\%$; $p = .000$) that was reduced in a complementary analysis without the study by Xue et al. ($I^2 = 52.8\%$; $p = .031$) without the loss of the favoring effect towards IGS. Such findings could be attributed to several factors, including the comparison of different organ surgeries, types of surgery, sample sizes, surgeons' experience, software used for reconstruction, and different levels of surgery complexity. However, secondary subgroup analysis to try to identify the sources of heterogeneity, including those mentioned above, could not be performed due to the limited number of studies included in the meta-analysis. However, by using standardized mean differences, we tried to minimise the influence of some of these variables in our analysis. Second, we only included three solid organs that are among the most common sites of resection surgery of nodular lesions. Future studies using other organs could help to validate the benefits of IGS systems further. Third, there were limitations inherent to any meta-analyses, such as selection bias, publication bias, missing information from studies. Finally, most of the included studies were not prospective randomized clinical trials comparing IGS vs. non-IGS.

In summary, our data demonstrated that 3D-imaging virtual planning for resection of lung, kidney, and liver nodules could reduce operation time and estimated blood loss with no effects on immediate postoperative hospital stay and postoperative events.

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Availability of data and material

Data will be provided online once the article after the article is accepted.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent

This article does not contain patient data.

Contributions

Matheus Zanon: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualisation; Roles/Writing - original draft; Writing - review & editing.

Stephan Altmayer: Formal analysis; Investigation; Methodology; Validation; Visualisation; Roles/Writing - original draft.

Guilherme Watte: Formal analysis; Investigation; Methodology; Validation; Visualisation; Software; Roles/Writing - original draft.

Gabriel Sartori Pacini: Formal analysis; Investigation; Methodology; Validation; Visualisation; Roles/Writing - original draft.

Tan-Lucien Mohammed: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing - review & editing.

Edson Marchiori: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing - review & editing.

Darcy Ribeiro Pinto Filho: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing - review & editing.

Bruno Hochhegger: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualisation; Writing - review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2021.101598.

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