ASR
ARCHIVES of SURGICAL RESEARCH

Archives of Surgical Research

A Peer Reviewed Journal of Surgical Research & Education

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Archives of Surgical Research (ASR) is dedicated to the local, national, and global advancement of surgical research, education and clinical practice. It aims to promote continued development in surgery through the dissemination of knowledge, ideas and good practice across surgical specialties. ASR provides readers with critically peer-reviewed, carefully selected and edited, and up-to-date publications about advancements in all surgery specialties.

As a journal covering all surgical specialties, ASR aims to facilitate the transfer of important ideas and thought systems between and across specialties. Hence, ASR will help prevent the trend of increasing sub-specialization which leads to 'tunnel-vision' and the unfortunate concealment of important surgical advances within specific specialties.

Published by
Pakistan Endocrine & Thyroid Surgeons Association (PETSA)
537-S, Imperial Garden Homes, Paragon City, Lahore, Pakistan

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Editor in Chief: Prof Khwaja M Azim FRCS

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About Archives of Surgical Research

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The journal aims to uphold the highest standards at the cutting-edge of research, provide a focus for evidence-based medicine through the publication of review articles and special issues, and give the findings context through the publication of editorials, commentaries and letters from the surgical community. We ensure enforcement of reporting guidelines and mandate the registration of all research involving human participants in a publicly accessible research registry.

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Editor in Chief

KMA

Editorial Team

PREFACE

Shalamar Medical & Dental College has exceptionally excelled in the field of science, education and research over the last decade and has produced quality graduates who are currently serving around the world. Quality of education and research in surgery has been instrumental in this regard under the leadership of Prof Khawaja Muhammad Azim to achieve our core objective of producing quality education. Inception of Pakistan Endocrine & Thyroid Surgeons Association (PETSA) has aligned well to my vision, institutional requirements and overall rapport of the institution.

I witnessed and supported the birth of Pakistan Endocrine & Thyroid Surgeons Association here at Shalamar Medical College three years back and during this period it has evolved into a mature tree and is bearing fruits to surgical education and training here at our institution. Legacy of its founding visionary, Late Prof Syed Zafar Haider has continued. PETSA has been conducting Annual Thyroid & Parathyroid Master Class since its inception with great reception. Currently, we are the largest endocrine surgery center in Pakistan with highest volume turnover.

Now the introduction of "Archives of Surgical Research" is another feather into our institutions' cap. This journal would not only satisfy the needs of the society but would also serve to promote culture of science, education and research within our institution. This culture advocacy remains instrumental in promoting the quality of learning process of the medical graduates within our institute and is aligned with my vision about this medical college.
In the end, I am happy to write about "Archives of Surgical Research" and its inaugural issue and wish the editorial team best of luck for their endeavors for years to come.

Prof Zahid Bashir

Principal

Shalamar Medical & Dental College, Lahore

MESSAGE FROM THE PRESIDENT

Pakistan Endocrine & Thyroid Surgeons Association (PETSA)

Prof Zafar Haider was the teachers of the teachers and a great surgeon. He was the one who made thyroid and endocrine surgery safe in Pakistan and we carry the light now with aim to improve the endocrine surgery in light of modernization in the field of the surgery.

Archives of Surgical Research aims at improving the standard of surgical research and education. It would function as official Journal of Pakistan Endocrine & Thyroid Surgeons Association (PETSA).

The journal would cover endocrine, breast and surgical oncology primarily. It would also focus on the surgical education for medical students and residents to enhance the learning process through addition of technology, blended learning and modern concepts in medical education.

Prof. Khwaja M Azim FRCS
President PETSA

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Archives of Surgical Research | Syed Zafar Haider Memorial Feature

In Memory of Late Prof Syed Zafar Haider FRCS England

Syed Abul Hasan Kazmi

IMPORTANCE Prof Syed Zafar Haider, an exceptional teacher, trainer, surgeon, orator, leader and above all a great human being has influenced a generation of surgeons in Pakistan over the past 70 years. His belief in quality, systematic surgery and surgical discipline was instrumental in producing a great cohort of people who have or are serving this nation and abroad. His contribution to surgical discipline in Pakistan remains outstanding and on top.

SZH Memorial Feature

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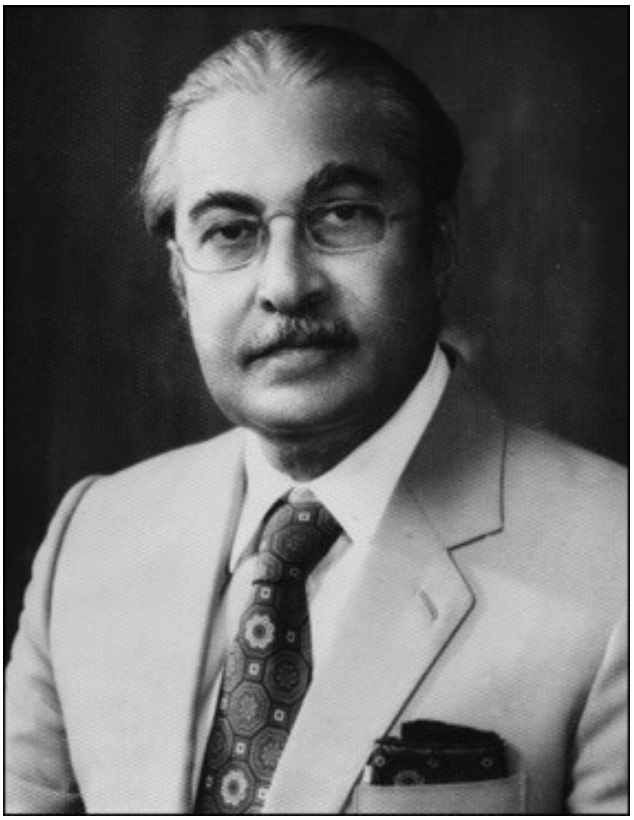
I am Syed Abul-Hasan Kazmi. I am at present in Scotland, United Kingdom. I retired a few years ago from the post of a Consultant Surgeon at Ninewells Hospital and Dundee University Medical School.

I had the privilege of being very close to Professor Syed Zafar Haider during the 70s, firstly as a medical student and then as an SHO and registrar in the First Surgical Unit of Nishtar Hospital, Multan along with my two other great colleagues, Dr Hamid Ali Shah as my senior registrar and Azim Khawaja as my SHO. Professor Haider and Hamid Shah taught me how to hold the knife for health and all the important bits and bobs in life that I cherish and carried with me all along.

I feel very honoured that Professor Azim Khawaja and Dr Talat Waseem asked me to write something about a great man who we all hold in high esteem as our mentor and father figure. I am so glad to see his name and picture at the fore front of PETSA that gives a long due credit to a man who pioneered Thyroid Surgery in Pakistan in the days when the whole nation and the system were in the cradle.
Syed Zafar Haider Sahib was born on 27 December 1927 in Lahore. The family's ancestral home was in Bazaar-e-Hakiman in the Bhaati Gate of Lahore. He belonged to a highly educated family that was settled in Pakpattan as they had their farm land in two villages called Chak Amir Ali Shah and Chak Haider Shah.

His paternal grandfather, Syed Haider Shah, was an officer in the British Army, and maternal grandfather was the fifth Muslim Barrister of India in 1886 and founder of Anjuman-i-Hamayat-i-Islam, the oldest teaching institution of Punjab. Allama Iqbal, our national poet, got his recognition as a poet in his home.

His father Mohammad Shah was a lawyer and held a Master's degree in English literature. His mother studied English at home along with Persian. His elder brother Abbas Haider was a dentist firstly in De Montmorency Lahore and later he was the pioneer in setting up Dental College at Nishtar, Multan. His younger brother Afzal Haider is an eminent lawyer in Lahore.



During his early life, Prof. Haider was brought up in an intellectually and culturally stimulating atmosphere. He started his primary school at Pakpattan in 1932. He completed his matriculation in1942 from Government High School, Pakpattan, where he topped his class. He did his FSc from FC College Lahore in 1944. These were the days when Pakistan was in the making.

Me with Syed Zafar Haider & Dr Tahira Bokhari - 1978

He joined KE Medical College, Lahore in 1945 and graduated in 1950. He did his first house job in Surgery with Professor Amir-ud-Din who was his teacher and mentor. I always heard a lot of things about him from Zafar Haider Sahib while I worked with him and even after and Prof Azim Khawaja can vouch for that.

In 1952 he moved to England where he got his fellowship from the Royal College of Surgeons of England in 1957. There he worked with very eminent surgeons and professors of that time.

He returned to Pakistan in 1957 as Assistant Professor in Nishtar Medical college, then moved to Services Hospital Lahore in 1962 and to KE as Assistant Professor in 1964. He then moved back to Nishtar in 1966 where he stayed till 1980.

At Nishtar he pioneered Oesophageal and Head & Neck Surgery including Thyroid and carried out the first partial nephrectomy there.

In 1980 he moved to King Edward Medical College, Lahore. At Mayo Hospital he did the first parathyroidectomy in Punjab and made East Surgical ward the centre for Thyroid Surgery doing more than two thousand thyroidectomies.
He retired in 1988. Following this, he continued teaching at KEMC and at Shalimar Hospital Medical School on honorary basis. He also lectured at the College of Physicians and Surgeons, Karachi and served as principal of Islamabad Medical & Dental College. Later he had to stop these activities due to ill health.

Syed Zafar Haider, a handsome man and always immaculately dressed who was self-disciplined, straightforward and forthright with tremendous resilience, who expected the same from his students, younger colleagues and peers. He made concerted efforts to groom his students not only in medicine but in their language, communication skills, mannerism and dress code.

Staff of First Surgical Unit, Nishtar Hospital Multan - 1976

A charismatic speaker, having complete command over language and subject, imparting knowledge was his passion for which he used unique methods. While teaching he spoke in a slow deliberate manner, particularly while stressing on an important point. He would spend his own resources and time to prepare the teaching material such as slides and clinical photographs and surgical pathology specimens to elaborate his lectures. This was when such material was difficult, expensive and time consuming to prepare. I saw this all happening, and I am proud to be part of this.

He was dedicated to his patients and would ensure that no one was treated without proper supervision of seniors and

that every patient got the best possible treatment, given the resources.

He married Dr Tahira Bokhari in 1958, who was our Histology teacher in Nishtar and later she moved to King Edward with him. They had three children, two daughters and a son. Zahra the eldest is now Professor of Anatomy and Khadija, though studied Medicine and graduated, branched to Psychiatry specialising in Trauma Therapy.

His son, Ali Haider, got his fellowship in Ophthalmology from the Royal College of Surgeons of Edinburgh. He became an eminent professor, teacher and trainer in Eye Surgery in Lahore and was a great philanthropist. On 18 July 2013, he fell victim to the targeted sectarian violence and was martyred along with his younger son Murtaza.

Their martyrdom was a turning point in the life of Syed Zafar Haider. After this he went down in health and emotions, and passed away on 3rd August 2017, grief stricken for having lived to see the loss of his only son and a grandson at the hands of the nation he had dedicated his life to.

Syed Zafar Haider strived and struggled for Pakistan during the independence movement and it was for the love of his country that after FRCS he opted to return to Pakistan and serve the nation. He also made his son, Ali, do the same. An optimist for Pakistan to the hilt, even at the time of extreme grief of his son's and grandson's epic tragedy he said,
"This country is only 66 years old, which is not enough for a nation to mature, till then we will have to endure such tragedies".

His optimism and faith in Pakistan would bring tears in the eyes of those around and immeasurable admiration for the deep love for Pakistan in his heart.

I was fortunate to be under his tutelage during my initial stages of career before coming to the UK for further studies and training. In him I saw a professional par excellence, a mentor with great personal touch, a silent philanthropist, a Pakistani imbued with love for his country and above all a Doctor devoted to humanity with no worldly ambitions, who was bearer of all attributes of Medicine making it the noblest profession.

Though I had left Pakistan, yet I was always in touch with him and when visiting, would endeavour to spend maximum possible time with him. His affectionate voice radiating hope and wisdom still rings in my ears. The warmth and feel of his soft hands in my hands, I would miss for the rest of my life. But I have the lifelong satisfaction of knowing him intimately and being with a man, an institution in himself, Syed Zafar Haider.

We pray for him and wish him the best and peaceful place in the world hereafter. May Allah bless his soul in eternal peace.

I must Convey my thanks to Shah Sahib family, which is like my own family that include, my respected teacher Dr Tahira, My dear sisters Zahra and her husband Nazim, and Khadija and her husband Tahir for providing me with his personal and family facts to enable me write this and also his obituary on the Royal College of Surgeons of England website, with a link to Plarr's Lives. You can search it either on Google or via RCSEng website and then going to the link Plarr's Lives and by typing Zafar Haider or my name as Kazmi. Or the following direct link can be used to assess it: https://livesonline.rcseng.ac.uk/client/en_GB/lives/search/detailnonmodal/ent:$002f$002fSD_ASSET$002f0$002fSD_ASSET:381821/one?qu=kazmi&te=ASSET

Love from Scotland
Dr Syed Abul-Hasan Kazmi

Archives of Surgical Research | Meta-Analysis

Preoperative Use of Lugol's Iodine in Graves' Disease- Clearer Surgical Field but No Effect on Outcomes: A Meta-analysis of Controlled Studies

Safia Zahir Ahmad, Zaitoon Zafar, Nida Maryam, Talat Waseem

BACKGROUND Recently, the American Thyroid Association (ATA) assessed their guidelines regarding the treatment of Graves' disease and its compliance. These guidelines emphasized on preoperative treatment with Lugol's Iodine before surgery, but said guidelines are based on historical practice rather than on evidence to the benefit of Lugol's Iodine in the preoperative period. We conducted a meta-analysis to analyse the effect of Lugol's Iodine in the preoperative patient with Graves' disease.

DATA SOURCE Studies were identified using the Medical Subject heading and free-text words: "Graves'' disease" "Thyroidectomy" "Preoperative Treatment" "Lugol's Iodine" "Potassium Iodine" "Hyperthyroidism" in Pubmed Central, Pubmed, Cochrane, Embase, ICTRP, CINAHL and Google Scholar.

METHODS Randomized and controlled studies which compared the Lugol's Iodine therapy with non Lugol's Iodine or placebo therapy prior to thyroidectomy for Graves'' disease were included in the study. Single arm study, non-comparative study, euthyroid and non-toxic thyroid nodules were excluded from the study. Meta-analysis data was assessed using random effect with pooled results using mean difference and Odd's ratio where applicable. Outcomes assessed were intraoperative and postoperative parameters.

RESULTS We found 4 randomised control trial and 6 comparative studies which compared the effect Lugol's Iodine with non-Lugol's Iodine in the preoperative period in a patient of Graves' disease. A total of 977 patients were identified with 372 administered Lugol's Iodine and 605 not administered Lugol's Iodine in the preoperative phase. Mean blood flow, vascular density and estimated blood loss was significant in patients who were administered preoperative Lugol's Iodine solution, while there was no significant difference in difficult thyroidectomy scale, thyroid volume, and post-operative outcomes such as mean-operative time, hypocalcaemia, vocal cord paresis, hematoma formation in both the groups.

CONCLUSION Administration of Lugol's Iodine decreases the vascularity and estimate blood loss intraoperatively, but has no effect on difficult thyroidectomy scale, its volume and weight and on postoperative parameters. We found no clinical evidence that Lugol's Iodine improves patient outcomes.

KEY WORDS Graves' Disease, Thyroidectomy, Lugol's Iodine, Preoperative preparation, Hyperthyroidism

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Meta-Analysis

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Thyrotoxicosis is one of the more common endocrine conditions, having an incidence of 1 in 2000 in the European population[1], 1.2% in the U.S. population and 1 to 1.5 % in the general global population. Within the thyrotoxicosis spectrum, Graves' disease is the most common presentation[2]. Graves' disease is an autoimmune disorder and various treatment option exist to treat the condition[3]. The initial treatment options are: medical management with antithyroid drugs which are well tolerated with a success rate of approximately 50%, when given for 12-18 months or Radioactive Iodine (I-131) can be administered in cases where indicated[4]. However, the definite cure for this condition is surgical treatment when other options fail, or relapses occur. To surgically excise the thyrotoxic thyroid in the form of subtotal or total thyroidectomy is the preferred surgical treatment of choice. The patient is optimized preoperatively with antithyroid drugs and Lugol's Iodine is given before the procedure[5]. It is an ongoing historical practice which was introduced in 1920 and has been established as standard practice [6]. Preoperatively, 10 drops are given, three times a day for 7-10 days. The practice of dosage and the duration of Lugol's Iodine given preoperatively varies globally. Since the introduction of this practice, advances in medical practice have introduced

various other medications, such as beta-blockers, thiouracil derivatives etc.[7].

The ATA and other clinical endocrinologists have introduced guidelines to manage thyrotoxicosis prior to surgical thyroidectomy. The requirement for preparing for thyroidectomy is in order to reduce bring the patients to a euthyroid state with methimazole medication. In urgent cases, where immediate thyroidectomy is required or in patients who are allergic to antithyroid medication, beta-blockers and Lugol's Iodine is used[8]. However, these guidelines are adherent to a historically preferential practice and the efficacy of the preparatory treatment has not been validated.

Based on the ATA guidelines, which recommend strongly the use of Lugol's Iodine, Tsai and his colleagues performed the first meta-analysis study reviewing the surgical outcomes of preoperative treatment with Lugol's Iodine[9]. The study demonstrated that there was a decrease in vascularity and blood flow but there was no difference in the complication rates. The study was limited due to a small sample size available in the literature. Recently, a large sample size has become available in medical literature, which can aid in reaching a more precise conclusion.

The aim of this meta-analysis is to compare the outcomes of Lugol's Iodine on preoperative preparation for Graves' disease before surgery with controlled studies which did not administer Lugol's Iodine. By adding the recent large sample size-controlled study to the previous conducted meta-analysis to review the effect of the Lugol's Iodine in vascularity and complication rates.

MATERIAL AND METHODS:

Search Strategy and inclusion:

A comprehensive literature search of randomized controlled and non-randomized controlled trials conducted on the database of Pubmed, Cochrane library, Pubmed Central, Embase, ICTRP, CINAHL and Google Scholar and studies were time framed from 1985 to 2020. The Medical Subject Heading, and the free text used in the search "Graves'' Disease" "Thyroidectomy" "Preoperative treatment" "Potassium Iodide" "Lugol's Iodine" and "Hyperthyroidism". Further studies were extracted, and data was explored using the cited authors and references. Boolean Operator method was used for studies exploration. All language barriers were overcome.
All comparative controlled trials which used the intervention of any form of Iodine therapy for preoperative preparation prior to a total/subtotal thyroidectomy in order to optimise the thyrotoxicosis to a euthyroid state were included in the study. Studies mentioning the vascularity, difficulty index of thyroidectomy, thyroid volume, and weight, per operative outcomes and complication rates were included.
Single arm studies/ non-comparative studies, duplicate studies, reviewer letters, abstracts with no full articles were excluded. Trials with multi-arm studies and management, studies with radioactive Iodine therapy and studies without clear description of outcomes, qualitative study, study size of less than 10, were excluded to avoid confounding bias.

Study Selection and Outcome:

All prospective and retrospective controlled studies that compared preoperative Lugol's Iodine therapy with placebo or non-Iodine therapy prior to total/subtotal thyroidectomy in Graves' disease were included in this study. The primary outcomes analyzed were difficulty thyroidectomy scale, thyroid volume, thyroid weight, mean blood flow, vascular density, resistance index, estimate blood loss, and post-operative outcomes in terms of mean-operative time, hypocalcaemia, vocal cord paresis and hematoma. The outcomes measured were quantitative variables.

Data Extraction:

The selected studies were identified and Preferred Reporting of Items of Systematic Review and Meta-analysis (PRISMA) guidelines were observed[10]. Two Authors reviewed the articles and screened the selected studies from the extensive literature search. Data was explored further by the third author to identify discrepancy and was discussed. Duplicate studies and the studies that were excluded were reviewed by the third author to confirm the decision. Eligibility criteria was discussed further in case of queries. Included studies were counterchecked and in case of doubt, were explored further. The quality of the randomized controlled trial studies was observed using Cochrane Collaboration risk of bias tool[11]. Random sequence and allocation concealment were used to assess the selection bias, blinding the patient and personnel was used to for performance bias, reporting bias, detection bias and attrition bias was reviewed. The study scoring more than 4 was considered as a high-quality study. For non-randomized comparative trial, ROBIN-1 of intervention assessment tool was used[12]. The preintervention domain used to detect selection bias, at intervention domain was used to assess bias in classification of intervention and postintervention domain was used to assess to detect performance, detection, attrition, and reporting bias. Consensus was reached after discussion and critically appraised.

Data Analysis:

After reviewing and discussing the quality of the studies, meta-analysis was performed on the selected studies with comparable studies and the outcomes were assessed using continuous and dichotomous variables, where appropriate, of patients who received preoperative Lugol's Iodine

compared to who did not, prior to a thyroidectomy. The continuous variables were calculated using mean difference with inverse variance and dichotomous variable using Odd's ratio with Mantel-Haenzel method with 95% confidence interval. Studies in which median range were calculated, mean and standard deviation was extracted after conversion. Random and fixed effect method was used as accordingly to the heterogeneity of the population with a cut-off of 50%. The meta-analysis data was quantified and calculated using 2x2 chi-squared test in RevMan 5.4 software.

The sensitivity of the studies was analyzed by excluding individual studies and reviewed the pooled results to review if the pooled results are influenced by it. Q test and I^2 test was used for statistical analysis for heterogeneity assessment within the studies. The pooled results of the intervention were described in Forest Plot and the publication bias was assessed using Funnel plot.

RESULTS:

After extensive literature search using Boolean method, 2150 articles were found, 60 full text articles were reviewed for eligibility, irrelevant studies were excluded. 10 articles were identified and selected, which fulfilled the inclusion criteria, after a detailed review. The articles excluded were due to nature of non-comparative/single arm study, non-availability of full text form, unclear results, studies which included I-131 therapy, multiple arm management studies, limited abstracts and qualitative studies. The PRISMA flow chart shown in Fig 1.

The selected 10 studies include 4 randomized control trial[13-16]and 6 non-randomized control trial[17-22]. The characteristics of the studies is shown in Fig 2. Out of 10, two studies were retrospective while rest were prospective. All the studies were conducted on Graves' disease, toxic goitre, and hyperthyroidism. Lugol's solution was given in 6 studies while 4 studies administered potassium iodide in the intervention group with none given in control groups. Duration of the intervention given in six studies was 10 days of preoperative Lugol's Iodine prior to the surgery while 2 study gave 7 days and 13 days, respectively. Most of the patient of Graves' disease underwent near or total thyroidectomy except in the Kaur et al. study, which included partial thyroidectomy and Yabuta et al. did not mention the type of surgical treatment performed.

A total of 977 patients where included in the study with 372 patient's receiving Lugol's Iodine in the preoperative period and 479 patients not receiving the intervention. In RCT group, 67 participants received Lugol's Iodine while 64 did not. In Non-RCT group, 305 were identified who had received the preoperative preparation of Lugol's Iodine while 541 did not receive the intervention.

The quality of the 4 randomized control trial showed low risk on Cochrane Collaboration assessment tool as shown in Fig 3. The Non-randomized control trial was assessed using the Cochrane risk of bias in nonrandomized studies of interventions showing moderate risk of bias in few domains as in Fig 4.

Difficult thyroidectomy scale parameter was mentioned in two studies with 43 patient who received Lugol's Iodine in preoperative phase while 49 did not receive the treatment. The pooled results showed no significant difference in both the groups with P value of 0. Moreover, 3 articles assessed the thyroid weight, in Lugol Iodine group, 166 patients were reviewed and 488 in non Lugol's Iodine Group. The mean thyroid weight in non-Lugol's Iodine was found 44g as compared to who received Lugol's Iodine was 61g with mean difference in pooled result of 15.3% with heterogeneity of 93%.

Regarding thyroid volume, 3 studies reviewed, and pooled results of mean thyroid volume found was 74mls in LI group and 68mls in non-Lugol's Iodine group with no significant difference in P value with pooled result of mean difference 2.9% (95% CI -5 to 11%) with a low heterogeneity among the study.

Thyroid vascularity was observed in 5 studies by assessing the mean blood flow and vascular density. The thyroid vascularity was assessed by colour flow Doppler ultrasonography identifying the four vascular pedicles and monitoring the peak systolic and diastolic velocity, vessel diameter and blood flow. The resistance index was noted and sampled at the entrance of the thyroid gland. The microvascular density was assessed by the vessels with number of areas covered with staining or without staining. The overall pooled results show significant difference in the group who received Lugol's solution preoperatively causing reduction in the thyroid vascularity.

Moreover, 5 studies reviewed the estimate blood loss in thyroidectomy with 156 in Lugol Iodine group and 88 in Non-Lugol's Iodine group. The pooled results of mean difference were 62.40% (95% CI 102-22%) with random effect model and heterogeneity of 84%, and favoured patient who received Lugol's Iodine due to the reduction in the thyroid vascularity during the procedure.

Mean operative time was reviewed in 4 studies with total of 647 patients, 257 in Lugol Iodine group and 390 in the non-Lugol's Iodine group. The mean difference in pooled results were 100 min in Lugol's Iodine group and 101 min in non Lugol's Iodine group with 0.15% (95% 1.7 -2%) showing no effect in the results of both the groups.

Postoperative parameters in terms of hypocalcaemia and vocal cord paralysis were observed in five studies and hematoma in four. The pooled results were calculated with Odd's ratio, random effect model and moderate

heterogeneity was found. Outcomes showed no difference in both the groups.

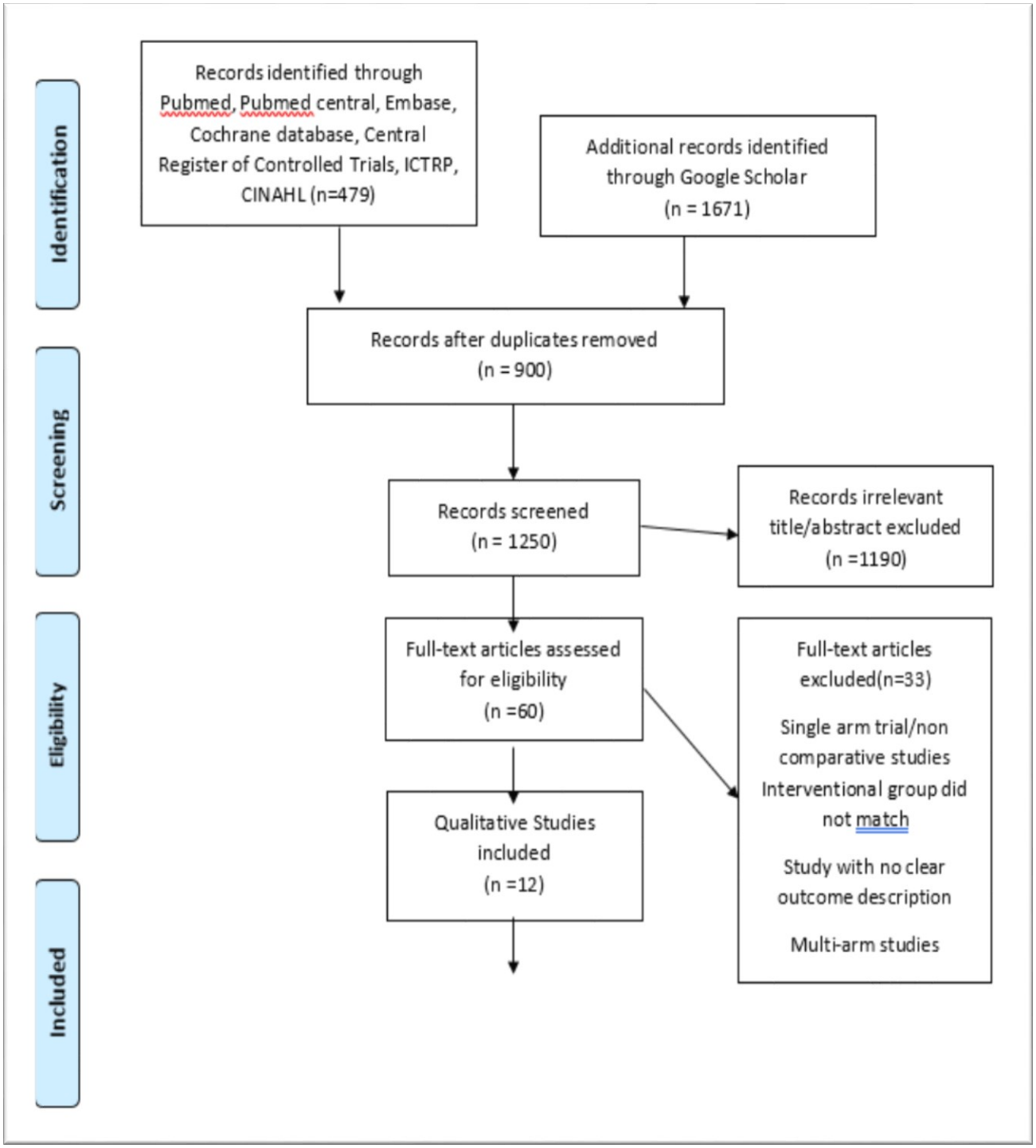


Fig 1: Flow Chart of studies included using PRISMA guidelines.

Characteristics of Studies, its Intervention and Outcomes

Authors	Study Design	No. of Patient in LI	No. of Patients in Non LI	Age	Diagnosis	Procedure	Intervention	Outcomes
Whalen 2017	RCT	18	15	40.2±11.5	Graves' Disease	Total Thyroidectomy	SSKI, 8 qtt/d in 7 days, control: none	Operative time, blood loss, complication
Yilmaz 2016	RCT	20	20	43.0±8.4	Graves' Disease/Toxic Multinodular goiter	Total Thyroidectomy	Lugol's solution, 0.8 mg/kg in 10 d, Control :None	Thyroid volume, blood flow,blood loss, complication
Erbil 2007	RCT	17	19	41.9±11.07	Graves' Disease	Near/Total Thyroidectomy	Lugol's solution, 10 qtt/d in 10 d, Control: None	Thyroid volume, blood flow, microvessel density, blood loss
Kaur 1988	RCT	12	10	33.7+9.34	Graves' Disease	Partial Thyroidectomy	Lugol's solution, 0.4 mL tid in 10 d, Control:None	Thyroid size, blood vessel density, Estimate blood loss, hospital stay, complication
Randle 2018	Non-RCT (Prospective)	25	34	42.7±13.5	Graves' Disease	Total Thyroidectomy	potassium iodide, 1 qtt tid in 10 d, control: None	Thyroid weight , complication
Yabuta 2009	Non-RCT (Retrospective)	89	24	32.7±12.2	Graves' Disease	Surgery	potassium iodide, 64.6± 18.3 mg/d in 11.0± 3.7 d, control :None	Thyroid volume, operative time, blood loss
Hassan 2008	Non-RCT (Retrospective)	16	137	Median:33 (male),36 (Female)(Range 10-75)	Graves' Disease	Near/Subtotal/Total Thyroidectomy	B-blocker, Lugol's solution, 3-6 qtt/d in 3-12 d, control: None	Microvessel density, complications
Linder 2020	Non-RCT (Prospective)	125	317	Median:37in KI (12-77), 45 in Non-KI(11-80)	Graves' Disease/Hyperthyroidism	Total Thyroidectomy	Vitamin C+ Potassium Iodide, 3qtt bid in 13 days, Control: None	Thryroid weight, operative time, hospital stay, Complications
Ansaldo 2000	Non-RCT (Prospective)	25	19	Median:32(24-56)	Diffuse Toxic Goiter	Near Total Thyroidectomy	Lugol Solution starting with 5qtt to 15 qtt in 7 days, Control: None	Resistance index of thyroidal artery flow, blood loss
Huang 2015	Non-RCT (Prospective)	25	10	32.2±5.6	Graves' Disease	Near Total Thyroidectomy	Treatment: Lugol Solution 10qtt in 10 days, Control :None	Blood Flow, VEGF, IL-16

Fig 2: Characteristics of the included study. LI: Lugol's Iodine, KI: Potassium Iodide, RCT: Randomized control trial, VEGF: Systemic angiogenic factor, IL-16: Interleukin 16

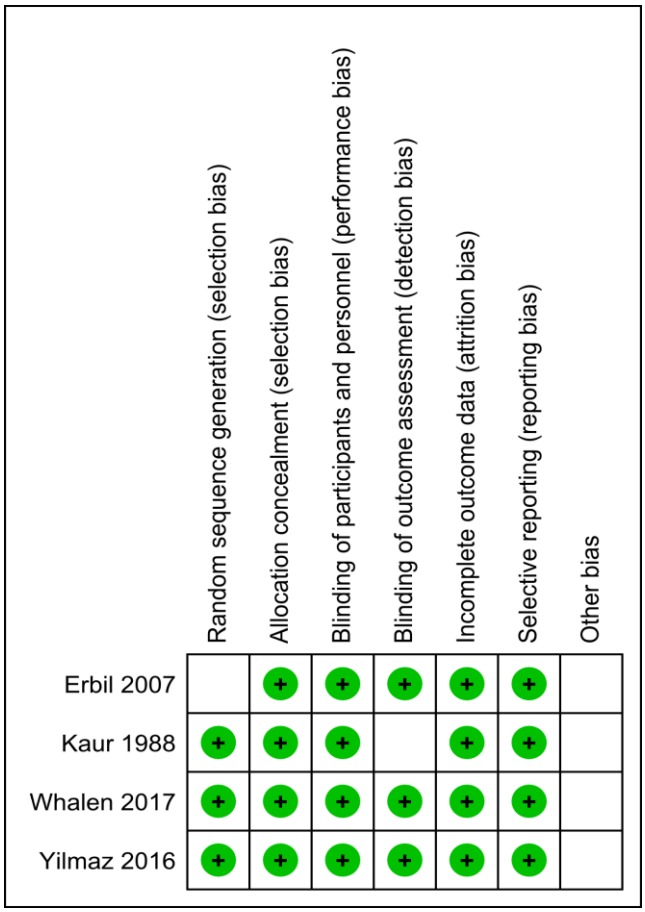


Fig 3: Cochrane Risk of Bias Assessment tool for Randomized Control Trial.

The sensitive analysis of the randomized articles was reviewed individually, exploring the effect on the pooled results. There was no difference in the individual exclusion and the pooled results. However, in non-RCT studies in outcomes of thyroid weight, Randle et al. study exclusion decreases the heterogeneity and increases the sensitive analysis whereas mean operative time heterogeneity decreases to 0% when excluding Linder et al. Moreover, there is no difference in the results of estimate blood loss, thyroid vascularity and mean blood flow contributing to the sensitivity of the results which are collectively like the main results.

Asymmetry of the studies were not found in the funnel plot.

DISCUSSION:

Graves' disease is a common cause of thyrotoxicosis associated with hypervascularity [23]. A thyroidectomy in Graves' disease can be challenging due to the toxic state which increases vascularity and blood flow of the gland, increasing the risk of bleeding when compared to a non-toxic gland[24]. Various preoperative preparations have been used to reduce the vascularity and improve outcomes in operative times and ease the surgery during the operative period[25].

Lugol's Iodine was introduced in 1829 and was established as a standard preoperative treatment in Graves' disease by 1920[26]. It compromises of potassium Iodide 10% and elemental Iodine 5% with distilled water. Lugol's solution reduces the thyroid hormone by increasing the uptake of Iodine and inhibiting the enzyme peroxidase which helps in conversion of thyroid hormones in stages of oxidation and organification and block the release of the thyroid hormones. This escape of the Wolff-Chaikoff effect helps in reduction of thyroid hormone synthesis and trapping the Iodine and makes the thyroid organ less vascular and firmer, this aids the surgeon during the surgery[27].

Surgery during the hyper vascular state causes excessive bleeding and prevents from delineating the anatomy which results in an increase in morbidity and iatrogenic injury. Various attempts have been made to minimize complications by reducing the blood flow which in turn reduces the vascular density, thyroid gland weight, severity of the disease and the amount of blood loss during the surgery[14, 16].

Author	Baseline Confounding	Selection of Participants	Classification of intervention	Deviation from Intended intervention	Missing data	Measurement of outcomes	Selection of Reported Results	Overall Risk of Bias
Randle 2018	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Yabuta 2009	Low	Moderate	Moderate	NI	Low	Low	Low	Moderate
Hassan 2008	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Linder 2020	Low	Low	Low	Low	Low	Low	Low	Low
Ansaldo 2000	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Huang 2015	Low	Low	Low	NI	Low	Low	Low	Low

Fig 4: ROBIN 1 quality assessment tool used for Non-RCT studies.

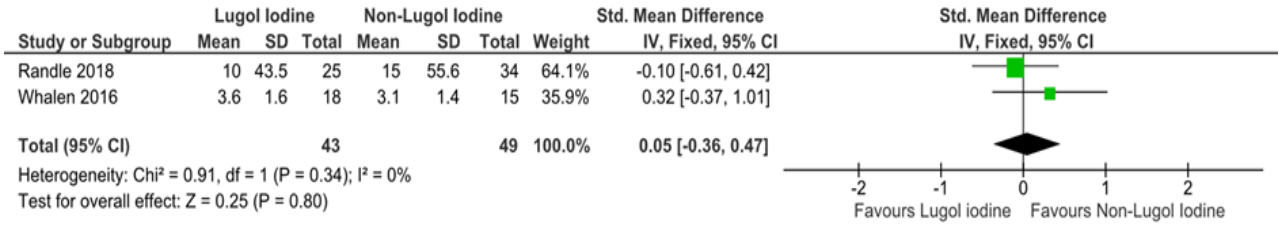
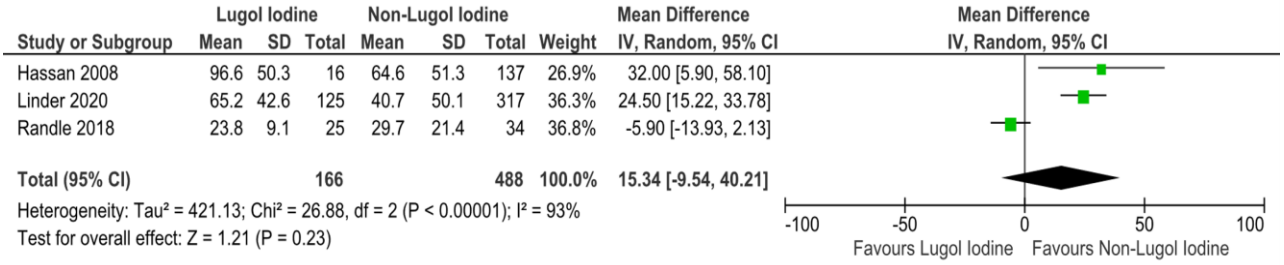


Fig 5 showing Forest plot of difficult thyroidectomy scale in Lugol Iodine versus non-Lugol's Iodine showing pooled result of 0.5% (95% CI 0.36 -0.4%)



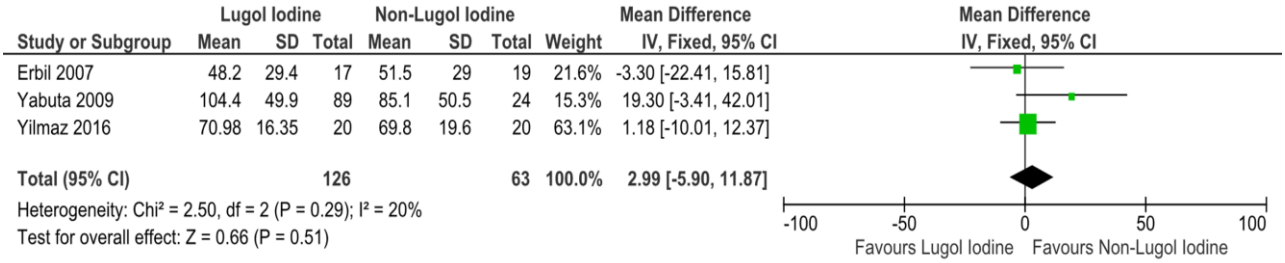


Fig 6 Showing Forest plot of Thyroid weight and volume in Lugol Iodine compared to non-Lugol's Iodine therapy with pooled results of 15.3%,2.9% (95%CI- 9.5-40%) (-5.9-11%) respectively

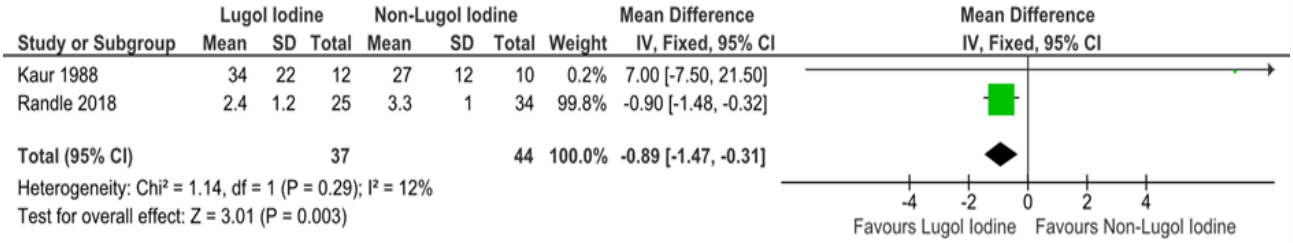


Fig 7: Forest plot of thyroid vascularity with pooled results of 0.89% (95% CI 1.4-0.3%) with heterogeneity of 12%.

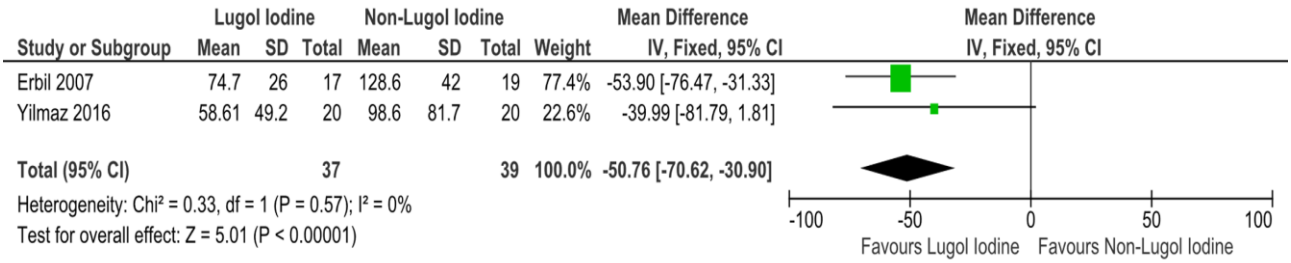


Fig 8: Forest plot with mean blood Flow with pooled result of -50% (95% CI -70- -30%)

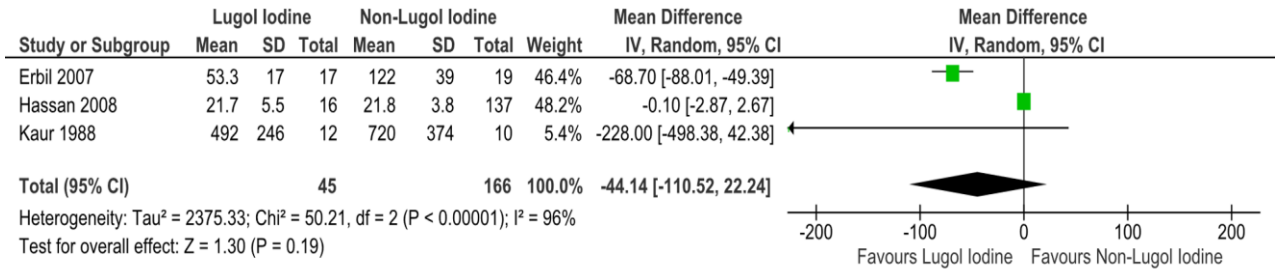


Fig 9: Forest plot of thyroid vessel density with pooled result showing -44% (95% CI -11-22%)

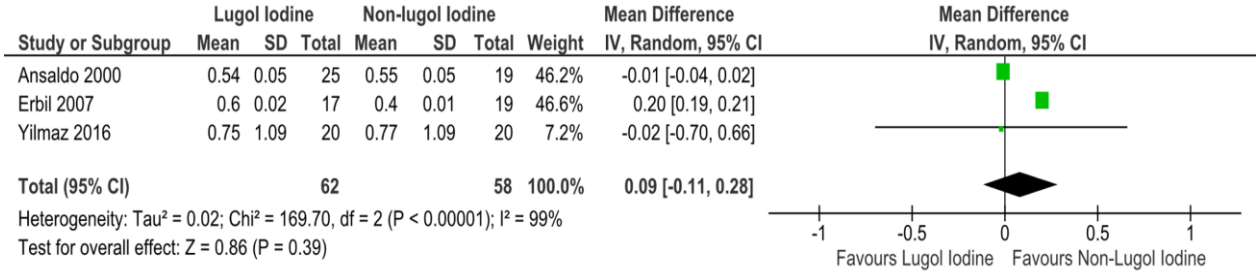


Fig 10: Forest plot showing resistance index in the vessels sampling in Lugol Iodine compared to non-Lugol's Iodine preoperatively demonstrating pooled results of 0.9% (95%CI 0.11-0.2%)

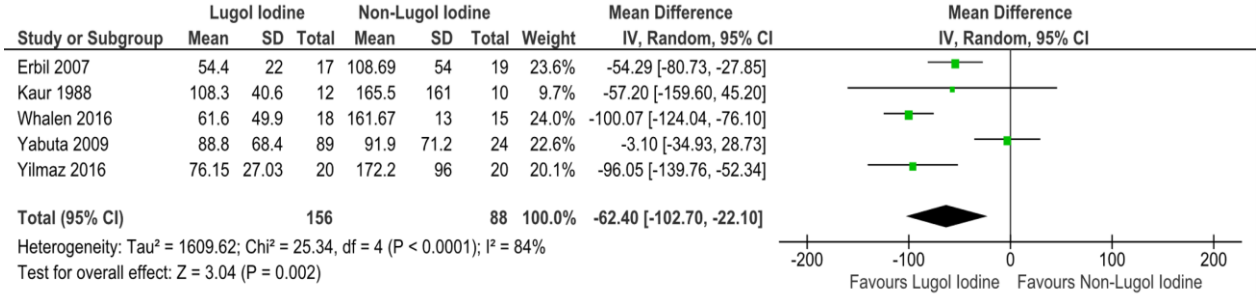


Fig 11: demonstrates estimate blood loss in both the group favouring Lugol Iodine group with pooled result of -62%(95% CI-102 to -22%)

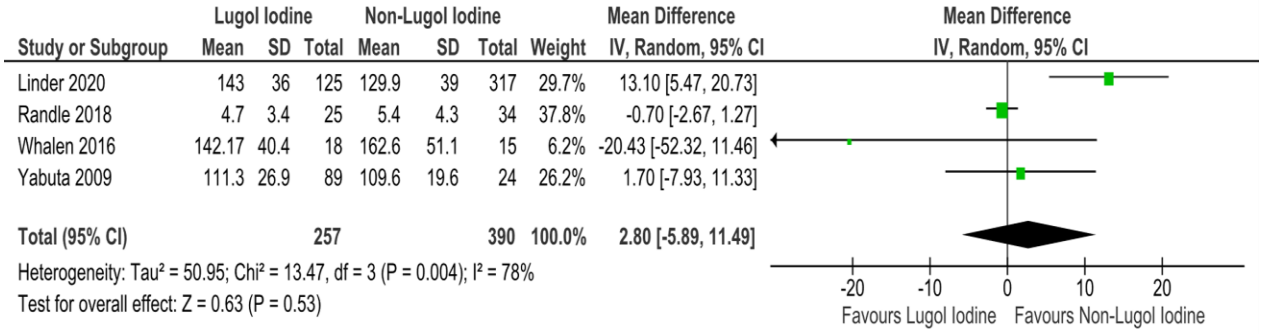
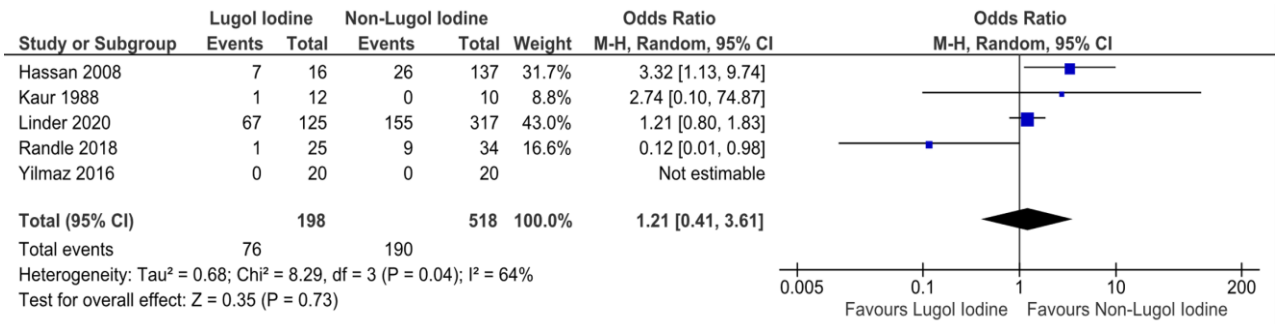
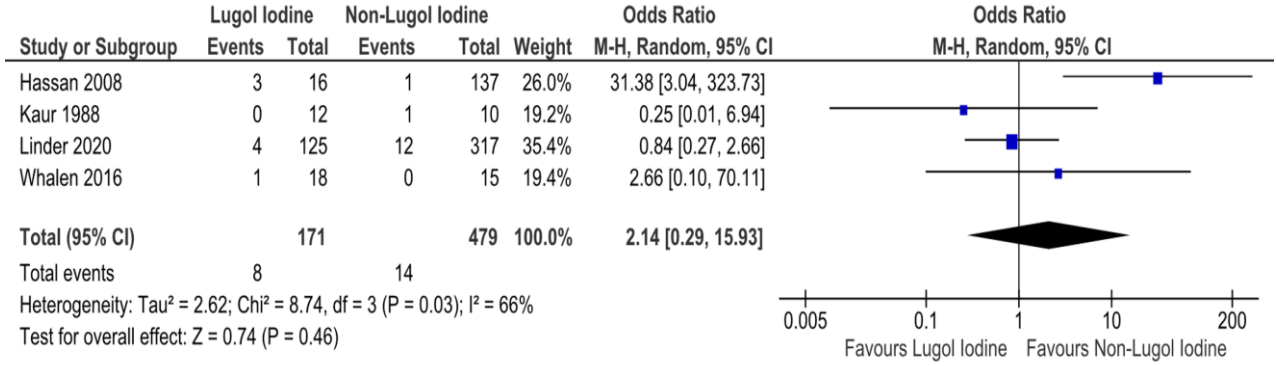


Fig 12: Forest plot of Mean operative time in both the group showing pooled result of 2%(95% CI -5.8- 11%)





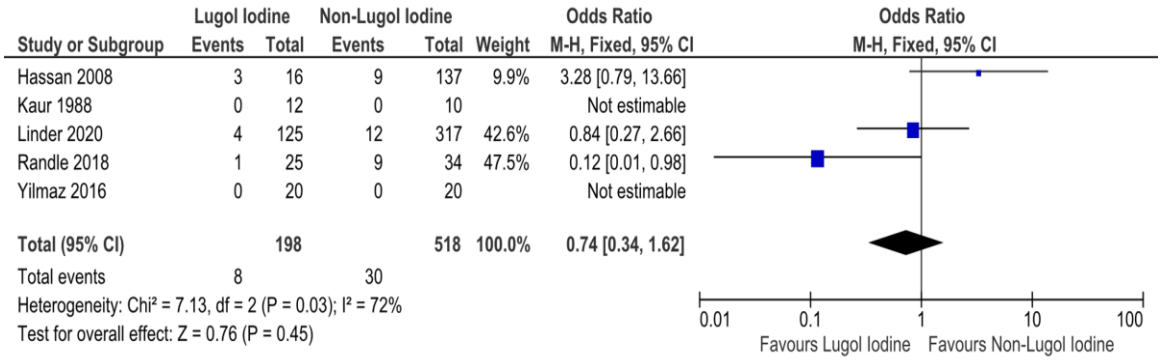


Fig 13: Forest plot showing hypocalcaemia, Vocal cord palsy and Hematoma in preoperative Lugol's Iodine compared to non Lugol's Iodine with pooled result of 1%, 2%.0.7% respectively (95% CI 0.4- 3.6%) (95% CI 0.2%-15%) (95% CI 0.3-1.6%).

During the introduction of the Lugol solution, Plummer observed decrease in mortality by 75% in Graves' disease[4] and Thomson et al[28] found it effective in inducing euthyroid state. However, the introduction of antithyroid drugs, beta-blockers and I-131, has discouraged the use of Lugol's solution, finding it inefficient to control the symptoms and hyperthyroidism in preoperative settings[7]. According to the current ATA guidelines, the use of Lugol's Iodine is recommended but its practise is on historical basis and its efficacy has not been validated. They found that, while assessing their guidelines, Lugol's solution when prescribed preoperatively offered better control in blood pressure but no differences in the heart rate, or the complication rate, even when compared to beta-blocker usage. Their analysis was restricted due to cohort studies and the size of the population as they did not have many comparisons.

We conducted this meta-analysis and added additional, most recent study conducted by Lindner[20] et al. to the previous meta-analysis to review the effect of the Lugol's Iodine in the preoperative period. We found that the vascularity of the gland is markedly decrease with the use of Lugol's solution and it causes reduction the blood flow and vascular density as a result in decrease the estimate blood losses remarkably. Huang et al.[22] in their study demonstrated a 60 % reduction in the mean blood flow from the preLugol to post Lugol state with a reduction in the serum VEGF and IL-16 level to 55% and 50% respectively. Ebril in his study depicted a reduction in the mean blood flow alongwith a reduction in vascularity and subsequent better visualization of anatomical structures which caused a reduction in intraoperative bleeding.

However, the meta-analysis found no difference in the thyroid weight, mean operative time or difference in the

postoperative complication of hypocalcaemia, injury to recurrent laryngeal nerve making the usage of Lugol's solution open to debate. Moreover, Randle et al. [17]found no difference in the thyroidectomy difficulty scale score in terms of friability, mobility, size, or fibrosis but found an increase in thyroid vascularity in patients who did not receive potassium iodide, making surgery more difficult than those who received potassium iodide. Similarly, Whalen and colleagues in their randomized control trial found similar results in the difficulty in surgery but the mean operative time and blood loss were reduced in the group which received potassium iodide preoperatively.

With the additional study including the comparison study of 442 patients to the previous meta-analysis[9] and increasing the number of participants who received preoperative Lugol's Iodine to 372 when compared to 605 who did not receive preoperative Lugol's Iodine treatment and we found the results similar and reconfirming the outcomes and benefit of receiving preoperative Lugol's Iodine in aspect to decrease in the vascularity to the gland but no additional benefit in the postoperative complications.

Linder and colleagues found increase in the operative time and thyroid weight in patient who received potassium iodide with no difference in the postoperative complication of hyperparathyroidism or recurrent laryngeal nerve injury and in postoperative bleeding. However, the meta-analysis found a decrease in hematoma formation in postoperative period in patient who received potassium iodide.

The quality of the study assessed included are randomized control trials with low risk of bias and non-randomised control trials have a strength of low reporting and selection bias with a good size of population analysed in comparison making it a reliable study. However, the study is limited in terms of variation in the strength and duration of the Lugol's Iodine given. In addition, different regimen of Iodine was given in different study. The severity of the hyperthyroidism is not mentioned in most of the study and patient who was induced euthyroid the time of remaining euthyroid was not mentioned. The duration of the antithyroid medication given or what kind of treatment received was not mentioned adds up to the weakness of the study. Moreover, the type of surgery received varies from partial, subtotal to total thyroidectomy making it a potential weakness in our meta-analysis.

CONCLUSION:

In conclusion, our meta-analysis shows that there is a significant reduction in the mean blood flow with a decrease in vascular density causing a decrease in angiogenesis in the gland, this, as a result, eases the surgeon's work owing to a decrease in vascularity and blood loss. However, there was no difference in the postoperative outcomes, operative time or difficulty in thyroidectomy scale with the use of Lugol's Iodine making it debatable if the use of Lugol's Iodine is beneficial, especially when compared to newer, and long term antithyroid medication.

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Archives of Surgical Research | Review Article

Secondary and Tertiary Hyperparathyroidism: When to Operate and When Not to!

Muhammad Afzal

INTRODUCTION Chronic kidney disease-mineral and bone disease is a systemic disorder which is manifested by laboratory abnormalities of calcium, phosphorus or calcitropic hormones. It also involves the abnormalities in bone turnover, mineralization, volume, linear growth, vascular or soft tissue calcification. Secondary hyperparathyroidism is defined as adaptive parathyroid gland hyperplasia and increased production of PTH. Tertiary hyperparathyroidism is severe, persistent, and progressive elevation of serum parathyroid hormone (PTH) that cannot be treated adequately by medical therapy (including both vitamin D analogs and calcimimetics) without causing significant hyperphosphatemia or hypercalcemia.

KEYWORDS Secondary Hyperparathyroidism, Tertiary Hyperparathyroidism, Surgery

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Review Article

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Chronic kidney disease-mineral bone disease is a systemic disorder which can lead to abnormal levels of calcium, phosphorus and parathyroid hormone. It can affect the bone mineralization and bone growth. It can also result in vascular and soft tissue calcification. Parathyroid hormone level starts increasing with progression of chronic kidney disease and decline in eGFR around 45 mL/min per 1.73 m^2 or lower. Almost all the dialysis patients have secondary hyperparathyroidism which is an enlargement of parathyroid gland and increased production of parathyroid hormone. Persistently elevated parathyroid hormone despite the medical therapy with vitamin D analogs and calcimimetics is defined as tertiary hyperparathyroidism.

EPIDEMIOLOGY

The prevalence of refractory hyperparathyroidism is estimated by the rate of parathyroidectomy. It is less common in non-dialysis patients. Among dialysis patient, the rate of parathyroidectomy for refractory hyperparathyroidism is approximately 7-10 per 1000 patient-years[1].

PATHOPHYSIOLOGY

The pathophysiology of secondary hyperparathyroidism involves several organs like kidneys, parathyroid glands, bones, intestines and the vasculature. Parathyroid gland has calcium sensing receptors and vitamin-D receptors. Series of abnormalities occur with the progression of kidney disease. Circulating fibroblast growth factor-23(FGF-23) increases early in chronic kidney disease and suppresses 1 alpha hydroxylase in the kidney leading to deficiency of 1,25-dihydroxy vitamin D. Vitamin D deficiency results in hypocalcemia which stimulates parathyroid hormone secretion. Phosphate retention causes hypocalcemia and also directly stimulates PTH secretion[2]. Elevated PTH in return causes bone resorption and calcium mobilization to maintain calcium homeostasis. In tertiary hyperparathyroidism, there is a decreased expression of calcium sensing receptors and vitamin D receptors, resulting in lack of suppression of PTH. Thus hyperparathyroidism is refractory to medical therapies such as vitamin D analogs and calcimimetics. The persistent stimulation of parathyroid cell growth results in renal osteodystrophy, nodular hyperplasia of parathyroid gland, and sometimes parathyroid adenoma.

CLINICAL FEATURES

The patients with secondary and tertiary hyperparathyroidism can present with hypercalcemia, hyperphosphatemia, bone pain, fractures, proximal muscle weakness, vascular calcification, pruritus and calciphylaxis.

Renal Osteodystrophy

The major bony lesions involved in renal osteodystrophy are osteitis fibrosa (increased remodeling-resorption), adynamic bone disease (no remodeling, hypocellular bone), osteomalacia (defective mineralization due to aluminum deposition), and mixed uremic osteodystrophy involves

both, high turnover with mineralization defects[3]. Patients with renal osteodystrophy are at increased risk of bone fractures as compared to general population due to change in quality of bone. It is more common in dialysis patients.

Calciphylaxis

Hyperparathyroidism, hyperphosphatemia and increased plasma calcium x phosphate product is associated with soft tissue and vascular calcification. Secondary hyperparathyroidism is associated with higher levels of circulating alkaline phosphatase in dialysis patients and it is stronger predictor of coronary artery calcification in dialysis population[4]. Other risk factors include vitamin D analogs, calcium based binders, female gender, obesity and diabetes. Biopsy is needed to confirm the diagnosis. Calciphylaxis or calcific uremic arteriole apparently is associated with poor prognosis.

Resistant Anemia

Parathyroid hormone may be directly toxic to bone marrow erythroid progenitors resulting in increased hemolysis and may also be associated with bone marrow fibrosis. This results in failure to achieve target hemoglobin in spite of adequate iron stores.

PHARMACOLOGICAL MANAGEMENT OF SECONDARY AND TERTIARY HYPERPARATHYROIDISM

Vitamin D therapy: Vitamin D analogs and calcitriol are effective in reducing the level of parathyroid hormone in chronic kidney disease. These are widely used in dialysis population. The excessive use of vitamin D analogs is associated with increased risk of hypercalcemia and hypophosphatemia promoting vascular calcification.

Calcimimetics: Calcimimetics increase the sensitivity of calcium sensing receptor in parathyroid gland to circulating calcium. These agents in combination with vitamin D analogs often lower serum calcium and phosphorus in dialysis patients. Their role to decrease the mortality, cardiovascular events or fracture rate remains controversial. The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events trial evaluated cinacalcet versus placebo in 3883 patients on hemodialysis and noted a nonsignificant reduction in the primary composite end point of all-cause mortality, nonfatal myocardial infarction, hospitalization for unstable angina, congestive heart failure, and peripheral vascular events .

Phosphorus binders: Phosphorus retention in chronic kidney disease is an important factor in pathogenesis of early secondary hyperparathyroidism. Hyperphosphatemia can also be a consequence of secondary hyperparathyroidism. Calcium based phosphorus binders increased risk of hypercalcemia and vascular calcification. Calcium free binders such as sevelamer and lanthanum carbonate or iron based binders may be less associated with arterial calcification. Survival benefit from use of phosphorus binders is unclear[5].

SURGICAL MANAGEMENT

Parathyroidectomy is indicated in patients with hyperparathyroidism that is refractory to medical therapy like vitamin D analogs and calcimimetics. It is usually required in about 15% of patients after 10 years and 38% of patients after 20 years of dialysis therapy[6].

Parathyroidectomy is indicated for persistently elevated PTH level (generally greater than 800-1000 pg/mL) for more than 6 months despite optimized pharmacological therapy including vitamin D analogs and calcimimetics. Improved survival with parathyroidectomy noted from observational studies especially in case of nodular parathyroid hyperplasia. Other indications include 1) refractory hypercalcemia (corrected calcium >10.2 mg/dL) and refractory hypophosphatemia (phosphorus >5.5 mg/dL) in spite of dietary compliance and maximized pharmacological treatment, 2) increased risk or presence of vascular and soft tissue calcification, 3) calciphylaxis, 4) anemia resistant to erythropoietin therapy despite adequate iron stores. Parathyroid ultrasound and 99mTc-sestamibi scan may help to reduce the risk of recurrent disease by detection of ectopic thyroid tissue and identifying which parathyroid has lowest sestamibi uptake and can be used as a remnant tissue. Hyperparathyroidism resolves in most patients after renal transplantation however may need parathyroidectomy in patients with severe refractory hyperparathyroidism with moderate to severe symptoms. Persistent hyperparathyroidism and hypercalcemia have been associated with decreased graft function.

Surgical options: Dialysis patients with secondary and tertiary hyperparathyroidism usually have multiple enlarged parathyroid glands. Surgical options are total versus subtotal parathyroidectomy. Surgical outcomes among both options are about the same. Subtotal parathyroidectomy carries low risk of postoperative hypocalcemia as it reserves remnant parathyroid tissue with its original blood supply. This option is preferred when there is only single or double parathyroid adenoma whereas total parathyroidectomy with auto-transplantation is preferred in patients with several comorbidities and reasons (like previous history of neck surgery, recurrent laryngeal nerve injury, poor functional status) to avoid reoperation.

Survival benefit after parathyroidectomy: There are no randomized clinical trials to evaluate the outcomes after parathyroidectomy however several observational studies have shown that parathyroidectomy is associated with

improved survival. In meta-analysis by Chen et al obtained from 13 cohort studies involving around 20,000 patients, out of which 10,000 had a parathyroidectomy and it was associated overall 28% decrease in all-cause mortality and 37 points reduction in cardiovascular mortality[7]. Parathyroidectomy can also improve many symptoms related to hyperparathyroidism like better control of serum calcium and phosphorus, reduced risk of fractures[8], increased bone mineral density and improvement in overall quality of life[9].

Limitations and complications: Adherence to medical treatment is important to be evaluated before surgical intervention. Parathyroidectomy is associated with significant postoperative morbidity and increased hospitalization. Some of the common symptoms in dialysis patient like pruritus, weakness and generalized pain may not improve even after surgery.

Hungry bone syndrome: Hungry bone syndrome is characterized by hypocalcemia, hypophosphatemia and hypokalemia due to abrupt bony uptake of calcium, phosphorus and magnesium into bone due to sudden drop in PTH levels after surgery. It often requires intravenous calcium replacement followed by higher doses of oral vitamin D and calcium supplementation[10].

When not to operate: Parathyroidectomy is contraindicated in patients with familial hypocalciuric hypercalcemia presenting with elevated calcium and PTH levels. Other contraindications include contralateral recurrent laryngeal nerve injury and vocal cord dysfunction.

CONCLUSION

Secondary hyperparathyroidism is common with the progression of chronic kidney disease. Pharmacological treatment includes administration of vitamin D analogs and calcimimetics. About 15% of dialysis patients will need parathyroidectomy. Based on the available observational data, parathyroidectomy is a reasonable choice in patients who are refractory to maximized pharmacological treatment.

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Archives of Surgical Research| Systematic Literature Review

Evolution of Intra-operative Nerve Monitoring as a Revolution in Thyroid Surgery: A PRISMA Compliant Systematic Review

Haleema Sadia, Hira Ashraf, Talat Waseem

INTRODUCTION In the past two decades, intra-operative nerve monitoring (IONM) has turned into a powerful risk minimisation tool. The importance and superiority of IONM over visual identification of RLN during thyroidectomy in the absence of IONM, has not been completely justified in meta-analysis and articles related to this topic. Continuous IONM (C-IONM) is superior to intermittent IONM (I-IONM) due to its real time electromyographic tracings intra-operatively and thus reducing the RLN palsy, in turn decreases vocal cord paralysis post-operatively. C-IONM urges surgeons to reverse the harmful surgical manoeuvres to avoid the permanent traction related nerve injury; it also plays an important part in the surgical concept of staged thyroidectomy.

OBJECTIVEof this review article is to shed some light on IONM technique, discuss its pros and cons and detailed review of its two types and how it is taking the neck surgery by storm, how it's equipping young surgeons with confidence by honing their surgical skills.

METHODSThis review article is written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses abbreviated as PRISMA guidelines. Literature search was done through Google Scholar, PubMed and ERIC. Search terms were: "intra-operative neuromonitoring" AND "continuous intro-operative nerve monitoring" or "intermittent intra-operative nerve monitoring" AND "recurrent laryngeal nerve" or "RLN" AND "thyroid gland" or "thyroidectomy". 397 articles were identified out of which 41 articles were reviewed at length and were used for identification of themes.

RESULTSIn recent years, the volume of thyroid procedures are expanding so did risk minimization measures protecting RLN, although the incidence of injury to RLN is low in experienced hands, it may diminish the patient's quality of life resulting in permanent post-operative compromise of voice quality and that in turn can result litigation for malpractice for the surgeon responsible. IONM especially C-IONM helps decreasing the incidence of imminent RLN palsy by providing the real-time neuromonitoring intra-operatively also helps in perfecting the surgical skills of young surgeons. Proper documentation of IONM helps in case of litigation as well.

CONCLUSIONThis review article concludes that IONM could greatly decrease the incidence of RLN injury, total, transient and permanent injury, as compared to conventional visual identification of RLN. IONM has proved itself useful in timely predicting the post-operative vocal cord palsy intra-operatively by signaling the impending nerve injury early on. This enables surgeons to withdraw surgical maneovers causing the nerve injury and in turn hone their surgical skills.

KEYWORDS Intra-operative nerve monitoring (IONM), recurrent laryngeal nerve (RLN), recurrent laryngeal nerve palsy, thyroidectomy, continuous IONM (c-IONM), intermittent IONM (I-IONM).
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Systematic Literature Review

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A case of total thyroidectomy was planned for papillary carcinoma of thyroid under the guidance of IONM in the Department of Surgery, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey. Surgeons started their dissection from right lobe of thyroid gland containing the malignant solid nodule. Sound signals were obtained after stimulation of vagus nerve and recurrent laryngeal nerve (RLN) before dissection while recording the wave amplitude. Right RLN was completely exposed and isolated during dissection. After dissection of the nodule, anatomically intact RLN was stimulated and showed the loss of signal (LOS) without recordable amplitude. Stimulation of vagus nerve confirmed the LOS, indicating post dissection permanent or transient injury to the nerve. Due to LOS after right hemi-thyroidectomy further resection of left lobe was halted and patient was closed. Electrophysiological

monitoring of the right RLN showed a segmental (type1) injury. Post-operative laryngoscopy was done and it confirmed right unilateral vocal cord (VC) palsy. The diagnosis on the basis of pathological report was papillary thyroid cancer of the right lobe. The right vocal cord normal function was recovered in third post op month. Completion left lobectomy was performed after 4 months of the primary surgery, as a delayed procedure with IONM as well. Laryngoscopy done post-operatively confirmed the normal function of both vocal cords.[1] Timely identification of LOS of anatomically intact RLN intra-operatively and delaying the left lobectomy on that basis, with the use of IONM technique, saved bilateral vocal cord palsy (VCP) in this papillary thyroid carcinoma patient.

Recurrent laryngeal nerve palsy (RLNP) is a very common and feared complication of thyroid and parathyroid surgery. However, RLNP rates have markedly decreased due to routine visual identification of the RLN[2,3]. Unilateral RLNP causes hoarseness of voice and that in turn affect the quality of life of the patient massively. Fortunately, this impairment is short-lived in most cases, in contrast to bilateral RLNP which mostly causes permanent kind of hoarseness[4,5]. The gold standard has always been the visual identification of RLN before dissecting into the thyroid gland itself.

One of the products of technology in surgical domain is intra-operative nerve monitoring during thyroid surgery (IONM). After its invention there is a continuous debate whether it significantly reduces the RLNP rates or not. Also, there is an open debate front regarding intermittent IONM (I-IONM) and continuous IONM(C-IONM). According to recent literature on the use of I-IONM, there was no significant reduction in RLNP rates with I-IONM[6]. Also according to some, the main advantage of I-IONM is the prevention of bilateral RLNP with the implementation of two staged thyroidectomy[7].

Continuous intra-operativenerve monitoring (C-IONM) is rather latest technique and it potentially enables the surgeon to react before irreversible damage to the RLN occurs[8,9]. An electrode is applied on the vagus nerve in C-IONM during the entire operation to measure the electromyographic activity of the muscles innervated by the RLN. Commonly, injury to the RLN or injury to any nerve intra-operatively, occur mostly due to thermal injury or traction followed by clamping, as shown in a multi-centre study of 115 cases with loss of signal (LOS) caused by traction to RLN in 80% of the cases[10]. All kind of injuries cannot be prevented by IONM hence the difference between each type of injury is critical when it comes to C-IONM. If tension or traction is released when detected early by IONM, injuries can be avoided and potentially reversible. This has been shown by Phelan[8]and Schneider et al. [9] that more than 73% and 82% of events, respectively, were reversible during surgery when prompt corrective measures were applied. C-IONM offers higher sensitivity for early and prompt detection of RLNP incidence upon comparing RLNP rates between the two techniques I-IONM and C-IONM [9]. Furthermore, electrode positioning was reported to be safe during C-IONM in an analysis of 400 vagal nerve dissections [11]. On the contrary, Terris et al. [12]reports two cases of LOS, one due to hypotension and bradycardia after the vagal electrode was used, and the second case was, vagal nerve injury resulting in temporary RNLP due to ecletrode application, concluding this to be a harmful and invasive technique. Another group, Katrin et al., studying high-risk neck surgeries reports one case of loss of signal which was caused by vagal electrode and multiple situations of EMG artefacts[13].To sum it all up, C-IONM is superior in affectivity over I-IONM in prevention of RLNP [14]. In 2012, C-IONM was introduced in Geneva for selective use in complicated surgeries for example invasive thyroid cancer, retro-sternal goitre, Grave's disease and re-intervention surgeries.

METHODS

This review article is written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses abbreviated as PRISMA guidelines with the objective to analyse data available for IONM in thyroid surgery.

Search Strategy and Data Extraction:

Narrative approach was used to review the literature in order to perform comprehensive, critical and objective analysis of the available data. A comprehensive literature search was done via the databases PubMed, ERIC, Google Scholar and Sci-Hub from 1996-2020. Relevant articles were added manually as well by going through the references. Search terms used in search engines were: "intra-operative nerve monitoring" AND "continuous intra-operative nerve monitoring" OR "intermittent intra-operative nerve monitoring" AND "recurrent laryngeal nerve" OR "RLN" AND "thyroid gland" OR "thyroidectomy". All search papers were reviewed according to the selected search strategy.

Selection Criteria and Quality Assessment:

433 articles were identified using the computer literature search of PubMed and Google scholar. Titles and abstracts of all the papers were reviewed using the inclusion and exclusion criteria. 32 articles were excluded for duplication, remaining 401 articles were viewed and 41 articles related to the topic were included in this literature review. 103 full-text articles were assessed for eligibility and 62 articles were excluded on the basis of exclusion criteria. No language, age or gender restrictions were applied. All papers from 1996 to 2021 were included. Exclusion criteria included duplicate articles, poster presentations, articles not related to the topic, articles on minimally invasive video thyroidectomy, articles on endoscopic thyroidectomy, papers on paediatric thyroidectomy and articles on robot assisted thyroidectomy. The article selection process is given in Diagram 1.

Data Extraction and Detailed Analysis:

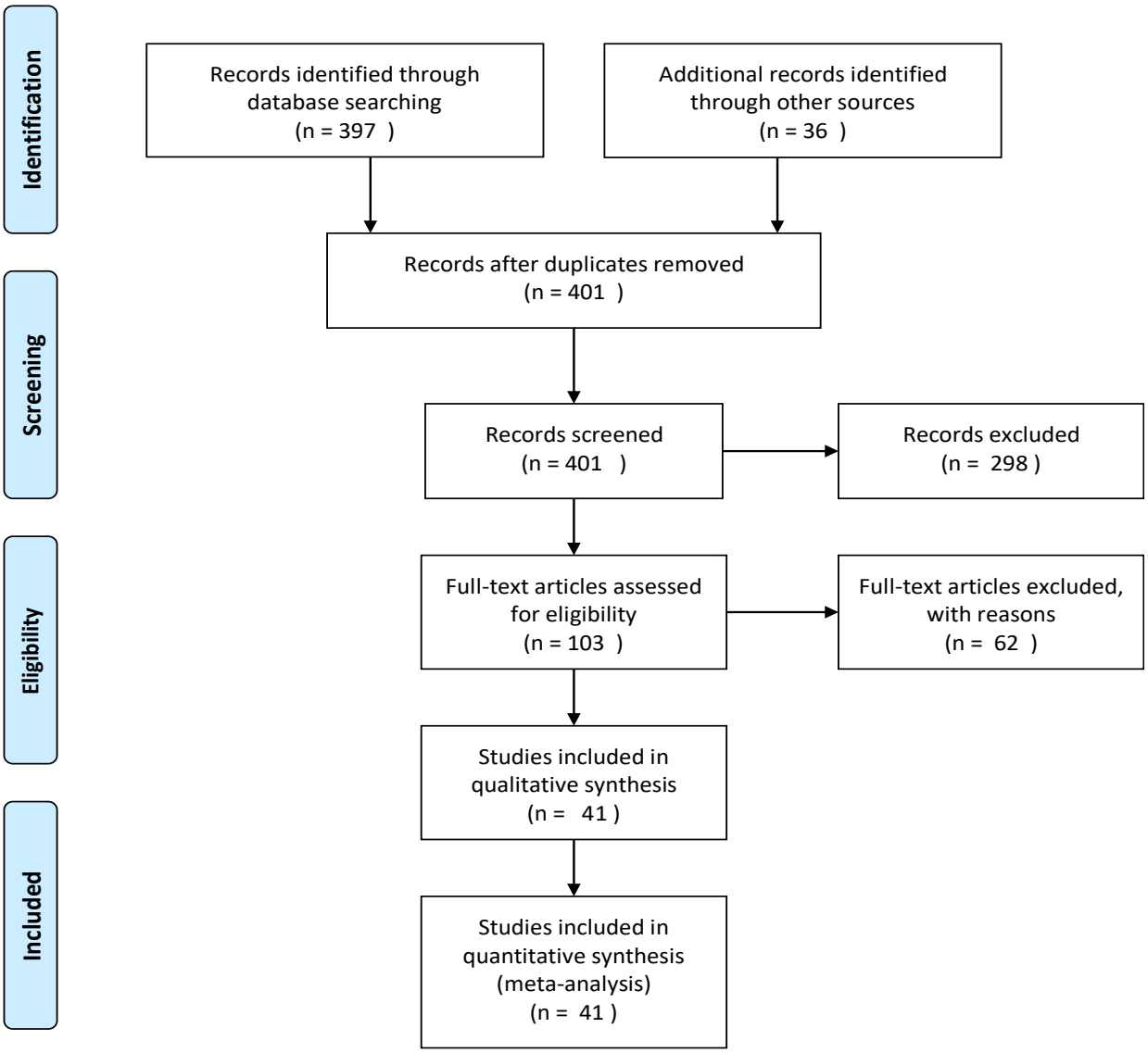
Thematic analysis of each paper was done. Information about year of publication, name of the author, country of

origin, methods of study and themes identified were collected and coded. The themes identified through analysis of the data are given in table 1.

RESULTS

433 articles were identified through comprehensive computer literature search. 41 articles were included after the screening process after removing duplicate articles. Some recurrent themes were identified after detailed analysis of the selected papers which are described in Table1.

Figure 1: PRISMA Flowchart- Article selection process through computer literature search and analysis:



Year	Author	Country	Research Method	Themes Identified
1996	Lamade (Lamade et al., 1996)	Germany	Initial Wet Lab Technique development	IONM system for RLN is reliable and easy to use, even the imminent injury to RLN can be demonstrated by signal changes.
1996	DavidW. Eisele(DW Eisele,1996)	USA	42 RLN were monitored in 31 patients by direct RLN stimulation with electrodes on ETT at the level of true vocal cords	NIM-2 EMG ETT is a safe, effective and simplified method for RLN monitoring during thyroidectomy or parathyroidectomy
2005	Dionigi (Dionigi et al., 2005)	Italy	Review article on the influence of new technology on thyroid surgery including IONM	RLN monitoring and stimulation may be a useful technique when identification of RLNis expected to be difficult (redo surgery) also specific training is required for this new device.
2007	Shindo (Shindo, Chheda, 2007)	USA	Retrospective study of 684 patients (1043 nerves at risk) who underwent thyroidectomy under GA	Monitoring of the RLN does not appear to reduce the incidence of post-operative vocal cord paralysis
2007	Lamadé (Lamadé et al., 2007)	Germany	Original article discusses c-IONM of RLN with a new vagal electrode	Continuous RLN monitoring by stimulation of the vagal nerve is feasible, safe, easy to handle andcompatible with all thyroid operations technique
2008	Dionigi (Dionigi et al., 2008)	Italy	A review article	Prevention of post-operative complications, such as laryngeal nerve paralysis with IONM
2009	Schneider (Schneider et al., 2009)	Germany & Austria	An original article about c-IONM of RLN by vagal nerve stimulation	The vagal anchor electrode is safe to use and allows c-IONM without any threats, this new technique will provide more security.
2010	Jonas (Jonas et al., 2010)	Germany	Original paper, in 100 patients thyroid resection was performed using vagus electrode for continuous stimulation	Parameters e.g. signal amplitude, latency and stimulation threshold cannot be reliable warning criteria, LOS remains the most important criteria for the surgeon and this gives surgeon the possibility to react immediately.
2010	Dionigi (Dionigi et al., 2010)	Italy	Opinion paper on monitoring of RLN in thyroid surgery	New technologies have been applied in thyroid surgery, this is a transition period from the era of visualisation to era of neurophysiology of RLN
2011	Lee (Lee & Stack, 2011)	USA	Review article on intraoperative neuromonitoring during thyroidectomy	IONM Still needs to improve, there is a strong argument for its use as a teaching and research tool, residents and less-experienced thyroid surgeons may benefit from its use.
2012	Angelos (Peter Angelos, 2012)	USA	Literature review of ethical and medicolegal issues in neuromonitoring during thyroid surgery	Neuromonitoring can provide valuable information to surgeons about the functioning of RLN, but should not overestimate the benefits when discussing the technology with patients.
2012	Barczyński (Barczyński et al., 2012)	Poland	Randomized controlled trial of 210 patients for visual inspection vs neuromonitoring	Use of IONMsignificantly improved the identification rate of the nerve, as well as reduced the risk of post-operative phonation changes following thyroidectomy.
2012	Friedrich (Friedrich et al., 2012)	Germany	Prospective controlled study of 40 patients scheduled for thyroid or parathyroid surgery	C-IONM via vagal nerve stimulation appears to be safe and effective
2012	Refoyo (José Luis Pardal-Refoyo, 2012)	Spain	An original article of 259 RLNs at risk during thyroidectomy with neuromonitoring (group A: 129nerves) and without neuromonitoring (control group B: 130nerves)	Neuromonitoring helps to identify RLN and increases the security of the surgeon in the technique. It is advisable to perform neuro monitoring routinely in thyroid surgery.
2013	Schneider (Schneider et al., 2013)	Germany	Original article of 52 patients whounderwent C-IONM for thyroid surgery via vagus nerve stimulation	C-IONMReliablysignaled impendingRLN injury, enabling immediate corrective action.
2013	Dionigi (Dionigi et al., 2013)	Italy	A PubMed indexed literature review of the limitations of I-IONM and commentary about C-IONM.	C-IONM by vagal nerve stimulation enhance the standardisation process, intra-operative information of RLN, documentation, protection, training and research in modern thyroid surgery.
2013	Sadowski (Sadowski et al., 2013)	Switzerland	An original article discussing; bilateral thyroidectomy was delayed after LOS of unilateral lobectomy.	The systematic use of IONM and the change in operating strategy will lead to an almost 0% rate of bilateral recurrent laryngeal nerve palsy
2014	Barczyński (Barczyński et al., 2014)	Poland	A retrospective cohort study of 854 patients having re-operations of thyroid,now with IONM	IONM decreased the incidence of transient RLN paresis in repeat thyroid operations compared with nerve visualisation alone.
2014	Phelan (Phelan et al., 2014)	USA	Prospective multicenter tertiary study	C-IONM is safe and provides real-time RLN evaluation during surgical manoeuvres
2015	Schneider (Schneider et al., 2015)	Germany	An original article comparing C-IONM and I-IONM	Operation with C-IONM resulted in fewer permanent vocal fold plasies compared with I-IONM after thyroid surgery in patients with benign disease

2015	Deniwar (Deniwar, Kandil& Randolph, 2015)	USA	A literature review	C-IONM prevent nerve injury by detecting EMG waveform change indicating impending nerve injury.
2015	Angeletti (Angeletti, B. Musholt, J. Musholt, 2015)	Germany	An original article discussing c-IONM	C-IONM potentially enables the surgeon to react before irreversible damage to the RLN occurs.
2016	Schneider (Schneider et al., 2016)	Germany	A review article	C-IONM facilitate for early corrective action before permanent damage to the RLN has been done.
2016	Refoyo (Refoyo&Sangrador, 2016)	Spain	Systematic review of 40 articles and 54 case studies (without NM, 25; with NM, 29) with 30,922 patients	The risk of bilateral paralysis is lower in studies with neuromonitoring
2016	Schneider (Schneider et al., 2016)	Germany &USA	An original article	C-IONM can prompt corrective actions before LOS occurs, C-IONM provide better nerve protection than I-IONM, permanent RLN plasy rates are 0% with c-IONM vs. 0.4% with I-IONM
2017	Schneider (Schneider et al. 2017)	Germany	Review article	Review summarises the current key achievements of IONM; outlines opportunities for improvement regarding clinical implementation and suggests areas of future researchin this rapidly evolving field.
2017	Qurayshi (Qurayshi, Kandil& Randolph, 2017)	USA	A Markov chain model was constructed based on IONM use	Use of IONM is cost effective in patients undergoing bilateral thyroid surgery
2017	Randolph (Randolph &Kamani)	USA	Retrospective study of electrophysiologic response of 1381 RLNs	IONM of the RLN can aid in the nerve mapping, nerve identification and prognostication of post-operative vocal cord function, which can influence the surgeon's decision to proceed to bilateral surgery
2017	Christoforides (Christoforides et al., 2017)	Greece	A retrospective cohort study	Staged thyroidectomy seems very promising procedure for both patient and surgeon since it nearly eliminates one of the most fearful complications in thyroid surgery, RLN palsy
2017	Mannelli (Mannelli et al., 2017)	UK	Research article	IONM with automated periodic stimulation (APS) technical and practical steps, encourage surgeons to widen their skills and gain knowledge about its potential use
2018	Bai (Bai& Chen, 2018)	China	Literature review article	Literature search indicated that IONM could reduce the incidence of total, transient and permanent RLN injury compared with conventional visual identification
2018	Arteaga (Arteaga et al., 2018)	Switzerland	Retrospective study	C-IONM provides real-time evaluation of the RLN function, allowing for adaptation of surgical maneuvers to prevent RLNP
2018	Basarrate (Basarrate et al., 2018)	Spain	A prospective cohort study,248 consecutive thyroidectomies were included	Continuous vagal nerve monitoring is safe and allows us to assess nerve function intraoperatively
2018	Singer (Michael C. Singer, 2018)	USA	50 patients scheduled to undergo thyroidectomy were enrolled, a lead designed for CIONM was placed on the nerve	This study demonstrates the apparent safety and viability of a CIONM technique using a lead placed directly on the RLN, widespread adoption of CIONM during thyroidectomy may reduce RLN injuries.
2019	Yu (Yu et al., 2019)	China	A total of 344 patients who underwent high-risk thyroid surgery, with 238 patients operated with I-IONM and 106 patients operated with C-IONM.	Both I-IONM and C-IONM are equally safe and effective in high-risk thyroid surgery. C-IONM can help predict impending recurrent laryngeal nerve injury in real time,thereby minimizing critical maneuvers in high-risk thyroid surgery.
2019	Gürleyik (EminGürleyik, GünayGürleyik, 2019)	Turkey	Case study	IONM establishes the outcome of the neural palsy, affects the surgical decision-making, and prevents the risk of bilateral palsy.
2020	Schneider (Schneider et al., 2020)	Germany	Literature review	Review summarizes the advances of continuous IONM technology that caused a quantum leap in risk minimization for thyroid surgery, shifting current paradigms.
2020	Kim (Kim et al., 2020)	USA	An original article	Nationally, IONM is used in nearly two thirds of thyroid surgeries. IONM is associated with a lower risk of RLN palsy.
2020	Kartal (Kartal et al., 2020)	Turkey	Clinical study	Intraoperative neuromonitoring may decrease the incidence of total VCP and prevent the development of bilateral VCP, which has unfavorable results for both patients and health-care professionals.
2021	Sinclair (Sinclair et al., 2021)	USA	Observational case-control study	CIONM significantly decreased rates of postoperative transient VF paralysis and paresis over intermittent IONM alone.
2021	Abdelhamid (Abdelhamid, Aspinall, 2021)	UK	An original article	Use of IONM is associated with a decreased risk of RLN injury in thyroidectomy.

In recent years, the volume of thyroid procedures has expanded and so did risk minimization measures to protect RLN. In experienced hands, the rate of RLN palsy is low. RLNP results in permanent post-operative compromise of voice quality that may significantly affect patient's quality of life and can open a law suit for the surgeon[15]. IONM includes three steps of nerve monitoring: pre-operative, intra-operative and post-operative monitoring of RLN function.These three levels of monitoring add another dimension to thyroid surgery[16]. The prerequisites are advanced surgical skills, dissection and isolation of the RLNfollowing its visual identification.

Evolution of IONM:

- Intermittent IONM done with handheld mono-polar probes which stimulate the RLN, and needle electrodes inserted into the vocal muscle through cricothyroid membrane and through this system electrophysiological response signal is recorded.
- Intermittent IONM with handheld mono-polar probes which stimulate RLN, and surface electrodes fixed on the endotracheal tube (ETT), record the electrophysiological response signal.
- c-IONM is performed with a clip electrode attached on vagus nerve and surface electrodes fixed to the ETT to record the electrophysiological response signal intra-operatively.

c-IONM advances have produced a quantum leap in risk minimization of thyroid surgery. In some countries c-IONM is considered a standard of care in thyroid surgery patients and has gained popularity on the basis of decreased RLNP rates. Although, the cost effectiveness of this technology will remain controversial in resource-conscious environments until it becomes gold standard in the world of thyroid surgery[17].

Meta-analysis and systematic reviews on IONM:

There are multiple systematic reviews and meta-analysis which compares IONM against visual identification of RLN in the absence of IONM[17–26]. Astonishingly, many of these reviews contradict each other. There's evidence suggesting that IONM decreases both permanent and transient RLN injury rate[18,26], only transient RLN injury rate[17,25], or only permanent RLN injury rate [24]. On the contrary, other researchers did not find substantial data that proves reduction of permanent RLN injury rate [19] or reduction of both transient and permanent RLN injuries[21–23]. These contradictory results are best explained by the stepwise evolution of IONM technology from intermittent IONM to c-IONM as mentioned in detail in the previous heading and recognition of the importance of this technique and its standardisation based on the principles laid down by the International Neural Monitoring Study Group[27]. According to Schneider et al. IONM especially c-IONM is shifting current paradigms[28].

Intermittent and continuous IONM use among surgeons:

A survey by German Society of Endocrine Surgeons abbreviated as GAEK performed on 12,888 patients with benign goitre and 18,793 nerves at risk, concluded that IONM was used in 98.4% of patients and I-IONM (82.6%) was used more often than C-IONM (17.4%)[29]. A 2012 survey of German surgical units concluded that IONM was employed in 91% of thyroidectomies[30].

In 2016 survey of Surgeons of the American Head and Neck Society, 95% of surgeons said that they either used IONM routinely (60%) or selectively (35%). The most common reason for using IONM was improved surgeon confidence (55%) and increased patient's safety (54%)[31]. A survey conducted in 2019, among 1015 surgeons reported 83% of surgeons employing IONM for some or all of their operations[32]. Acceptance and usage rate of IONM is greater among younger surgeons. IONM uptake is unrelated to surgical volume, type of practice or fellowship training.

Honing surgical skills with the help of IONM by continuous feedback on nerve function:

Continuous electrophysiological feedback on the functional integrity of a nerve makes the surgical team to effectively withdraw any harmful maneuvering in turn significantly decreases the RLNP rates and also they can perfect their surgical skills[15]. This reassurance during surgery is most likely to decrease stress of the surgical team [34]. Introducing IONM routinely in thyroid surgery may also help young and less experienced surgeons to perform operations with more safety and comfort[35–37]. That can result in complication rates comparable to an experienced surgeon[38].

Documentation of and informed consent for IONM in case of Litigation:

Ethical considerations are involved in the use of reasonable risk minimization strategies [39]. In the event of litigation informed consent, containing all the strengths and weaknesses of IONM technique and in case of LOS the need to halter the surgery of the opposite side of thyroid gland to avoid bilateral vocal cord palsy, may serve as a line of defence[40].

A 2012 study, based on a 15-year period in Germany, by Dralle et al. showed 75 lawsuits of which 60% were due to RLN palsies, half of which were bilateral[41]. Gartland et al.

[42]supported these findings and found that bilateral RLNP was prediction of plaintiff verdicts, accounting for up to 18% of 128 malpractice suits in the US.These verdicts highlight the importance of properly documenting and implementing the use of risk minimisation strategies. Normal vagus nerve and RLN electrophysiological documentation pre and post dissection of the thyroid lobe provides a strong line of defence.

IONM superiority in thyroid surgery:

There are two types of LOS, type 1 is segmental LOS and type 2 is diffused LOS. Both I-IONM and c-IONM can differentiate between the two types. Whereas, c-IONM offers added benefits in minimisation of injury caused by traction, thermal injury, real-time RLN functional monitoring and EMG signal documentation. Both types of IONM suggest informed treatment plan to surgeons intra-operatively and provide strategic direction if staged thyroidectomy is required after definitive LOS on the first side of operation[15]. According to Australian College of Surgeons[43] and the German Association of Endocrine Surgeons [44] IONM has turned into a standard of care in some countries[45]. C-IONM provides real time intra-operative registration and documentation of nerve signals, it has been demonstrated that instant release of a distressed nerve decreases RLN injury chances.

Prediction of Post-operative vocal cord functions Intra-operatively:

The prediction of post-operative vocal cord palsy with the help of IONM is characterised by two scales:

- Sensitivity; 63-91% for I-IONM and 91-100% for c-IONM
- Specificity; 97-99% for I-IONM and 90-99.7% for c-IONM

In case of laryngeal nerve palsy the positive predictive value (PPV) is bound to be lower than the negative predictive value (NPV):

- PPV 38-80% for I-IONM and 48-88% for c-IONM
- NPV 97-99.8% for I-IONM and 99-100% for c-IONM

Post-operative vocal cord palsy rates are significantly lower with this technique

- Early palsy rates; 0.8-10% for I-IONM and 2.6-2.9% for c-IONM
- Permanent palsy rates; 0.2-1.5% for I-IONM and 0-1.5% for c-IONM[28].

The main difference between c-IONM and I-IONM is continuous and real time monitoring of functional integrity of RLN by c-IONM along the entire vagus-RLN pathway for detection and timely prevention of traction related injury of RLN [33,46,47]. In experienced hands c-I0NM can decrease permanent VCP rate to 0% as compared to 0.4% with I-IONM[9]. For accurate results it is important to get nerve amplitudes of greater than or equal to 500 microvolts at baseline with stimulation current of 1mA[46].

Mobilisation and resection of thyroid with greater flexibility:

C-IONM is a powerful technique which enables instant recognition of RLN injury. A multi-centre study for 115 nerves with LOS, concluded that 83% of RLN injuries were traction related, 60% among those happened near or at the ligament of Berry[10]. Findings of this multi-center study highlighted the importance of IONM-assisted thyroid mobilisation and resection. Injuries occurring due to traction are preceded by "combined events" which result in changes in the amplitude and latency relative to baseline reading. If no action is taken injury to the nerves may lead to LOS, which can be a serious and irreversible condition[8,46,47]. When these changes in amplitude and latency happen, surgeon should relax hold on the thyroid gland thus releasing tension on RLN until baseline amplitude of the nerve has regained. If change is baseline amplitude occur more than once it may be more advisable to take a median route to thyroid hilum instead of continuing a risky dissection.

C-I0NM can show its true importance when the operating field is scarred and surgical layers are annihilated such as during mobilisation of thyroid, dissection of thyroid capsule, or digital mobilisation of retrosternal thyroid. In these circumstances, it is often unfeasible to identify and map the involved nerves. A stimulating electrode attached on the vagus nerve is activated and the surgeon is constantly alerted of injury to a nerve that remains invisible[48].

Intra-operative amplitude recovery for restoring post-operative vocal cord function:

After loss of signal, segmental injury (type 1) usually resolves within 7-8 minutes and global injury (type 2) resolves within 13-15.6 minutes. This observation shows the ineffectiveness of waiting more than 20 minutes for the RLN nerve to re-gain half of its baseline amplitude [47,49]. Almost 50% of amplitude recovery predicts normal post-operative VC function in all patients after segmental or global injury. Vocal cord function is impaired upon examination post-operatively in 25% of patients with a temporary Type2 injury and 64% of patients with temporary type1 injury[49]

Staged Thyroidectomy vs same-session thyroidectomy:

When on the first side of resection loss of signal is detected and traction on the RLN nerve is stopped at once, standard procedure is to give the nerve around 20 minutes to recover 50% of its baseline amplitude. If it fails to do so, there is 85% risk of early post-operative VCP[47]. In such cases it is absolute necessity to postpone thyroidectomy (lobectomy) of the

unaffected side for at least three months to avoid bilateral VCP until VC function has fully recovered[30,50]. Contralateral surgery should only be pursued under exceptional circumstances such as advanced cancer[51]and only at hospitals which have experienced surgeons for complex neck surgeries.

Cost effectiveness of IONM:

Practice and adoption of this technique varies by geographic region and country, cost varies from $5000 to $40,000 for the equipment and from $72 to $5000 for disposables per application (recording surface tubes and vagus electrodes). In addition, indirect cost includes Glidescope video laryngoscope required for correct positioning of the recording electrodes, or ancillary staff in the operating theatre to aid in monitoring RLN function[28]. The utilisation of IONM may amount to 5 to 7% of the total thyroidectomy inpatient expense [52].

DISCUSSION

RLN injury resulting in RLNP is one of the most serious and major complications of thyroid surgery. It greatly affects patient's quality of life post-operatively. RLN injury rate is recorded to range from 0.5-10% [53]. Most surgeons believe that routine exposure and separation of RLN can protect anatomical integrity of the nerve and reduce its rate of injury[23]. Development of IONM has contributed in exposure and localization of RLN during thyroidectomy. Furthermore, it decreases the rate of RLN injuries[54].

Visually intact nerve does not necessarily means it is functionally intact[55–57]. Even if RLN is anatomically intact during surgery complete avoidance of injury to the nerve cannot be guaranteed after the operation. Technique of IONM has enabled surgeons to recognize temporary injury to RLN intra-operatively and indicate early warning signs for surgical team to manoeuvre themselves to decrease or eliminate damage caused to the nerve. IONM can indicate non-dissociative injury such as injury from traction, clamping, electric cautery and suction.

IONM technique uses the principles of electrophysiology. Severity of injury to RLN is determined by monitoring the amplitude and latency of the VC EMG signal. Scott et al. concluded that decreased amplitude and increased latency is indication of nerve injury and the signal returns to normal if function of nerve is restored [60]. Tian et al. found significant relationship between RLN's temporary injury and extent of resection. Temporary injury to RLN risk during total thyroidectomy was three times greater than during right lobectomy[3]. Dralle et al. showed that permanent RLNP risk was significantly higher in lobectomy (1.34%) in comparison to subtotal resection (0.68%)[61,62]. These conclusions suggest that surgical teams should consider benefits and complications while deciding extent of the surgery. American Thyroid Association abbreviated as ATA guidelines of 2015 says that hemi-thyroidectomy may be sufficient for patients without clinically or radiologically involved cervical lymph node metastasis or extra-thyroidal extension[63,64].

The anatomy of right RLN is different than left RLN. Left RLN circles around aortic arch and travels almost vertically up to the trachea. Right RLN present around subclavian artery and travels obliquely towards the larynx[65]. A few researches have concluded differences between left and right RLN injury[60]. Tian et al. [66] study concluded, left RLN is more prone to surgical manipulation as compared to right RLN.

Normal quantitative parameters of IONM were analysed by a multi-centre study involving six centres[8], it showed that the right vagus nerve implied a significantly larger median amplitude ($P<0.001$) and a significantly shorter latency ($P<0.001$) compared to the left vagus nerve. Phelan et al. concluded[8] that right and left RLN latencies were comparable. Latency of right vagus nerve was less than left vagus nerve but the difference was not very significant. Latency of RLN was significantly less as compared to vagus nerve. Amplitude of left vagus nerve was prominently less than right vagus nerve. However, between men and women, there was no difference in the amplitude of either the RLNs or the vagus nerves [60]. Another study concluded that the main latency of left vagus nerve was significantly more than right vagus nerve[67].

Among the two major categories of IONM,C-IONM is considered superior and more effective in preventing damage to RLN as compared toI-IONM[67].Study by Andres et al.[13] on 101 cases recorded with c-IONM in neck surgeries,13 patients showed temporary loss of signal. After changing the surgical approach LOS was prevented and recovered. In 3 cases LOS occurred due to placement of electrode on vagus nerve (3/101).In 1 case LRNP persisted even after 6 months due to anterior branch of RLN's accidental section (1/101 =1%). Vagus nerve was intact in all 3 cases; this trauma's exact reason is unclear but might be due to peri-neural bleeding or tractionto the nerve while exposing it. A study by Brauckhoff et al. [11] cites 2 cases of loss of signal in high-risk surgery by the electrode, 1 case was due to perineural bleeding at the time of placement of the electrode, and the other case was caused by torsion of the electrode which remained undetected. Mangano et al. [8,9,47] reported increase

in size of vagus nerve after placement of electrode of 0.82 mm and dislocation rate of electrode per procedure was 11%. Therefore, it highlights the importance of suitable electrode size selection and careful use of standardised technique for electrode placement on the nerve. The studies made us believe that loss of signal may be due to the upward traction caused by right-angel dissector, necessary for electrode placement, used for 360° nerve dissection. In addition to c-IONM signal from the electrode, it is necessary to check signal of vagus nerve proximal to electrode placement after surgery. Furthermore, it can be assumed that some traction injuries during I-IONM cases could have been avoided if c-IONM had been used. This assumption is based on the findings from other studies reporting events to be reversible when instantly corrective measures were applied intra-operatively [67].

CONCLUSIONS

IONM can decrease the incidence of permanent RLNP rates. IONM is recommended in bilateral operations and malignancy cases. The benefit of this technique in the re-operation cases needs to be further explored[68]. Among the two types of IONM, c-IONM is superior as it provides real-time monitoring of the RLN function, allowing surgeon to adapt surgical manoeuvres to decrease the incidence of RLNP intra-operatively. The risk-benefit ratio of c-IONM should be further evaluated as it indicates a risk at electrode placement. This technique is particularly useful in operations where the RLN is difficult to identify by the standard lateral approach for example redo surgeries, posterior nodule surgeries, large and/or retrosternal goiter or in some rare cases when RLN is invaded by a tumor.

In large or retrosternal goitre superior approach to reach RLN is favoured[68]. When using c-IONM, at the end of the procedure, to ensure functional integrity of the vagal nerve and RLN, vagal stimulation proximal to site of electrode placement should be done. It is also important to perform in order to avoid false negative IONM result. IONM has augmented the precision in signaling the nerve injury early on and in accurately predicting post-operative vocal cord palsy. This enables young surgeons to withdraw surgical maneovers causing the nerve injury and in turn hone their surgical skills. IONM has turned into a powerful and affective risk minimisation technique used in thyroid surgeries since 2010s. This technology needs to keep pace with the endoscopic and robotic surgeries which are gaining momentum and popularity in the Western Hemisphere.

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Archives of Surgical Research | Systematic Literature Review

Pre-Operative Parathyroid Gland Localization in Primary Hyperparathyroidism: A Systematic Literature Review

Hira Ashraf, Muhammad Muddassar Shafiq, Safia Zahir Ahmed, Talat Waseem

INTRODUCTION Primary hyperparathyroidism is amongst the most common endocrine disorders. Parathyroidectomy is the only definitive cure. Traditionally, bilateral neck exploration was performed; however, now surgeons largely prefer minimally invasive parathyroidectomy. Pre-operative localization aids in selecting candidates for minimally invasive parathyroidectomy. Non-invasive imaging modalities commonly used include ultrasound, sestamibi scintigraphy, 4-D CT, MRI, PET and PET/CT.

OBJECTIVE The objective of this literature review is to evaluate technique, accuracy, advantages and disadvantages of the non-invasive imaging modalities in order to propose algorithm in de novo and re-operative cases.

METHODS This systematic review is written according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines. A comprehensive literature search of PubMed/MEDLINE and Google Scholar was performed using search terms "primary hyperparathyroidism" OR "parathyroid adenoma" AND "pre-operative localization" OR "pre-surgical localization". 195 papers were identified through literature search. Following removal of 19 duplicates, titles and abstracts of 176 papers were reviewed. After thorough analysis, 41 papers were included in this literature review.

RESULTS Minimally invasive parathyroidectomy requires accurate pre-operative localization. Surgeons prefer two concordant imaging techniques prior to minimally invasive parathyroidectomy. In de novo cases ultrasound and sestamibi scintigraphy are the commonly employed techniques. However, 4-D CT has shown superior performance. In re-operative cases ultrasound and 4-D CT are used as first line modalities. MRI, PET or PET/CT are preferred prior to invasive methods of localization in inconclusive first line imaging of re-operative cases.

CONCLUSION Determination of accuracy of different imaging techniques can help select candidates for targeted tissue dissection with smaller incision and improved surgical outcome. However, devising a single algorithm for pre-operative localization using non-invasive imaging techniques remains undetermined.

KEYWORDS Primary Hyperparathyroidism, Ultrasound, Sestamibi Scintigraphy, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET).

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Systematic Literature Review

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Primary hyperparathyroidism is known as the most common cause of hypercalcemia and third most common cause of endocrine disorders, first two being diabetes mellitus and hyperthyroidism [1]. Its incidence increases with age and has 2 to 3 times greater predisposition in women than men [2]. Causative factors include single benign adenoma (85-90%), multiglandular hyperplasia (6%), double adenoma (4%) and carcinoma (<1%) [3].

Surgical excision of abnormal tissue is the recommended treatment of choice for primary hyperparathyroidism, parathyroid carcinoma, persistent primary hyperparathyroidism and recurrent primary hyperparathyroidism [4,5]. However, parathyroid surgeries are stalled because of problems with accurate localization, increased risk of intraoperative bleeding, injury to recurrent laryngeal nerve and transient or permanent hypoparathyroidism [6]. Anatomic position of parathyroid glands is not fixed which hinders the accurate localization of glands. In vast majority there are four glands, however, they are also seen in excess or less number. Superior glands are derived from fourth branchial pouch and are more

consistent in their position than lower glands, which develop from third branchial pouch and travel greater distance [7,8]. Ectopic glands, which may lie in retroesophageal position, retropharyngeal position, mediastinum, thymus, thyro-thymic ligament and carotid sheath, further increase the risk of surgical complications.

Traditionally, bilateral neck exploration was performed but surgeons now prefer minimally invasive parathyroidectomy in selected cases. Minimally invasive parathyroidectomy has become the preferred procedure as it involves targeted tissue dissection. It has shorter procedure time, shorter stay in hospital, lower cost, lesser surgical complications and better cosmetic result. Minimally invasive parathyroidectomy can also be effectively performed with locoregional and intravenous sedation [9,10].

Pre-operative localization is recommended for cases with biochemically proven primary hyperparathyroidism. Pre-operative localization of hyperfunctioning parathyroid glands aids in selecting the candidates eligible for minimally invasive parathyroidectomy and in determining presence of ectopic glands, thyroid neoplasia, persistent or recurrent disease. Precise localization increases success rate of parathyroidectomy while inconclusive localization is reported a risk factor for persistent disease [6].

In this article non-invasive imaging modalities used for pre-operative localization of parathyroid glands in primary hyperparathyroidism are reviewed. The accuracy of imaging modalities in de novo, re-operative, persistent and recurrent cases along with their advantages and disadvantages are summarized in this review using the up to date data available.

METHODS

This literature review is written according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines with objective of analyzing data available for pre-operative localization of parathyroid glands in primary hyperparathyroidism.

Search strategy: A comprehensive computer literature search of PubMed/MEDLINE and Google Scholar was performed. The search algorithm was based on combination of terms: "primary hyperparathyroidism" OR "parathyroid adenoma" AND "pre-operative localization" OR "pre-surgical localization". All the search papers were reviewed according to the selected search strategy. In addition, reference research papers were also included in this review to expand the search.

Inclusion of articles: 195 papers were identified using the computer literature search. Titles and abstracts of all the papers were reviewed using the inclusion and exclusion criteria.19 papers were excluded for duplication, remaining 176 papers were reviewed and 41 papers related to the topic were included in this literature review. Full text versions of the articles related to the topic were reviewed. No language, age or gender restriction was applied. All papers from the year 1996 to 2020 were included in the literature search. Exclusion criteria included duplicate papers, papers on animal studies, poster presentations, papers not related to the topic, papers on thyroid gland, papers on MEN syndrome or secondary and tertiary hyperparathyroidism. The article selection process is given in Diagram 1.

Data extraction and analysis: Thematic analysis of each eligible paper was done. Information about year of origin, author name, country of origin, method of study and theme identified was collected and coded. Metrics of diagnostic accuracy from each study were obtained which included sensitivity, pooled sensitivity and pooled positive predictive value (PPV). The themes identified through analysis of the data are given in Table 1.

Results: 195 papers were identified through comprehensive computer literature search. Titles and abstracts of 176 papers were reviewed following removal of duplicates. 41 papers related to the topic were included after thorough analysis. Recurrent themes were identified in the included papers and these themes are coded in Table 1.

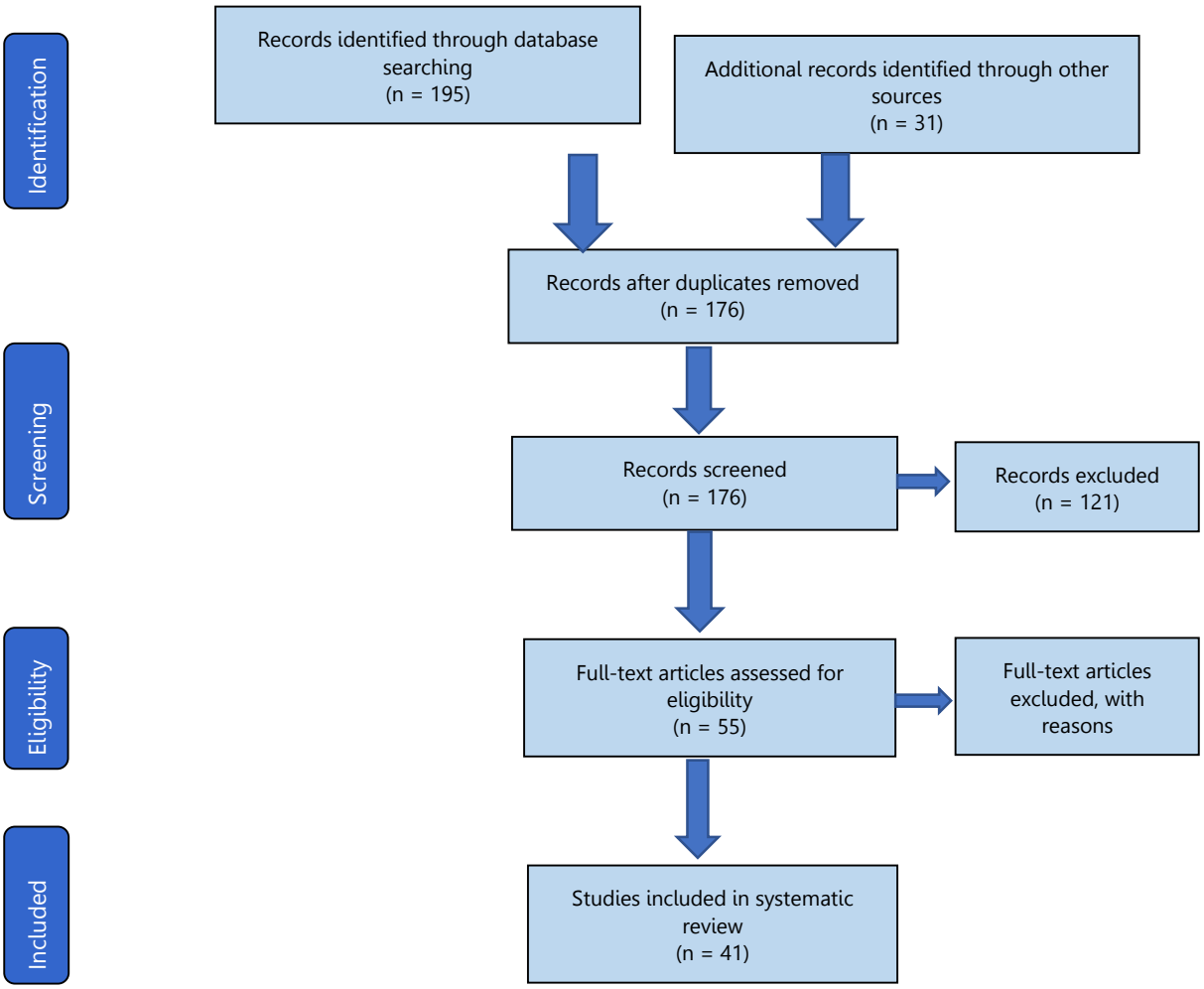
FINDINGS

Ultrasound is the first line non-invasive imaging modality used for preoperative localization [11]. Assessment of the anterior cervical region with a high frequency linear transducer is required. Patient lies in supine position with neck extended, special attention is paid to posterior and inferior thyroid margins [12]. Normal glands are not detected by ultrasound. However, adenoma appears as ovoid, homogenous, hypoechoic and well-circumscribed mass in contrast with the thyroid tissue [10,13]. Though, differentiation from calcification, cystic degeneration, hemorrhage and fibrosis should be kept in mind for accurate localization [14]. Color doppler demonstrates the presence of polar feeding vessel or peripheral vascularity of the adenomatous mass, which differentiates adenoma from lymph node [15]. Ultrasound also guides fine needle aspiration of parathyroid lesions. The need for surgery in thyroid lesions is reduced from 30% to 6% by obtaining fine needle biopsy through ultrasound [16].

Sensitivity of ultrasound in pre-operative localization is 79% for solitary adenomas, 34.9% for multi-gland hyperplasia and 16.2% for double adenomas [3]. In de novo patient's ultrasound has a pooled sensitivity of 76% and pooled positive predictive value (PPV) of 93% [17]. Lee at al. showed that ultrasound has highest sensitivity of 91.5% regarding pre-operative localization [18]. With contrast the sensitivity is reported greater than 95% in certain studies [19]. However, the sensitivity of ultrasound in re-operative cases decreases and is reported between 54%-68% in persistent or recurrent disease and nearly 40% in cases with multi-gland disease [20,21].

Ultrasound is the preferred first line modality as it is inexpensive, readily available and radiation free. Ultrasound also gives good anatomic resolution [10]. It aids in concurrent evaluation of thyroid neoplasia and fine needle aspiration of parathyroid tissue. However, its effectiveness is highly operator dependent [12]. It has inability to assess ectopic glands located in mediastinum, tracheoesophageal groove, retroesophageal position and retro-clavicular position [11]. Ultrasound is insensitive for enlarged glands and intrathyroidal lesions [22]. Ultrasound has reduced sensitivity for multi-gland parathyroid disease and concurrent thyroid nodules [23]. Ultrasound fails to localize adenomas in obese patients [11].

Figure 1: Prisma Flowchart- Article selection process through computer literature search and analysis:



Parathyroid scintigraphy is another first line imaging modality used for pre-operative localization. Tc99m sestamibi is the principal radiotracer used for localization of abnormal parathyroid tissue [11]. It accumulates in parathyroid glands and thyroid gland depending upon their metabolic activity and blood flow [24]. It typically accumulates in mitochondria rich cells of hyperfunctioning parathyroid glands [25]. Hence, its sensitivity depends on oxyphil cell density, number of mitochondria, co-existing neck pathology and solid or cystic nature of gland [26].

Several scintigraphy protocols have been proposed but the most widely employed is single-isotope dual-phase scintigraphy [27]. It doesn't require patient preparation [28]. Following administration of radiotracer, early and late phase planar images of neck and mediastinum are obtained at 10-30 mins and 90-180 mins respectively [24,28]. Radiotracer rapidly accumulates in both parathyroid and thyroid tissue following administration. However, parathyroid adenoma appears as focus of accumulation on early images and intensifies on delayed images because radiotracer washes out of 60%-85% parathyroid adenomas more gradually than

normal parathyroid and thyroid tissue [10]. The remaining 15%-40% adenomas exhibiting rapid wash-out are difficult to diagnose [28].

Table 1: Studies included in the systematic literature review and their corresponding outcomes

Year	Author	Country	Research Method	Study Outcome
1996	Mazzeo (Mazzeo et al, 1996)	US	Ultrasound and Scintigraphy imaging used in 73 cases as first line	Ultrasound and scintigraphy have comparable sensitivity in detecting parathyroid lesions when used as first line
1999	Ishibashi (Ishibashi et al,1999)	Japan	3-D CT and Scintigraphy used in 2 cases with ectopic parathyroid gland	Scintigraphy detected ectopic glands in both patients. 3-D CT aided in surgical planning with anatomic resolution
2003	Kaczirek (Kaczirek et al, 2003)	Austria	99m Tc-sestamibi/X-ray-CT used in 4 cases with ectopic parathyroid glands	99m Tc-sestamibi/X-ray-CT localized ectopic glands in all 4 cases
2004	Timm (Timm et al, 2004)	Germany	Prospective study of 40 cases of primary hyperparathyroidism 21 cases had minimally invasive parathyroidectomy 7 cases had bilateral neck exploration 12 cases had unilateral parathyroid exploration and thyroid resection	With accurate pre-operative localization 95% patients can be scheduled for appropriate surgical approach.
2005	Beggs (Beggs & Hain 2005)	UK	Retrospective study after 11C-metionine PET scanning in 51 cases of hyperparathyroidism with other failed imaging techniques	11C-methionine PET showed high accuracy (88%) in detecting parathyroid adenomas
2006	Malinvaud (Malinvaud et al, 2006)	France	Retrospective study of 51 cases for treatment with pre-operative localization with ultrasound in 51 and sestamibi scan in 49 cases	Accurate pre-operative localization allows targeted surgery with shorter hospital stay, shorter procedure duration, lesser complications and cost effectiveness
2007	Singh (Singh & Krishna 2007)	India	Retrospective study of 28 cases to determine role of scintigraphy in parathyroid adenoma detection	Scintigraphy exhibits high sensitivity in parathyroid adenoma detection and can be used as first line imaging
2008	Bybel (Bybel et al, 2008)	Canada	Narrative review	SPECT/CT provides anatomic resolution for localization in cases where SPECT fails.
2011	Evangelista (Evangelista et al, 2011)	Italy	Retrospective study of 5 cases with parathyroid carcinoma using fluorodeoxyglucose PET/CT at initial staging, restaging and post-surgical evaluation	PET/CT has high sensitivity for parathyroid carcinoma
2012	Saengsuda	Thailand	Retrospective study of 71 cases (to assess scintigraphy accuracy) with hyperparathyroidism who underwent surgery. 18 cases with primary hyperparathyroidism and 53 cases with secondary-tertiary hyperparathyroidism	Scintigraphy has sensitivity and accuracy for localization in primary hyperparathyroidism. Scintigraphy cannot be classified as essential pe-requisite in secondary tertiary hyperparathyroidism and multi-gland disease prior to surgery.
2012	Kim (Kim et al, 2012)	Japan	Retrospective study of 31 cases with hyperparathyroidism to assess efficacy of 99m-Tc sestamibi SPECT/CT for minimally invasive parathyroidectomy	99m-Tc sestamibi SPECT/CT can detect parathyroid adenomas and multi-gland disease missed by conventional imaging and SPECT.
2012	Treglia (Treglia et al, 2012)	Switzerland	Meta-analysis for detection rate of 99m-Tc sestamibi SPECT/CT	99m-Tc sestamibi SPECT/CT has sensitivity for localization in primary hyperparathyroidism
2014	Philippon (Philippon et al, 2014)	France	Retrospective study of 182 patients treated for primary hyperparathyroidism with bilateral neck exploration	Discordant and negative imaging results are seen in both multi-gland disease and single adenoma.

2014	Exposito (Exposito et al, 2014)	Spain	Case report	99m Tc-scintigraphy helps in localization of intrathyroidal adenoma.
2014	Keidar (Keidar et al, 2014)	Israel	Retrospective study of 36 cases with primary hyperparathyroidism to assess accuracy of Tc-99m scintigraphy SPECT/CT	Tc99m-scintigraphy SPECT/CT has an accuracy of 83%
2015	Barczynski (Barczynski et al, 2015)	European society of endocrine surgeons	Review article	Negative pre-localization studies are highly predictive of multi-gland disease. Pre-operative localization of multi-gland disease is challenging
2015	Ozkaya (Ozkaya et al, 2015)	Turkey	Retrospective study of 39 cases of primary hyperparathyroidism to evaluate accuracy of conventional imaging techniques	Sensitivity and PPV of ultrasound and scintigraphy when combined is greater than individual imaging. Concurrent application is more successful in detection of enlarged glands
2016	Thanseer (Thanseer et al, 2016)	India	Case report	18-F-fluoromethylcholine PET/CT localized the ectopic parathyroid adenoma missed by ultrasound and scintigraphy imaging.
2017	Reid (Reid et al, 2017)	UK	Retrospective cohort study	Ultrasound is highly accurate in lateralizing parathyroid adenomas. 18-fluorocholine PET/CT maybe helpful in localization when conventional imaging fails
2017	Ozderya (Ozderya et al,2017)	Turkey	Retrospective study of 65 patients who underwent ultrasound guided fine needle aspiration	Ultrasound guided fine needle aspiration can improve accuracy. Metastatic lymph node and thyroid nodule can give false positive with 99m technetium scintigraphy.
2017	Al-Githmi	Saudi Arabia	Retrospective study	Minimally invasive parathyroidectomy has better cosmetic result with shorter hospital stay, cost effectiveness and lesser complications
2017	Raruenrom (Raruenrom et al, 2017)	Thailand	Retrospective study	Dual tracer scintigraphy has higher accuracy than dual phase scintigraphy. SPECT and SPECT/CT have higher diagnostic accuracy
2018	Grimaldi (Grimaldi et al, 2018)	France (EJNMMI)	Prospective study of 46 patients for pre-surgical evaluation of hyperparathyroidism by 18-F-fluoromethylcholine PET/CT	18-F-fluoromethylcholine PET/CT has high sensitivity and specificity for localization. it has added value in inconclusive imaging, re-operative cases and multi-gland disease.
2018	Kim (Kim et al, 2018)	South Korea	Systematic review and metanalysis on diagnostic performance of 18-F-fluoromethylcholine PET/CT	18-F-fluoromethylcholine PET/CT has high sensitivity and specificity for localization in primary hyperparathyroidism but requires large multicenter studies to establish its beneficial role.
2018	Tay (Tay et al, 2018)	US	Retrospective study of 138 patients	Sestamibi scintigraphy readily detected ectopic glands which more commonly arise from inferior glands. Sestamibi scintigraphy has high accuracy for localization and lateralization
2018	Thimmappa (Thimmappa et al, 2018)	US	Retrospective study	Ultrasound has better predictive value than scintigraphy. Pre-operatively, ultrasound and scintigraphy are the two preferred concordant imaging techniques
2018	Zajickova (Zajickova, Zogala & Kubinyi, 2018)	Slovakia	Retrospective study of patients with previous negative or discordant imaging	18-F-Fluoromethylcholine PET/CT has a sensitivity of 92%. It has high sensitivity for small, hyperplastic and multiglandular disease
2018	Bossert (Bossert et al, 2018)	Italy	Retrospective cohort study of 34 cases	18-F-Fluoromethylcholine PET/CT can be recommended as first line imaging but requires large scale studies and it has high sensitivity for small glands. It can detect disease in early stages.
2018	Piccardo (Piccardo et al, 2018)	Italy (EJNMMI)	Retrospective study of 44 cases of primary hyperparathyroidism with inconclusive first line imaging	18-F-fluoromethylcholine PET/4D contrast enhanced CT is the most accurate second line imaging in patients with negative or inconclusive first line techniques
2018	Treglia (Treglia et al, 2018)	Switzerland (EJNMMI)	Systematic review and meta-analysis	PET/CT has high accuracy for localization in primary hyperparathyroidism. It requires prospective studies and cost-effective analysis before its recommendation for routine use
2019	Uludag, 2019	Turkey	Literature review	In primary hyperparathyroidism localization can be done in 80-90% using non-invasive imaging. Ultrasound and scintigraphy are first line imaging techniques. In negative or inconclusive imaging 4-D CT or PET/CT can be done.

2019	Miguel (Miguel et al, 2019)	Spain	Literature review	Dual-tracer scintigraphy is preferred in cases with concomitant thyroid disorder. PET/CT or MRI or CT are preferred in cases with inconclusive first line imaging techniques which is usually the combination of ultrasound and scintigraphy.
2019	Assante (Assante et al, 2019)	Italy	Retrospective study of 46 cases with primary hyperparathyroidism and inconclusive ultrasound, to compare SPECT/CT and scintigraphy	Combination of anatomic and functional information has led to higher sensitivity and specificity of SPECT/CT than planar scintigraphy
2019	Boccalatte (Boccalatte, Higuera & Gomez, 2019)	Argentina (JAMA)	Systematic review	18-F-fluoromethylcholine PET/CT is effective imaging technique in difficult cases and inconclusive first line imaging
2020	Parikh (Parikh, Grogan & Moron, 2020)	US	Review article	First line modalities in re-operative cases should constitute both ultrasound and 4-D CT. In re-operative cases with negative first line imaging PET/CT or MRI should be considered prior to invasive techniques
2020	Hindie (Hindie, Urena-Torres & Taieb, 2020)	France	Literature review	Re-operative cases require combination of imaging techniques. 4-D CT and MRI have high accuracy for ectopic glands
2020	Maissin (Maissin et al, 2020)	France	Retrospective study of 273 patients who underwent ultrasound and 99m-Tc sestamibi scintigraphy	The sensitivity and PPV of ultrasound and sestamibi scintigraphy is higher when used in combination than individual sensitivities and PPV
2020	Vazquez (Vazquez et al,2020)	Spain	Prospective cohort study of 34 cases with primary hyperparathyroidism	PET/CT has higher accuracy in small adenoma, re-operative cases and hypocalcemia than gold standard techniques
2020	Evangelista (Evangelista et al, 2020)	Italy	Systematic literature review	18-F-fluoromethylcholine PET/CT has higher accuracy in detecting parathyroid adenoma than conventional ultrasound and SPECT
2020	Minhas (Minhas et al, 2020)	US	Retrospective study of 18 cases with primary hyperparathyroidism.	4-D CT has higher sensitivity and specificity than SPECT
2020	Morland (Morland et al, 2020)	France	Retrospective study of 47 cases who underwent 18-F-fluoromethylcholine PET/CT as second line imaging	Fluoromethylcholine PET/CT is a promising second line imaging. It requires large scale prospective studies

Sensitivity of sestamibi scintigraphy in pre-operative localization is 88.4% for solitary adenomas, 44.5% for multi-gland hyperplasia and 30% for double adenomas [3]. Sestamibi scintigraphy has a pooled sensitivity of 63% and pooled PPV of 90% [29]. However, Lee et al. showed sestamibi has the lowest sensitivity of 56.1% regarding pre-operative localization [18]. Sensitivity of sestamibi scintigraphy in re-operative cases with persistent and recurrent disease is 53% to 74% and between 23% to 45% in multi-gland disease [30,31]. Addition of SPECT/CT after the early, delayed or both planar images aids in surgical planning [28]. Though many centers prefer SPECT imaging in early phase to detect rapid wash out adenomas [32]. It offers combination of a better anatomic visualization in 3 dimensions and improved contrast resolution for functional analysis into a single image [25]. Addition of SPECT/CT aids in detection of ectopic glands, deep seated adenomas and relation of abnormal mass with adjacent structures [10]. SPECT acquisitions are not associated with additional radiation exposure; however, CT is associated with increased radiation exposure [28]. Single-isotope dual-phase SPECT has pooled sensitivity of 79% and pooled PPV of 91% [17]. Meta-analysis of 18 studies showed single-isotope dual-phase SPECT/CT has pooled sensitivity of 84% and pooled PPV of 95% [29].

Single-isotope dual-phase scintigraphy is preferred as first line modality because of its ability to detect ectopic and far posterior glands. Its effectiveness is independent of operator. It gives both anatomic and functional information with SPECT/CT [10,11]. However, it is associated with radiation exposure, long imaging duration, motion degradation and poor anatomic resolution. It is insensitive for rapid wash out adenomas and normal parathyroid tissue. It has reduced sensitivity for multi-gland disease and patients taking calcium channel blockers (decreased sestamibi uptake) [33]. It fails to localize hyperplastic glands. Delayed wash out from thyroid nodules and enlarged cervical lymph nodes gives false positive results [25].

An alternate scintigraphy protocol is dual-isotope single-phase technique. In this technique sestamibi radiotracer taken up by both parathyroid and thyroid gland and iodine-123 or technetium Tc99m pertechnetate radiotracer taken up specifically by thyroid gland are used [34]. Images are sequentially acquired. First image is acquired after administration of thyroid specific radiotracer and second image is acquired following administration of radiotracer

taken up by both thyroid and parathyroid gland. Abnormal parathyroid tissue is identified by visual comparison of the two images or via digital subtraction [22]. Dual-isotope single-phase technique is preferred in a European study because of decreased possibility of false positive results with thyroid nodules and enhanced sensitivity for multi-gland disease [22]. However, it is associated with higher radiation exposure, requires patient preparation and depends on motion free images [10].

4-D Computed Tomography (4-D CT) is more commonly used for pre-operative localization of cases with inconclusive first line imaging. However, its use is rapidly increasing with some employing it as first line modality. Several protocols are in use but the most common one involves 3 phase (non-contrast phase, arterial phase and venous phase) CT acquisition of neck and upper thorax [35]. The four dimensions are axial, coronal, sagittal and time [13,32]. Arterial and venous phase are acquired at 30 sec and 60 sec respectively following contrast administration. Attenuation exhibited by parathyroid adenomas in contrast with thyroid gland is lower in non-contrast phase, greater in arterial phase and lower in venous phase [36]. Familiarity with mimicking lesions, such as calcification, cystic degeneration and fibrosis, is necessary for accurate localization [37].

In primary hyperparathyroidism 4-D CT has sensitivity range of 62%-92 and PPV range of 88%-94% when used as first line modality [38,39]. When used as second line modality in inconclusive prior imaging it has sensitivity range of 67%-89% and PPV range of 65%-87% [40]. In re-operative cases it has sensitivity of 93% for localization and 97% for lateralization [41,42]. It has sensitivity range of 43%-69% for accurate multi-gland disease localization [43,44]. In re-operative setting 57%-75% of the lesions missed by 4-D CT are multi-gland disease [45]. In addition, it is more accurate in lateralizing lesions with mild hypercalcemia and low weight glands than sestamibi scintigraphy [38].

4-D CT gives high-resolution spatial anatomic display which is helpful in re-operative cases for identifying important landmarks and surrounding structures [11]. It is well suited in re-operative cases because its sensitivity in de novo and re-operative cases is comparable, unlike ultrasound and scintigraphy [46]. Comparatively, it has superior performance in pre-operative localization of persistent and recurrent disease [47]. 4-D CT enables minimally invasive parathyroidectomy in difficult re-operative cases because of its ability to differentiate unilateral and bilateral disease in up to 96% re-operative cases [20,48]. It has relatively high sensitivity for multi-gland disease, ectopic glands, setting of mild hypercalcemia, mildly enlarged glands and patients with inconclusive first line imaging [10]. In addition, it has short imaging time. However, it is associated with increased radiation exposure and requires experienced radiologist [35].

Magnetic Resonance Imaging (MRI) is commonly used second line imaging modality parallel to 4-D CT for pre-operative localization of parathyroid glands [13]. Protocols of conventional MRI include pre-contrast axial T1 and T2 weighted images and post-contrast T1 weighted images with fat saturation [11]. On pre-contrast T1 and T2 weighted images and post-contrast T1 weighted images, parathyroid adenomas appear isointense, hyperintense and strongly enhancing to the muscle, respectively [49]. Dynamic 4-D contrast enhanced (DCE) MRI is a multiphase modality based on the principle of hypervascularity of the parathyroid adenomas [10]. DCE MRI makes use of perfusion characteristics to differentiate parathyroid adenomas from mimicking lesions such as lymph nodes and thyroid tissue. Parathyroid adenomas show faster arterial enhancement and higher wash in and wash out compared with mimicking lesions [50].

Conventional MRI has sensitivity of 91% for localization in primary hyperparathyroidism [13]. MRI increases localization sensitivity from 75% to 92% when used in combination with ultrasound and sestamibi scintigraphy [49]. MRI has sensitivity of 82% in re-operative cases [49,51]. In a research authors stated that MRI can be preferred to select candidates with parathyroid adenoma for minimally invasive parathyroidectomy. MRI could localize 2 out of 7 adenomas missed by ultrasound and 6 out of 8 adenomas missed with scintigraphy, however, combined use of MRI and ultrasound could detect all the cases of multi-gland disease and ectopic adenomas [52]. DCE MRI has sensitivity of 91% for parathyroid adenomas in unselected cases [50]. DCE MRI has sensitivity of 90% for adenomas in re-operative cases [49].

MRI is not associated with radiation exposure unlike scintigraphy and 4-D CT, hence can be preferred in patients with contraindication to radiations. Its sensitivity in de novo and re-operative cases is comparable. When used as first line modality it shows significant sensitivity but its use in re-operative cases gives added benefit as accuracy of ultrasound and scintigraphy markedly suffer in such cases [49]. However, in contrast to CT it is expensive, inaccessible and time consuming. It requires large sample investigations before establishing its significant role in cases with persistent and recurrent disease [11].

Positron Emission Tomography (PET) and Hybrid PET/CT is emerging as significant imaging modality in difficult parathyroid cases [10] [13]. It has gained popularity for consideration prior to invasive methods of localization in scheduled re-operative patients with persistent or recurrent disease [34]. The radiotracers administered in this technique show particular avidity for metabolically active tissues such as parathyroid adenomas which appear as focal areas of uptake [11]. Methionine is precursor amino acid for parathormone while choline is required for cell membrane synthesis [53,54]. The investigated radiotracers used in this modality include 11C-methionine, 18F-fluorodeoxyglucose and 18F-fluoromethylcholine. This modality gives enhanced spatial anatomic resolution. Hybrid imaging with PET and low dose CT gives better anatomic resolution in addition to functional analysis.

11C methionine PET has pooled sensitivity of 77% and pooled PPV of 98% for both de novo and re-operative patients [55]. 11C methionine PET has a sensitivity range of 75%-88% in re-operative cases of primary hyperparathyroidism [56–58]. Similarly, 18F-fluorodeoxyglucose PET has a sensitivity of 62% in re-operative cases [59]. 11C-methionine PET/CT has a sensitivity of 61% in re-operative patients and this figure maybe as low as 40% in difficult cases [60]. 18F-fluoromethylcholine PET/CT has sensitivities of 96 and 100% in persistent or recurrent disease [61]. 18F-fluoromethylcholine PET/CT has sensitivity of 79% and PPV of 100% for multi-gland disease [62]. In a meta-analysis of 11 studies 18F-fluoromethylcholine PET/CT has shown localization of 97% in patient-based and 94% in lesion-based analysis. This study stated that it could replace sestamibi scintigraphy in parathyroid imaging [63]. In addition, the combined use of 18F-fluorodeoxyglucose and 18F-fluoromethylcholine in PET/CT has demonstrated beneficial role for determining extent of primary disease, metastases and recurrence in parathyroid carcinoma [64].

18F-fluoromethylcholine PET/CT gives better spatial resolution with shorter study time and lesser radiation exposure than SPECT/CT [65]. PET enables detection of small glands by giving better spatial and temporal resolution than SPECT [55]. In a study of 29 patients 18F-fluoromethylcholine PET/CT is seen to be more sensitive for parathyroid localization in re-operative cases than ultrasound, sestamibi scintigraphy and 4-D CT [61]. However, PET/CT is expensive, infrequently used and requires larger samples to establish its role in localization in persistent and recurrent disease [11]. 18F-fluorocholine PET/CT usually fails to detect ectopic adenomas and hyperplastic glands [62,66].

DISCUSSION

A universal shifting of practice from traditional bilateral neck exploration to unorthodox minimally invasive parathyroidectomy requires accurate preoperative localization. Pre-operative localization in primary hyperparathyroidism has enabled surgeons to perform procedure with smaller incision and targeted tissue dissection. Precise pre-operative localization is a predictor of success of parathyroidectomy. Moreover, precise localization in re-operative or persistent cases is crucial. Negative or discordant imaging can be a risk factor for operative failure, hence, requiring additional imaging modalities when first line techniques are inconclusive.

Based on the data reviewed, ultrasound is the preferred first line modality as it has increased sensitivity and PPV for pre-operative localization. In addition, it is radiation free, readily available and cost effective. However, its sensitivity significantly reduces in re-operative cases and multi-gland disease. It is unable to detect ectopic glands. Sestamibi scintigraphy is another first line modality with high sensitivity and PPV, but it requires radiologic expertise more than ultrasound and 4-D CT. In addition, it is expensive and associated with radiation exposure. It has reduced sensitivity in re-operative cases and multi-gland disease. However, addition of SPECT CT aids in detection of ectopic glands. Cost effectiveness and overall superior performance favors 4-D CT over sestamibi scintigraphy as second line imaging modality. The performance of 4-D CT in de novo and re-operative cases is comparable. 4-D CT has higher sensitivity in re-operative cases, multi-gland disease and cases with inconclusive first line imaging compared with ultrasound and sestamibi scintigraphy. MRI has comparable sensitivity in de novo and re-operative cases unlike ultrasound and sestamibi scintigraphy. MRI has high sensitivity for multi-gland disease and ectopic glands. However, it is expensive, time consuming and not readily available. PET/CT has beneficial role in parathyroid carcinoma as well as in detection of small glands and is seen to be more sensitive in re-operative cases than ultrasound, sestamibi scintigraphy and 4-D CT in certain studies. However, it is expensive and infrequently used. Both MRI and PET/CT require larger sample size to establish their beneficial role in persistent and recurrent disease.

Following biochemical diagnosis of hyperparathyroidism surgeons usually prefer two concordant imaging modalities prior to minimally invasive parathyroidectomy. Observation showed highest sensitivity of 95 % with ultrasound and CT combination and lowest of 88.3% with sestamibi scintigraphy and CT combination. Combination of all three modalities showed a sensitivity of 95.4% [6]. 4-D CT has higher sensitivity of 88% for precise localization of abnormal parathyroid glands compared with ultrasound or scintigraphy [67]. 18F-fluoromethylcholine PET/CT is useful for ectopic and small gland localization and has higher accuracy of 96.3% than ultrasound and scintigraphy [68].

On basis of the data reviewed two different algorithms can be proposed for localization, in first time operations and re-operative cases. In de novo cases ultrasound is the main and also the first line examination, followed by sestamibi scintigraphy or CT. Overall, 4-DCT has superior performance than sestamibi scintigraphy. Yet in most centers sestamibi scintigraphy is more commonly used second line modality, due to its availability and radiation exposure considerations in younger patients with 4-D CT [10]. In re-operative cases imaging depends upon modalities used in initial work-up. First line modalities used in re-operative cases include both ultrasound and 4-D CT. Sestamibi scintigraphy is usually not used in recurrent or persistent cases. However, first line imaging is usually negative or discordant in re-operative cases. In such cases PET/CT or MRI are preferred prior to attempting invasive localization [11]. Even though the emerging techniques, 4-D CT, PET/CT and PET/MR have shown promising results yet they are not widely available and require larger sample size to prove their beneficial role [69].

Limitations Possible limitation of this review is that pre-operative localization can be most accurate only when each technique is performed by an expert radiologist. Correlation between imaging techniques used and surgical outcome can help propose definite algorithm in first operations as well as re-operative cases. Accuracy of pre-operative localization largely depends on local practices, techniques available in different centers and radiologic expertise. Large sample size is required for PET/CT, 4-D CT and MRI to develop beneficial role. Non-availability of high-performance techniques in institutions is a limiting factor to correctly determine their accuracy. Large scale prospective studies need to be conducted.

CONCLUSIONS

Pre-operative localization of parathyroid glands in primary hyperparathyroidism using different imaging techniques permits targeted evaluation of abnormal tissue. Technique, accuracy, advantages and disadvantages of non-invasive modalities are reviewed in this article. However, a single algorithm cannot be devised due to variation in practice, availability of techniques and patient population in different institutions. When used in concert the aforementioned and discussed techniques enable surgeons to perform targeted tissue dissection with improved surgical outcome.

ARTICLE INFORMATION

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Archives of Surgical Research | Systematic Literature Review

Application of Radiomics in Breast Cancer Diagnoses

Zahid Hussain, Rosheen Zahid

IMPORTANCE The emerging technology of Radiomics has brought a revolution in the field of medicine regarding the diagnoses. The technique is being used to diagnose and interpret the various types of cancers based on imaging characterizations. The manual methods of diagnosis have many limitations in terms of reliability. There are many annotations of tumors, and to recognize a specific type of tumor is not less than a challenge, which could be fulfilled through this technology. In this study, diagnostic approaches and the potential of radiomics has been assessed. Moreover, all the MRI-derived parameters were also explained to make the discussion strong.

METHODS The analyses of data were made based on secondary data. 450 researched articles were reviewed, 57 articles were identified and 9 articles were selected for the scientific literature review.

RESULT Radiomics modalities are advanced and accurate in their approach. The value of Ki67 is associated with the growth rate of a tumor. Radiologists have increased the accurate diagnostic percentage by using radiometric technology. Texture technique as a diagnostic has the highest accuracy level. Various imaging techniques depict different diagnostic results based on their principles. The Expression of the Ki67 strongly correlated with three texture features.

CONCLUSION This study aimed to help clinicians and radiologists to know the basic information of radiomics for better application in clinical practice.

KEY WORDS Radiomics and Breast cancer, Radiomics modalities, Prognostic factors, Tumors

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Systematic Literature Review

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Breast cancer is one of the most emerging and hot burning health hazards among women. A large number of women lost their lives, every day due to this disease [1]. The recovery and treatment of the disease depends upon early diagnosis. The survival rate in the disease depends upon accurate and timely diagnoses. The concept of data system and Breast imaging reporting provide strong and reliable communication between the radiologists and clinicians and help to evaluate the types of tumors in the patient of breast cancer. Moreover, a hormonal and molecular feature of the disease is also related to successful treatment. There are two major diagnostic tools for the disease; one is the conventional method and the other is the technology-based Radiomics method [2]. The former method is invasive and carried out by taking the tissue and making histopathological analyses. The method has many limitations and its reliability depends upon the expertise of the radiologists. The other drawback of the disease is that it couldn't provide the heterogeneity of the whole tumor rather provides a piece of limited information about the type of lesions [3]. While in the latter method, imaging data is extracted and analyzed by comparing tissue images with many parameters. Basically, It is the non-invasive and tissue-based imaging characterization technology that is developing day by day [3]. The quantitative data is extracted from the medical images and analyzed the underlying features of the pathological conditions of tumors through machine learning. The technique analyzes the condition on a molecular and genetic level for breast cancer, prostate cancer, and brain cancer [4]. The results obtained from these analyses are compared with the existing medical data of the disease, and most of the results are divergent. There are also some limitations of the technique including; the results of the Radiomics analyzes depend upon the inter-reader viability of the tumor annotation. Studies require manual or semi-automated segmentation of the tumor carried out by the radiologists. Due to this reason, the results which are obtained are divergent for different tumor annotations [4].

METHODS:

The research was carried out based on existing scientific data. Data was obtained from the most reliable scientific cites named, PubMed, NCBI online library, NIH, BioMed central, Web MD, and open MD. Qualitative and metanalyses were performed to analyze the selected data. The keywords to search the articles from the database are breast cancer and radiomics, Radiomics and mammography, breast-ultrasound, breast elastoplastic, Radiomics and breast lesions, texture analyses and mammography.

Inclusion and Exclusion Criteria

The data is not selected randomly, but has a certain inclusion criterion.

Inclusion Criteria

To include the data, the guidelines of PRISMA are followed in the research review. In the first category, 450 scientific articles were identified. Out of 450 articles, 57 were selected. For scientific review, 9 most reliable and relevant articles were selected. All the selected articles were peer-reviewed, randomized trials, review articles, and systemic review articles published from Jan 2010. All the researched articles were able to give detailed information about the application of radiomics in breast cancer diagnoses.

Exclusion Criteria

Articles without strong background or abstract were excluded. Articles that were very old and dated back to 20 years old were excluded. Articles in which sufficient numbers of references were not given were also excluded. No article from an ordinary website was included in research.

Data Extraction and Analyses

The electronic raw material from the articles was extracted and organized in a specific form. Irrelevant information was excluded and most relevant information about the hypothesis was organized in a table form. To locate the data specific coding was used, named physical coding. Extracted data organized in a table form. The selected data was cross-checked three times by two reviewers. The thematic analyses were also performed to make the analyses more advanced.

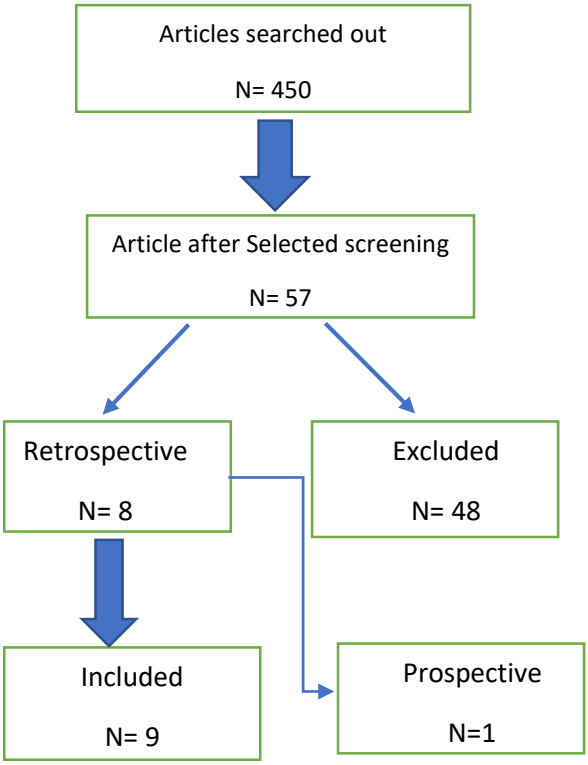

Figure 1: Demonstration method used to select articles

RESULTS:

After analyzing the data, it was confirmed that the radiomics modalities are far better than any other modalities in terms of efficiency and reliability. When median and coefficient median modalities were compared with the radiomics modalities, there was a clear difference between these modalities in terms of specificity and sensitivity for the diagnoses and differentiation of the lesions. The other study disclosed that expert radiologist when using constrained and unconstrained MRI, they perform better than the models of the radiomics. It was a peculiar and new discovery as it was always expected that radiomics models are more efficient, but it is not true under certain conditions. The efficiency and accuracy for diagnoses of breast cancer are increased when experts utilize the radiomics technology. So, the combination of manual expertise with technology always mimics in terms of efficiency.

Holli et al have investigated features of the tissue, based on texture. Then, he utilized the MRI-DCE technique to differentiate between normal breast tissue and breast cancer tissue. The accuracy level for the breast cancer diagnoses by using the texture technique was 100%. Another study disclosed that the accuracy of the diagnoses can be increased up to 90% by combining various models such as the multivariant model, kinetic parameters, morphological models, and ADC values. It was also found that the encashment of the normal breast tissues on the DCE-MRI would create a negative impact on the MRI radiological diagnoses. In this way, the accuracy rate of breast cancer decreased as normal tissues mimic the abnormal cancerous tissues leading to false diagnoses. The results of the texture-based macrocalcification for the breast tumors were high and accurate.

The results of the type of imaging are different from each other. The diagnostic results which are obtained through T1-weighted imaging are more accurate than the T2-weight imaging.

KI67 AS A PROGNOSTIC FACTOR:

Ki67 is an important prognostic marker of prognoses, especially in breast cancer patients. The factor is not only used to diagnose the tumors related to cancer, but also assess the therapeutic response. Basically, high and low ki67 lesions are classified through three machine learning methodologies or schemes. Those tumors which had a low rate of proliferation were found with a low level of Ki67, and conversely those with a high level of Ki67 have a greater proliferation rate of the tumor. The Expression of the Ki67 is linked with structural features including; entropy, contrast, and line likeness.

DISCUSSION

MAGNETIC REASONING IMAGING:

The technique of magnetic reasoning imaging is widely used in high-risk women for screening purposes. Moreover, the technology is used for many other purposes including; monitoring recurrence, evaluation of the curative effect, the provision of complementary information for ultrasonography, and monography. To make the precise diagnoses and to make the accurate differentiation between lesions of the tumor for various types of cancers, newly developed dynamic contrast-enhanced and diffusion-weight imaging are used for analyzing the breast lesions to make the diagnoses of breast cancer more accurately [5].

Diffusivity of the membrane is reflected through the integrity of the membrane and tissue of the microenvironment. The apparent diffusion coefficient is an important factor that is associated with the pathological process of tumor development. In studies, it has been proved that DWI is the most important tool to characterize and detect breast cancer[5].

MRI TECHNIQUE IN THE RADIOMIC TO DIFFERENTIATE BENIGN AND MALIGNANT LESIONS

To evaluate and visualize the radiological images, radiomics feature maps were generated and a correlation between breast tissues and Radiomics features was deduced from the findings. In this way, different breast tissues were compared with the Radiomics parameters. The entropy for malignant lesions was higher than RFM entropy. Accurate differentiation between benign and malignant lesions is the paramount factor for an accurate treatment plan. Studies have confirmed that the Radiomics technologies are the best analytical tools to provide the best approach towards breast cancer diagnoses and differentiation of such tumors. The discrimination abilities are clearer and more authentic than the conventional invasive methods of diagnoses. In terms of modalities, DWI and DCE are the first line modalities for the Radiomics analyses [6].

THE RELATION BETWEEN THE TUMOR AND HORMONE PRODUCTION

There are many hallmarks of breast cancer, but intra- and inter-tumoral heterogeneity are of the most important hallmark of breast cancer. The diagnoses are divided into three sub-categories; molecular classification, subtype, and pathological driven classification. Each type is specified with a certain risk factor and radiologists propose the treatment according to the type and form of a breast tumor. Studies have demonstrated that there is a strong link between the type of tumor and hormone production [7]. For instance, Progesterone and estrogen receptors give a positive response to luminal tumors. These tumors provide a positive response through hormonal intervention. The use of anti-HER2 to suppress the ERBB2 has been proved effective. The result based on T-weight imaging suggest that the imaging process based on T1 extracts more and accurate information than T2. The reason behind the process is not simple, but there are molecular and genetic factors that influence the T-based imaging process [7].

THE PREDICTION OF TUMOR RESPONSE

Non-adjuvant chemotherapy is carried out to treat patients with advanced stages of breast cancer. The response of tumors towards chemotherapeutic treatment is different. Some tumors show a remarkable positive response while some show the negligible response towards the treatment. Evaluation of the response is necessary to make the cost-effective and strategical treatment. Pathological assessment and solid-based evaluation of tumors were the gold standard to evaluate the action of chemotherapy in the past, but these methods couldn't make the exceptional results. MRI techniques now are able to make an accurate evaluation of the tissue response to the specific chemotherapeutic drugs[8].

ANALYSES OF THE LYMPH NODES METASTASIS

Axillary lymph node status is correlated with breast cancer tumors. Lymph node metastasis obtained from the DWI sequences is more closely related to the metastasis of the tumor than the ADC sequence. Some scientists use mammography MRI tomography to predict axillary metastasis. They proved that MRI is a great diagnostic tool in this regard.

CONCLUSION

Radiomics is a new and potential technology with boundless applications. Its applications in the diagnostic field are recent with high accuracy. As early diagnoses are the key to effective treatment, so the role of radiomics in breast cancer treatment is remarkable.

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Archives of Surgical Research | Critical Review

Emerging Trends in Managing Central Breast DCIS in Era of Oncoplastic Surgery: Where Do We Stand?

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IMPORTANCE The management of DCIS in today's era of rapid surgical advances is improving dramatically with time. Mastectomy rates have rapidly declined as breast diseases are being diagnosed at an earlier stage through screening procedures like mammograms and increased awareness regarding breast cancer. Oncoplastic surgical techniques have revolutionized this field by providing numerous options to deal with breast cancer while preserving the breast. Advances in the field of radiation and endocrine therapy have also translated into improved treatment algorithms with acceptable morbidity and recurrence rates. This analysis, thus, provides an overview of recent advances in the management of DCIS in light of a typical central DCIS lesion scenario and envisages evolving role of oncoplastic breast surgery in this regard.

KEYWORDS Oncoplastic Breast Surgery; Breast Reconstruction; DCIS

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Critical Review

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Management of Ductal Carcinoma in Situ (DCIS) is consistently evolving with our improving understanding in cancer biology[1, 2]. More management options are now available for breast conservation as plastic surgery intrudes into the field of breast surgery. These options range from wide local excision to bilateral mastectomies with or without breast reconstruction[3]. Endocrine therapy, however, remains instrumental for reducing recurrence and chemo-prophylaxis. Newer radiation therapy techniques are being tested to de-escalate the use of radiation depending upon the character of the tumor. Various oncoplastic techniques are currently available which have considerably better aesthetic outcome and are replacing treatment options for cases where, in the past, radical treatment was the only choice available. In this writing, we would be summarizing these advances in the management of DCIS, where oncoplastic breast surgery is done and would come up with a treatment plan for the scenario shown along[1].

DUCTAL CARCINOMA IN SITU (DCIS)

In US alone, 60,000 women are diagnosed with DCIS annually by screening mammogram[1]. It is recommended for the women to have annual mammogram starting from the age of 45 up to 55 with an option to start screening at the age of 40[1].

CASE SCENARIO

A 52-year-old factory worker is recalled following routine breast screening. She has well-controlled type 2 diabetes but has gained significant amount of weight since she had quit smoking. She has pain at the back of chest which she attributes to her increased breast size. There is no family history of breast cancer. Mammogram showed micro-calcification in the central right breast covering an area of 35mm, and extending to area within 5mm of the NAC. Ultrasound of the breast and axilla appeared normal. 14g core biopsies showed intermediate grade DCIS. The lady is keen to preserve her breast and NAC and achieve immediate symmetry. Please provide a comprehensive management plan for this case, including a discussion of the following issues. Management options including surgery, clinical trials, endocrine therapy, most appropriate surgical option, consent process, surveillance and follow-up, PROMS and medico-legal factors. Your plan should refer and critique relevant evidences and guidelines. You are encouraged to cite relevant examples from your own clinical practice to support your response.

The above mentioned is a typical case of DCIS which has been diagnosed on a screening mammogram. Mammogram is the most common investigation to diagnose a case of DCIS. It is an important investigation especially for cases of impalpable DCIS. Pleomorphic calcification is the pathognomonic feature for diagnosis of DCIS. It can also show multicentric and multifocal lesions. Recently, however, it has been recommended to have an MRI, as it is considered to be a more sensitive investigation to pick DCIS than mammogram[4, 5].

DCIS is a complex disease for which management needs collaboration among all available specialties; namely surgery, oncology, radiology, pathology and plastic surgery[6]. To balance the risks of disease and to avoid overtreatment, it remains imperative to head for a personalized treatment approach in a multidisciplinary setting[1]. This case again shows the value of multidisciplinary meeting.

Management Options for Breast & Axilla

36% of the patients with DCIS develop invasive disease at a later stage, hence no treatment is not an option[1]. Most of the centers argue in favor of surgical resection. Recently, LORIS, LORD and COMET trials have started with the intent to offer observation alone for the patients who have small low-grade DCIS[2]. The results would follow after few years. Since our patient has intermediate grade DCIS with size 3.5 cm, it would be inappropriate to enroll her into this trial and surgical resection would remain the mainstay of the treatment in this particular case.

For the cases of diffuse and multifocal DCIS, bilateral mastectomy has been advocated as it has low recurrence rates[7, 8]. Patients have an option of choosing mastectomy over the breast conservation surgery either for the fear of cancer or to avoid radiation. Traditionally, 10-year survival associated with mastectomies is 98% vs 81% for the breast conservation surgeries[1]. With the developing techniques, skin-sparing and nipple-sparing mastectomies are also available for the patients with 5.6% recurrence rate over a period of 5 years[9, 10]. Similarly, preservation of nipple also adds to recurrence rate making it 11.6% over a period of 5 years. However, it must be explained to the patients that skin-sparing and nipple-sparing mastectomies are associated with higher complication rate in up to 29% cases. In addition, the preserved nipple may be lost due to de-vascularization in 7.8% cases[11, 12].

25% of mastectomies done for DCIS show foci of invasive disease, demonstrating the reliability of mastectomy in terms of disease clearance[13]. For all mastectomies done for DCIS, SLNB should be performed because SLNB at a later time following mastectomy is not possible due to changes in lymphatic architecture.

Clinical Reasoning for Scenario

It would be especially important to have MRI done for this particular case to rule out multifocality and multicentricity where we have a plan to conserve the breast. Stereotactic biopsy and wire localization remain important when we have to perform the oncoplastic surgery. Other modality would be the use of radio-seeds which has shown to be associated with operative ease at the time of resection. It would be important to know the exact location of the micro-calcifications and distance and depth of the lesion from the NAC. By looking at the mammogram alone, it appears to be located in the lower deep central location. It is important to do MRI of both breasts as well as to exclude multifocality and multicentricity when we have planned for conservation of breast.

Trucut biopsy apart from diagnosing a case of DCIS preferably should include information regarding type of DCIS, Ki Index and status of the immunostaining with ER, PR and HER-2/neu receptors.

Large breast size by looking at pictures is likely in line with Grade III ptosis which would also be important part of the oncoplastic technique to be used for breast reconstruction.

Genetic counseling is recommended for the patients who have strong family history of the breast, ovarian or prostate cancer. The genetic screening should include many potential mutations including BRCA1/2. Since there is no strong family history in this particular case, there is no need to perform genetic screening per se.

It would be important to find the cause of the backache for which MRI of the spine and Bone Scan is appropriate initial investigations along with DEXA Scan. It would rule out spinal metastasis, osteoporosis or any impending spinal fracture. She might require an Orthopedics consultation at this stage too.

Planned weight reduction and control of diabetes should be ensured pre-operatively.

Since this patient does not have a strong family history and patient has opted for a breast conserving surgery, bilateral mastectomy is ruled out.

ONCOPLASTIC SURGERY OPTIONS

Therapeutic mammoplasty has extended the role of breast conserving surgeries by incorporating the principles of reduction mammoplasty and radiation therapy. The long-term oncological safety of oncoplastic techniques has been

accepted and are henceforth rapidly replacing the traditional treatment algorithms. There are number of mammoplasty techniques available in the armamentarium of an oncoplastic surgeon, which can be adapted according to the location and size of the tumor. For the larger breasts volume displacement techniques are used and for the smaller breasts volume replacements in the form of flaps has been advocated. These techniques not only improve the oncological safety but also improve the psychological and aesthetic well-being of the patients[14, 15].

Nottingham approach as described by Steve McCulley is considered a widely utilized methodology for catering the oncoplastic resection, although many other techniques can also be used as described by Clough et al[16, 17]. It is also widely accepted that Wise pattern incisions provide the best cosmetic outcome. Therapeutic mammoplasty hinges on the notion that patient has large breasts and the lesion usually lies within the Wise-pattern incision line (Scenario A as described by McCulley et al[16]. Although the lesions outside the Wise pattern incision can also be entertained with medial or lateral pedicles (Scenario B as described by McCulley et al) [16]. Patients with large volume breasts preferably C, D and E cup size with grade III and IV ptosis would be ideal candidates.

Like reduction mammoplasty, there are certain risk factors associated with failure or poor cosmetic outcome which include high BMI, smoking and very large breasts with grade IV & V ptosis. These factors need to be considered carefully and preferably need to be optimized prior to any surgical intervention. The complications, however, are less as compared to implant-based or flap based autologous reconstruction. Pre-operatively it remains imperative to rule out multifocality and multicentricity of the disease by mammogram or preferably MRI[14].

When the margins are in doubt, it would be appropriate to perform a WLE followed by an oncoplastic procedure at a later date when the patient is disease free.

For descriptive purposes, McCulley et al divided the breast into nine zones (Fig. 1)[16]. Mammoplasty incisions are the basis of the markings of these nine zones. Infra-mammary fold (IMF) is considered an important landmark to provide the markings for the future nipple areolar complex (NAC) area. Please refer to the markings in the figure 1 for Wise pattern markings. Zone II, III and IV are easily handled by the wise pattern technique. Zone I can either be handled separately if lesion is quite superficial and adherent to NAC or within the same above markings as Zones II, III and IV. Zones V and VI can be handled by lateral and medial pedicles. Zone VII, VIII and IX are the most difficult to be managed by Wise pattern incisions. Batwing, round block excisions, lateral and medial mammoplasty may instead be used for these difficult locations.

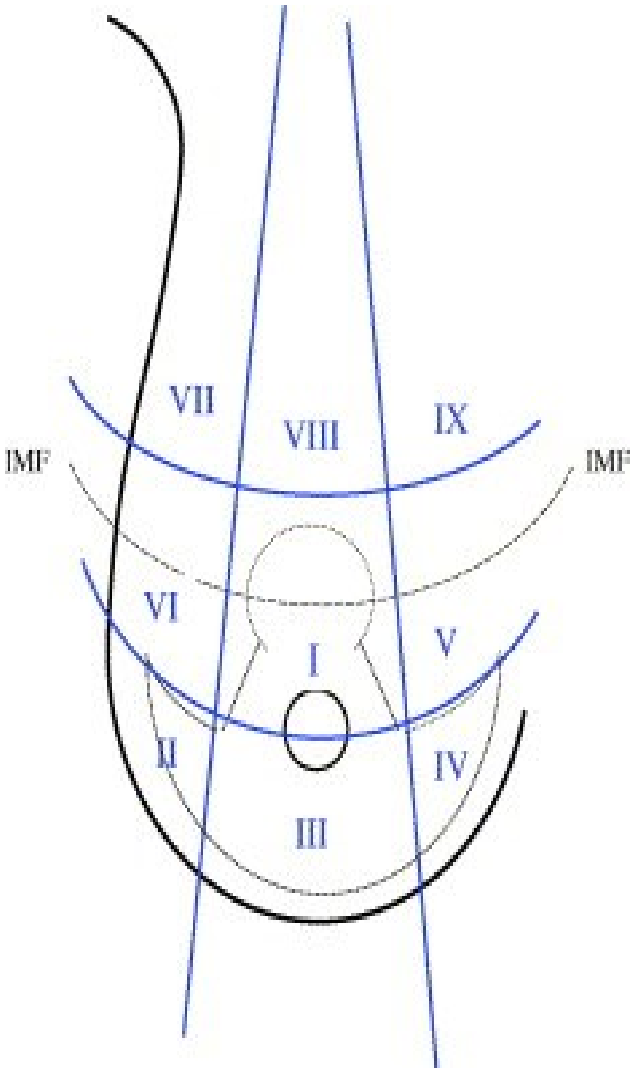


Figure 1
Zones of the breast for oncoplastic resection as proposed by McCulley et al[16].

McCulley has provided us with the table shown below to choose the location of the lesion and their respective incisions and pedicles. (Table 1)[16].

It is very important to differentially and accurately localize the exact position, size and dimensions of the lesion and its relationship with NAC. For this very purpose, mammogram and MRI are the best modalities. If the NAC is not involved then the patient would typically fit into Scenario A described by McCulley[16]. If the NAC is involved then it would be likely to scarify the NAC and follow the Scenario 3 for Zone I.

Table 1: Common options for planning therapeutic mammoplasty (adopted from McCulley et al) [16]

Common options for planning therapeutic mammoplasty							
	Scenario	**Common pedicle**	**Alternative pedicle**	**Common skin pattern**	**Alternative skin pattern**	**Ease to fill defect by extending pedicle**	**Ease to fill defect by secondary pedicle**
Zone I	A or B	Inferior	Medial	Wise	N/A	N/A	
Lateral	Vertical						
Zone II	A	Superior	Medial	Wise	Vertical	N/A	N/A
Sup/medial	Lateral						
Zone III	A	Superior	Medial	Wise	N/A	N/A	
Sup/medial	Lateral	Vertical					
Zone IV	A	Superior	Medial	Wise	Vertical	N/A	N/A
Sup/medial	Lateral						
Zone V	B	Sup/lateral	Inferior	Wise	Vertical	Fair	Fair
Lateral	Superior						
Zone VI	B	Sup/medial	Inferior	Wise	Vertical	Excellent	Good
Medial	Superior						
Zone VII	B	Sup/medial	Inferior	Wise	Vertical	Good	Fair
Medial	Superior						
Zone VIII	B	Inferior	Medial	Wise	Excellent	Fair	
Lateral	Vertical						
Zone IX	B	Sup/lateral	Inferior	Wise	Vertical	Fair	Fair
Lateral	Superior						

Scenario A—tumor lies within Wise pattern incision

The tumors within level I to IV can be easily handled with Scenario A provided they do not involve the NAC. Typically, this is the most feasible and cosmetically acceptable scenario for the lower tumors. Figure 2 describes the incisions and the resection pattern for the lesions involving the lower breast.

Pedicle orientation is decided by the position of tumor. Most of the Zone II-IV tumors are dealt with superior or superomedial pedicle. For the Zone 1 tumors, the pedicle can be drawn from anywhere depending on the location of tumor to avoid positive margins. The choice of Wise Pattern Incision depends both on the location of tumor and the size of the breast. For example, the central breast tumors and inferior Zone III tumors not involving NAC can be easily adapted in vertical Wise pattern incision. For larger breasts with grade III ptosis, it would be more appropriate to take the formal Wise pattern with excision of the lower zones as done in reduction mammoplasty.

As suggested previously, size and site of the tumor is of prime importance in deciding the markings of the incision. The tumor which are lying within Zone I-IV are easily dealt through the traditional markings, however the Scenario B cases can be dealt by carefully dissecting the tumors ensuring clear and negative margins through palpation of the normal and abnormal tissue. Undermining of the skin is also required in cases where the tumor lies outside the resection markings. In those cases, markers can be placed to predict the future recurrence. Specimen radiology can also be used to accurately document if excision is complete or incomplete. Superior, superomedial or superolateral pedicles can be used for the scenario A cases.

Central tumors (zone I) requiring removal of NAC

There are two important approaches to deal with such lesions but each depends on requirements or availability of the zones I-IV for excision. To give an example, if the tumor is involving the central zone and the patient has large breasts and can afford excision of the lower zones; then simple inverted T incision as in Wise pattern or Goldilocks' mastectomy can be used. As such an incision is suitable for tumors where NAC has to be sacrificed[16].

On the other hand, if the breast size is small and lower zones are not available for the resection, Grissoti's flap may be the right choice as it not only avoids the excision of the lower zones but also only targets the central zone and displacement of the inferior portion of the breast into the central zone[14].

Alternative to therapeutic mammoplasty is mastectomy with immediate or delayed reconstruction[10]. This approach is more likely to avoid radiotherapy and is likely to be associated with either implant based or autologous reconstruction[18]. The cosmetic outcome and complications of therapeutic mammoplasty are similar to reduction mammoplasty and are superior to complete reconstruction in terms of lower morbidity and nipple-related complications[19, 20].

The patient needs WLE/ Oncoplastic Resection depending on the location of the tumor with at least 2mm healthy margin as suggested by ASCO and ASTRO[21, 22].

The radial distance and depth of the area of calcification to the NAC and its size would dictate about the possible survival of the NAC. Considering the large breast and grade III ptosis, the tumor resection may be incorporated within the Wise Pattern or Nottingham approaches. Consequently,

if the nipple is not definitely involved by NAC, it may be used as a flap or a free graft depending on the location.

As it appears from the provided mammogram that DCIS lay quite deep in central lower portion, it may be feasible to save NAC in medial or lateral pedicle. If per-operatively NAC is found quite close to tumor, it would be wise to go for either NAC construction through free nipple grafting immediately or at a later stage. However, SLNB is not recommended in cases of low or intermediate grade DCIS with normal axillary ultrasound.

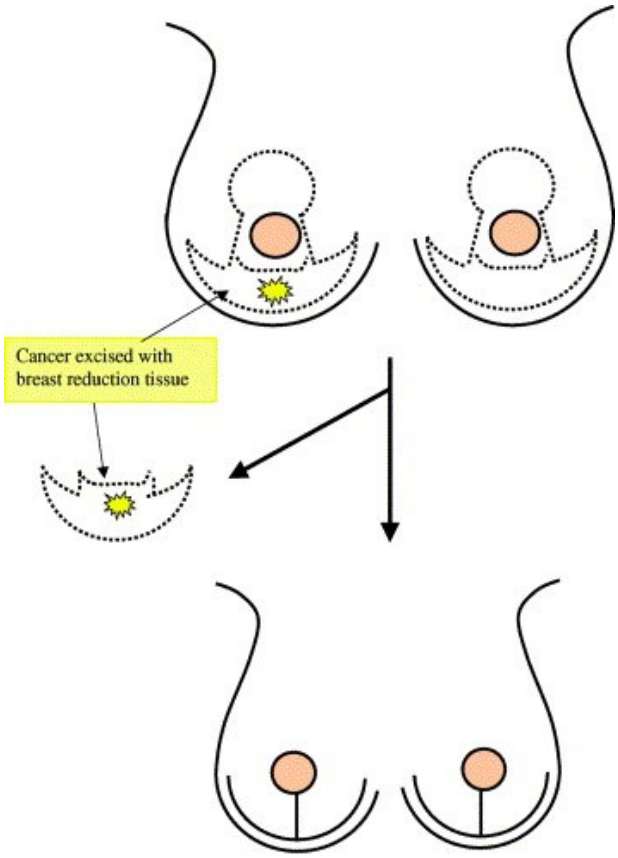


Figure 2
Incisions and the resection pattern for the lesions involving the lower breast[16]. (Courtesy: McCulley et al)

The figures below show two possible surgical options for this particular patient [16]:

Consent Process

The process of taking consent should include the information regarding the failure of flap, repeating the surgery if required, take-backs and the possible complications associated with the flaps. The modalities that would result in case of failure should especially be explained like thrombosis, infection and loss rates[20, 1].

Adjuvant Therapy

Adjuvant therapy can influence the outcomes of the reconstruction and overall treatment. The need to pre-operatively assess if adjuvant radiation therapy is needed or not is extremely significant, so that the reconstructed breast suffers the least[1].

Radiation therapy has traditionally been an essential component of the breast conserving surgery or oncoplastic resection even in cases of the DCIS in adjuvant setting, in the past. Whole Breast Radiation Therapy (WBRT) is the standard of care in most centers all over the world. At least five randomized trials have proven the efficacy of external beam radiation therapy in reducing recurrence rates following lumpectomy[23, 24, 25, 26, 27]. In a meta-analysis, addition of WBRT reduced the recurrence rates from 28.1% to 12.9% in 10 years without effecting the overall survival[28]. The most common dose of radiation used is 5000cGy delivered Monday through Friday with daily fractions of 200cGy spread over the 5 weeks. In a Canadian study however, hypo-fractionation has been postulated with 4250cGy in 16 fractions spread over 3 weeks with similar results[22]. Thus, 2018 ASTRO guidelines recommend hypo-fractionation. The role of external beam boost in lumpectomy bed is strongly considered for the positive and ER negative high grade tumors[29]. Recent advances in Intensity Modulated Radiation Therapy (IMRT) and Deep Inspiratory Breath Hold can dramatically reduce the toxicity of radiation to the surrounding structures[30, 31, 32, 33]. ASTRO also recommends Partial Breast Radiation Therapy (PBRT) for low grade unifocal up to 2.5 cm lesions of DCIS but is still not a standard practice. Radiation may be omitted in low grade small unifocal tumors as described in ECOG 5194 trial[34]. This forms the basis of LORIS and COMET Trials. Based on Oncotype Dx and gene analysis, low grade tumors may be identified and stratified for radiation regimen likely to be effective[35].

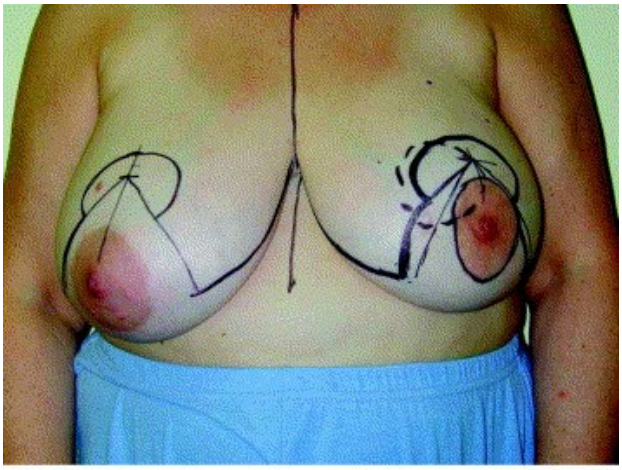
Endocrine therapy remains standard for the ER positive tumors. The NSABP B-24 trial randomized patients to 5 years of Tamoxifen, 20 mg daily, or placebo following lumpectomy and radiation and reduced the ipsilateral breast cancer by 32% which equates to the 7.3% risk of cancer in normal contralateral breast over a period of 15 years[36, 37]. This trial showed that tamoxifen reduced the incidence of invasive cancers in the ipsilateral breast by 32% compared to those who had lumpectomy and radiation alone. At 15 years, the rate for ipsilateral invasive recurrences for those who received tamoxifen was only 8.5%. This was very similar to the rate for a contralateral breast cancer event i.e 7.3%. NSABP-35 also shows aromatase inhibitors to be effective for such patients under the age of 60 years[38]. Targeting of HER2/neu is currently under investigation in NSABP-43 trial[39].

In this particular case, whole breast radiation WBRT or IMRT is recommended. Hypo-fractionation based on the Canadian study is also recommended. IOBRT may be considered in case of threatened margins. Partial Breast Radiation Therapy (PBRT) does not appear to be appropriate for a 3.5 cm lesion[22].

If ER positive should have Tamoxifen vs. Aromatase inhibitor for 5 years with Her 2 neu being positive, patient should be considered for enrolment in any trial like NSABP-43 if available. Lesion does not appear to be appropriate for enrolment in LORIS, LORD or COMET trial[1].

Surveillance and Follow-up

National guidelines argue for follow up to be 6-12 monthly for 5 years if patient undergoes oncoplastic resection and then yearly by mammogram till 65 years of age. New lesions have to be biopsied and treated appropriately if found to have DCIS or invasive breast cancer. For patients who commence the aromatase inhibitors should have baseline DEXA scan. Supplemental calcium and Vitamin D apart from the weight bearing exercises remain an appropriate part of the management. Bisphosphonate therapy may be the answer to the developing osteopenia. Risk of stroke and DVT should be communicated to the patient taking Tamoxifen. If the patients taking Tamoxifen develop vaginal bleed then U/S and adjuvant pelvic work up may be required.



PROMS

Breast-Q has importance in familiarizing the outcomes of the breast undergoing oncoplastic resection and they should be incorporated into surgical practice[40]. Recently, BCCT.core has also emerged as a tool for the assessment of aesthetic value of these techniques.

Medico-legal Factors

Patient education remains pivotal about the breast conservation, radiotherapy, endocrine therapy and complications associated with oncoplastic resection. Future recurrence, need for surgery, mastectomy, failure of the oncoplastic resection, loss of nipple and sensation around the nipple, seroma formation, and hemorrhage should all be clearly communicated.

Future Directions of Treatment for DCIS

There are many options available for the patients with DCIS now, which conform to our modern understanding of tumor

pathology. Now breast conservation coupled with oncoplastic techniques and radiation therapy is producing almost equivalent outcomes in terms of oncological control and aesthetic outcome. Mastectomy with immediate reconstruction is the alternative option for the patients with high risk, multifocal, diffused disease associated with significant family history. Oncotype DX can provide an additional molecular insight into the aggression of the tumor to help in individualizing the treatment options[41]. For low grade tumors, observation alone is being tested in LORIS, LORD and COMET trials. Efficacy of Trastuzumab is being tested for HER2/neu positive DCIS through NSABP-43 trial[39].

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42.

Archives of Surgical Research | Perspective

Bread & Butter of Instrument Design in Health Sciences

Rizwan Qaiser Danish

IMPORTANCE Information from respondents can be gathered through various sources and instrument or questionnaire or scale is one of these. One researcher can look from different perspectives just like an artist can see a seen and take his brush to capture it on canvass at the same time he has choices of oil or water or mixed medium. you first choose subjects but at the same time you have to consider proper methodology so that your focus may be on the right things you want to measure. Your personal beliefs and opinions ma y distort the independence and impartiality that need to be considered when getting responses from audience. The development of questionnaire starts from brainstorming from where you get the pool of items to be included.

KEY WORDS Instrument design, health sciences, survey design, questionnaire

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Perspective

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Information from respondents can be gathered through various sources and instrument or questionnaire or scale is one of these. One researcher can look from different perspectives just like an artist can see a scene and take his brush to capture it on canvass at the same time he has choices of oil or water or mixed medium. you first choose subjects but at the same time you have to consider proper methodology so that your focus may be on the right things you want to measure. Your personal beliefs and opinions ma y distort the independence and impartiality that need to be considered when getting responses from audience. The development of questionnaire starts from brainstorming from where you get the pool of items to be included.

This item stock can be obtained through various techniques but before that there must be clear purpose in mind regarding the study. Extensive review of literature is required for generating the themes whatever method focus group, interview, content analysis or any other is used. Purpose of study and aim of instrument must be articulated which later on can be testified for various type of validities which is actually the strategy of driving the nail aright. If you develop a statement of purpose you can get feedback and invite expert opinions on it to further refine your themes and items. Your development and design of instrument is reflective of your objectives. Of course, thinking process and creativity is necessary for starting the process of scale development. Psychologists suggest that the creative process occurs in a series of stages: preparation, incubation, inspiration, and verification (Lubart, 2001).

However, this process in intangible in nature and occurs as mental activities unconsciously. Literature review is the prime step that is indicative of previous research that has already been conducted in the area where scale needs to develop, here medical surgeries, on the assumptions that knowledge accumulates and it is necessary to develop credibility by the researcher being investigated. Literature also specifies the previous theories in medical field for the explanation of phenomenon. Moreover, methodologies are also studied in literature which describes the appropriateness of each method based on purpose and objectives of study.

In medical field normally mixed method study is conducted for development of instrumentation where first themes are generated on the basis of interviews, focus group discussion observation or any other method of primary data collection. Then pools of items is generated with the help of words, pictures, narrative and non-verbal cues and further tested numerically in form of quantitative results at scale that is admissible in such studies for establishing generalizability. Literature is also important to study because in it you can also find some questions related to your purpose and nothing is wrong in adopting questions from other articles. However, you should consider local setting and respondents to fit the questions accordingly before revising and adopting it. For example, if you want to study quality of learning environment in operation theater, you may gain help from quality of learning in school class room but caution should be made about the choice of proper terminology and jargons of the subject matter. The work should be referred

properly and the data on the basis of your instrument should be tested again for reliability and validity because previously reported validity and reliability was for another setting and context.

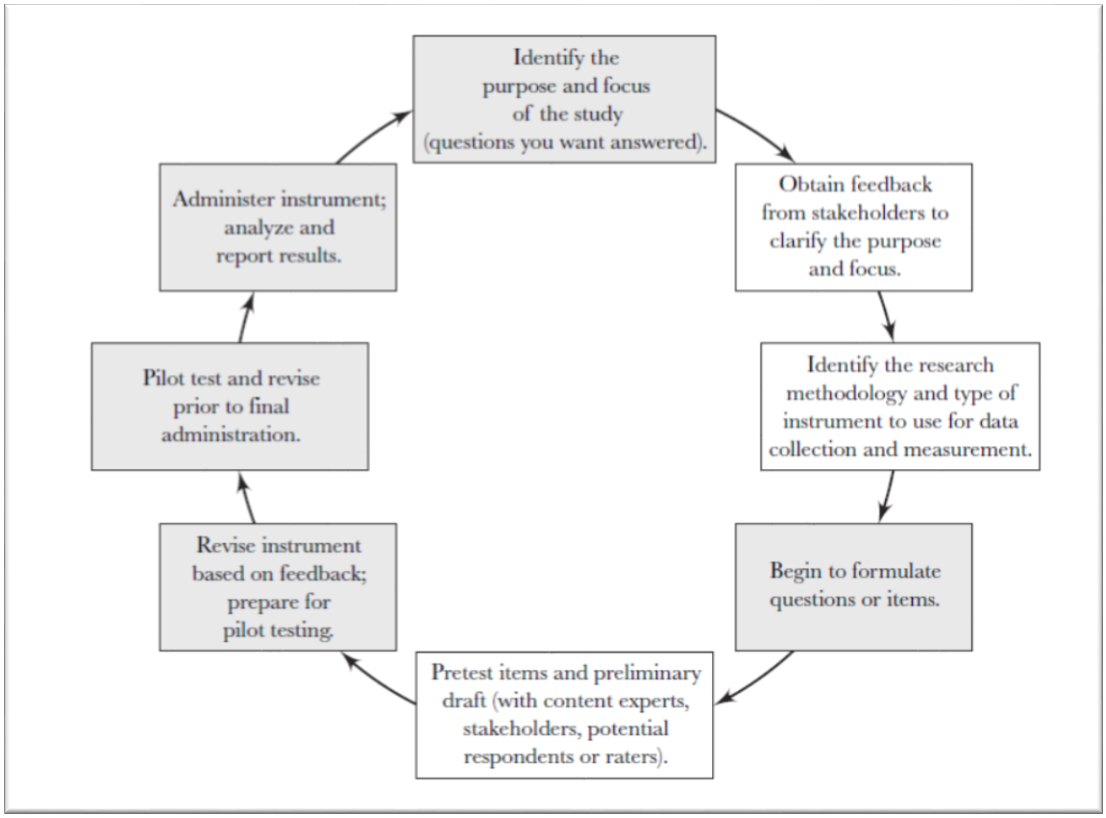
Behavior and attitudes in medical research can only be studied with the help of perceptions of respondents as converse to the more quantitative and rigid methods like experimentation where personal opinion doesn't matter. Perceptions are necessary to understand as our reactions are based on perceptions and not on reality as Kurt Lewin suggested (1935)

The question of sample size is based on the subject matter, for example some researchers focus on saturation point where themes start to repeat while others focus on number of responses on the basis of items, i. e. response to item theory (Hambleton & Swaminathan, 2013) and some others focus on 50 responses per theme for obtaining more generalizability. When themes are theorized the next step is to convert themes and sub themes into different items which need to establish face validity. Panel of experts may again be involved at this step. Pilot testing is necessary for cross validation and viewing if there are any problem regarding language, contents, formatting, structure and most importantly, indigenized requirements of the developed scale. The sample size for pilot testing generally consist of 20-40 observations but may vary for very large sample surveys and the purpose is not to test the statistical accuracy at this stage.

Instruments about perceptions are generally self-reported but they may also be based on observation and supervisor, subordinate or peer-based ratings. The word survey, questionnaire or poll is used interchangeably. A typical instrument generally consists of six basic elements but not limited to these, are, title, introduction, instructions for filling, items, demographic and closing section. The typical process of instrument design includes the following steps (Fig 1).

Figure 1: Processes in instrument development

Adopted from: Colton, D., & Covert, R. W. (2007). Designing and constructing instruments for social research and evaluation. John Wiley & Sons.



When a questionnaire is developed various types of validity and reliabilities are required to test for making it generalizable and credible for further use. Validity of an instrument refers to the extent to which we measure for what an instrument was purport to measure. As it is based on data so closer the data to your suggested theme, better would be the validity of an instrument. Various types of validity included but not limited to are:

Face validity: Is an instrument apparently appropriate for measuring desired information?

Construct validity: whether a theme is agreed upon on a certain understanding by the researcher and the respondent?

Content validity: whether an instrument measures the topic or process under investigation?

Criterion validity: how close the measured concept is with the external standard?

Predictive validity: can you predict the results of one variable from another measured variable?

Multicultural validity: whether a respondent of a particular culture understands what the question is purport to measure? (such as proposed by Kirkhart, 1995).
Reliability is "the extent to which an instrument produces the same information at a given time or over a period of time". (Colton and Covert, 2007).

Various methods in statistics are used for the evidence of reliability and validity depending upon the processes used to construct items for an instrument and level of measurement it opts (nominal, ordinal, interval, ratio)..

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Archives of Surgical Research | Systematic Literature Review

Why the Art of Clinician Is Dying? Opinions & Judgments: A Systematic Literature Review

Fatima Jamil; Sidra Farooqi; Talat Waseem

BACKGROUND The use of basic medical knowledge has been used since the time of Hippocrates by clinicians to manage patients. This medical knowledge can be divided into theoretical and practical knowledge, both of which are gained during the medical school years, by reading various course and reference books and further supplemented by learning clinical skills such as a physical examination of the patient. All such skills get polished throughout the medical school by attending morning rounds, spending time at the patients' bedside, performing a hands-on examination. But during recent years, there has been a decline in appropriate clinical skills acquired by clinicians due to many reasons and this interplay of several factors has resulted in the high dependence of medical professionals on modern medical technology. All these factors are a prime concern for the upcoming generation of doctors, as they are a threat to the humanitarian that must reside within every clinician.

METHODS A literature search was carried out regarding the decline of physical examination and clinical skills in modern-day medical practice. 1566 articles were identified through Google Scholar, Pubmed, and ERIC by using the keywords, 'Physical Examination' and 'Clinical Skills' out of which 21 are included in this literature review.

RESULTS The gradual decline in optimal knowledge of clinical skills and physical examination can be attributed to many factors, one for example, is sub-standard teaching practices being carried out during medical school and training programs. Clinicians fail to understand the therapeutic effect of a properly performed physical examination on the patient and its implication in the management plan. Moreover, the burden on a senior clinician is very high, leading to burn-out of the doctor, making him/her incompetent to teach young doctors and trainees during bedside rounds. This has led to the sole idea that such manoeuvres are time-consuming and tiring. Therefore, the clinicians have developed a low threshold to prefer laboratory investigations to diagnose and manage patients leading to the gradual reduction in clinical skills. This all makes us in dire need of doctors with a humanitarian spirit, who use their senses to at least probe a diagnosis rather than ordering a test without any clinical knowledge of the patient at hand.

CONCLUSIONS Identification of these influencing factors on the clinical skills of doctors needs further evaluation to properly understand the precise reasons for the decline in physical examination practices by doctors. The significance of advancements in medical technology and their influence on a doctors' clinical skills need further evaluation.

KEYWORDS Decline of clinical skills; Medical Technology; Physical Examination
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Systematic Review

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The use of clinical reasoning to manage a patient is being used since long ago. The clinical assessment began during the ancient times of Egyptians, Babylonians, and Indians, their findings depended on their abilities to hear, see, and feel to reach a working diagnosis [1]. This clinical assessment includes obtaining a detailed history of the complaint and performing a relevant physical examination to establish a working diagnosis until adjunctive laboratory testing or imagining is done to confirm the diagnosis.

Clinical history includes different aspects of patients present and past medical events and a thorough physical examination generally includes inspection, palpation, percussion, and auscultation which can be further extended depending upon the presenting problem. A humanitarian clinician, as postulated by Sasser, is the one who perceives practical data from examining the patient which can be used

to provide treatment and care to both the patient and his family [2]. Clinical skills like carrying out a physical examination, to help form a diagnosis should be taught during the time doctors spend in medical schools but recently as evidenced by several studies,[3] students severely fail to understand the utmost importance of a properly taken history and physical examination. Hence, the information collected through close-ended questions in the history is fruitless, making it difficult to collect specific details which are essential to clinical decision making [4]. Knowing how and when to perform a certain physical test is very critical while treating a patient and the inability to realize this, is why students fail to perform a successful and fruitful physical examination [5]. Medical students continue to become residents and even practice medicine with these deficiencies. Fred called such people hyposkilliacs, meaning physicians who cannot obtain an adequate history, don't know how to perform an authentic physical examination, failing to relate the information they collect, and finally unable to create a workable management plan. Such physicians do not spend time with their patients. They swiftly treat everybody without pondering upon the natural course of the disease [6].

Interaction with the patient is a distinctive experience both for the physician and the patient, making certain that it will culminate in the information necessary for proper diagnosis and management of the patient. But in recent times medical trainees and physicians spend very little time interacting with patients, resulting in the reduced practice of clinical skills which in turn leads to a low number of clinicians confident in their knowledge of examination skills [7].

It is a general agreement that there has been a decline in ample history taking accompanied by a shortage of an in-depth physical examination in medical practice. This can be attributed to the advancements in medical technology which have affected the doctor-patient relationship adversely.[8] Moreover, the practice of a hands-on approach in medical schools and residency programs is progressively declining, which makes the clinicians incompetent to perform a basic physical examination hence, they're inclined towards the laboratory and imaging studies as a means for diagnosing patients [9]. The purpose of this literature review is to analyze all available data related to why there is a gradual decline in the practice of physical examination.

METHODS

To analyze the literature, a qualitative meta-synthesis approach was used. This approach was specifically selected to identify, summarize, and review the relevant qualitative data to address the research question.

Literature Search Strategy:

A literature search was done through PubMed, ERIC, and Google Scholar. The keywords used were "clinical skills", and "physical examination". Additionally, the reference research papers were also included for a comprehensive literature review.

Inclusion of Articles:

Following PRISMA guidelines, 1566 articles were identified out of which 456 articles were initially selected after looking at the relevant titles for eligibility and 21 articles were used for thematic analysis after inspecting the abstracts independently of each article. The inclusion criteria for this review were the articles that described the importance of physical examination, its decline in medical practice, and the impact of advancements in medical technology on the physical diagnosis. The article selection process is discussed in diagram 1.

Data Extraction and Analysis:

The articles were thoroughly analyzed, and a thematic analysis of each article was done. The relevant information from each paper was physically coded. These codes were classified as themes. The information in each paper was identified according to the themes. These recurrent themes and their relevant article are described in the table below.

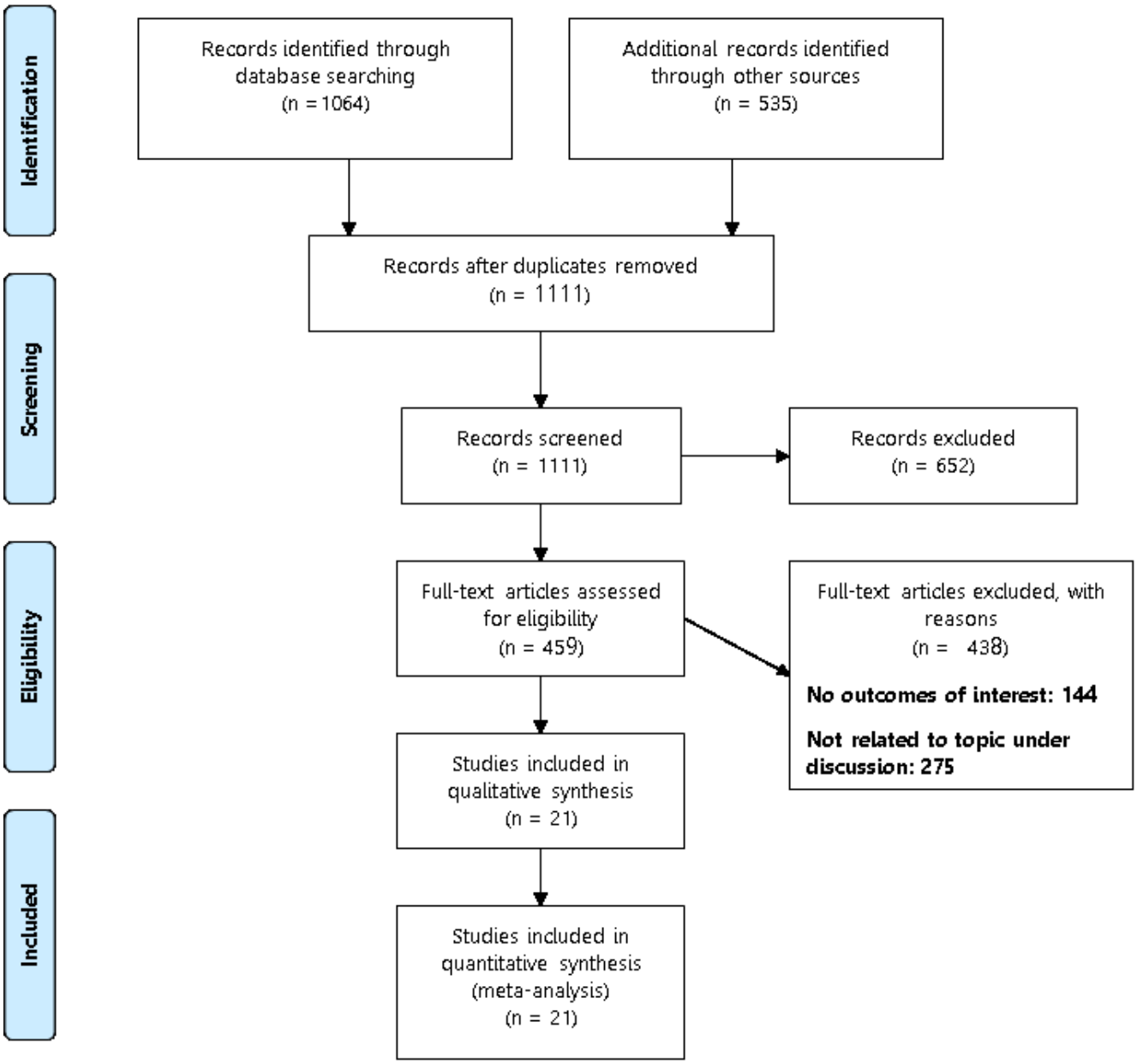
RESULTS & DISCUSSION

Clinical Judgment and Clinical Knowledge of Physician:

An unbiased and astute clinical judgment of the doctor is necessary for proper doctor-patient communication, diagnosis, and further treatment planning of the patient [10]. A doctor should be equipped with sufficient clinical knowledge and skills which is critical for a good history and physical examination highlighting the patient's chief complaint and directing towards a working diagnosis [11]. Despite the advancements in technology, clinical judgment plays a vital role in managing a patient, as many diseases may be diagnosed with an efficiently performed physical examination, way before they show up on imaging or lab testing [9].

It's a continuous observation that there has been a significant decline in clinical knowledge of physicians starting from the medical students and even among the residents, which go on to practice medicine. Several causes can be identified for this lack of proper clinical knowledge including, excessive reliance on tests, limited time for teaching the students including very less time spent next to the patient. Medical schools are inefficient in promoting an environment for the nourishment of clinical skills in undergraduates [3]. Moreover, even during the residency years, there is no proper supervised training offered to the residents where their history taking and bedside skills could flourish, hence resulting in incompetent doctors, who do not feel confident about their clinical knowledge and are reluctant to perform physical examinations and lean more towards ordering a laboratory test [12] [6]. This lack of unsupervised training produces an unconfident clinician who is unsure of how and when to perform a physical exam, which results in a low threshold to order laboratory tests [13].

Diagram 1: Prisma Flow Chart



The attitude of Clinician:

Whenever attending a patient, good rapport building is key to a positive doctor-patient relationship. This involves, listening to the patient, validating his/her concerns, and making the patient comfortable. Good history taking skills and appropriate physical examination knowledge is obligatory to develop a promising doctor-patient relationship, which in turn results in better health outcomes [14]. Despite the importance of history-taking and physical examination, clinical skills education has decreased since the 1960s, with a lot of deficiencies in the training of medical students and residents alike [15].

The emerging generation of doctors profoundly lacks in exhibiting efficient clinical skills, making their patient management highly dependable on laboratory testing. Such doctors are quick to order labs but fail to realize when to order one or how to interpret the results. This shortfall of competent doctors can be attributed to faulty training at both medical schools and during residency programs [6]. Clinicians nowadays lack the basic emotion of empathy and benevolence, effecting how they practice medicine overall.

TABLE 1: Thematic Analysis of the Literature

Year	Article	Author	Themes Identified
2018	The Outpatient physical exam	Artandi, Maja K. Stewart, Rosalyn W.	Use of prior clinical knowledge to carry out a proper physical exam leading to a working diagnosis
2011	Clinical judgement and the medical profession	Kienle, Gunver S. Kiene, Helmut	Role of gestalt clinical knowledge in patient management and the future of medicine
2003	Assessing Physical Examination Skills of Senior Medical Students: Knowing How versus Knowing When	Wilkerson, Luann Lee, Ming	Importance of teaching medical students when and how to perform a reasonable clinical examination
2018	The decline of clinical skills: a challenge for medical schools	Faustinella, Fabrizia Jacobs, Robin J.	Negligence in teaching of just clinical knowledge in medical schools and residency programs
2012	The stethoscope as metaphor	Mangione, Salvatore	Casual attitude of clinicians
2005	Dissatisfaction with medical practice	Fred, Herbert L	Poor clinical knowledge of medical professionals
2007	Diagnostic tools and the hands-on physical examination	Olson, Douglas P; Roth, Katalin E	Influence of advancements in technology on doctor patient relationship
2016	Physical Examination and the Physician-patient Relationship: A Literature Review	Iida, Junko Nishigori, Hiroshi	Impact of an adequate physical examination on patient
2010	The accuracy of the physical examination for the detection of lower extremity peripheral arterial disease	Wj, David; Bsch, Armstrong Rn, Colleen Tobin Matangi, Murray F	Why clinical skills should be preferred when ordering a lab test
2018	Treat the Patient, Not the Rule Book.: The Art of Psychopharmacology!	Iida, Junko; Nishigori, Hiroshi	Importance of equitable clinical understanding while treating a patient
2010	Where did the day go? - A time-motion study of hospitalists	Tipping, Matthew D., Forth, Victoria E.,; O'Leary, Kevin J.; Malkenson, David M., Magill, David B. , Englert, Kate; Williams, Mark V.,	Estimation of total hours actually dedicated towards direct patient interaction
2017	Importance Of Thorough Physical Examination: A Lost Art	Asif, Talal; Mohiuddin, Amena; Hasan, Badar Pauly, Rebecca R	Time constraints affecting an adequate physical exam considering the organizational aspect of the hospital
2016	Clinical history-taking and physical examination in medical practice in Africa: Still relevant?	Oyedokun, Ayo; Adeloye, Davies;Balogun, Olanrewaju	Proper use of relevant labs and investigations
2007	The Lost Art of Clinical Skills	Feddock, Christopher A.	In-efficient physician knowledge Misuse of technology
2016	Will Medical Technology Deskill Doctors?	Lu, Jingyan	Overreliance of physicians on medical technology and Unnessacery medical testing
2011	Does Health Information Technology Dehumanize Health Care? Virtual Mentor	Bailey, James E	Dependency on medical technology Lack of proper clinical judgment in physicians
1998	The rise and fall of students' skill in obtaining a medical history	Pfeiffer, C Madray, H; Ardolino, A; Willms, & J	Lack of proper teaching of clinical skills to students
1995	Physical Diagnosis Skills of Physicians in Training: A Focused Assessment	Mangione, Salvatore; Burdick, William P; Peitzman, Steven J	Deficiency of adequate clinical skills ; Absence of formal training of physical diagnosis in medical schools
2016	The art of self-knowledge and deduction in clinical practice	Gardiner, Fergus William	Significance of ample clinical knowledge
2017	Physical examination: The dying art	Puri, Bipin; Shankar Raman, V.	Decline in clinical skills due to advancements in medical technology Misuse of medical technology Overdependence of the physician on lab investigations
2010	The Humanistic Clinician: Traversing the Science and Art of Health Care	Sasser, Charles G. Puchalski, Christina M.	Affect of advancements in technology on the clinical skills

The deficiency of all such basic principles and the dependence of doctors solely on technology to treat their patients makes them mere technicians or scientists who lack the fundamental humanitarian spirit [16]. All these factors affect the doctor-patient relationship adversely making the patient at the suffering end. He/she may suffer from a lack of trust and anxiety while going to the doctor, anytime [9]. Clinical experience shows that if a therapeutic alliance is developed between the doctor and patient it significantly improves the patient's adherence to his treatment plan [17].

Advancements in Medical Technology:

Recent advancements in medical technology have shifted the focus of clinicians from performing a thorough clinical examination towards, ordering a random set of lab tests which seems time-saving for them [6]. Although the outburst of many new technologies has modified the doctor-patient relationship, it cannot replace the touch of a physician's hand to elicit tenderness in the abdomen or to palpate the pulse which creates a sense of care and kindness [1]. Such advancements which are causing a decline in the practicality of the physical exam, are leading to a deterioration in the clinical skills of doctors which makes the doctor incompetent to deal with acute issues faced by the patient, as he becomes reliant on medical technology [8].

Despite the dependence of clinician on the advanced lab tests or imaging to diagnose a patient, he/she may fail to properly manage a patient, as there is always a chance of false positive or negative results with testing, and considering his lack of clinical knowledge he might institute a wrong treatment plan for the patient, resulting in potential harm towards the patient [18]. As evidenced by David, an examination of the peripheral arterial system, including auscultation for femoral bruit has greater accuracy in the detection or exclusion of peripheral arterial disease when compared with the results of the ankle-brachial pressure index test performed for the same complain [19].

Misuse of technology is an ongoing problem[16], resulting because of the over-reliance of clinicians on technology, readily available testing services, lack of satisfactory clinical skills, and poor clinical judgment [20].

Organizational Aspects:

Most of the clinicians working in hospitals are given way more patients than they can manage effectively, resulting in patient dissatisfaction, misdiagnosis, maltreatment. This affects not only the patients but also the health professionals, causing them to burn-out. Clinicians fail to manage the time among different tasks assigned to them on daily basis leading to less time spent at the patient's bedside, failing to teach their juniors proper history-taking skills, or carrying out an appropriate physical examination [4]. It has been reported that hospital staff spends only 17% of its time in direct patient contact, whereas 64% of the time is utilized in indirect patient care, such as documenting or writing discharge summaries which result in the poor medical management of the patient [21] leading to overall dissatisfaction of the patient with the doctor and the hospital altogether.

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Archives of Surgical Research | Case Report

Hiatal Hernia With Volvulus Of Stomach: Classical Scenario

Fatima Jamil, Talat Waseem

IMPORTANCE Gastric volvulus is associated with abnormal rotation of the stomach. It can present as an emergency or as a chronic intermittent upper GI problem. It is rarely encountered, hence making its diagnosis difficult. We present a case of a 45-year-old lady who presented to the hospital with dysphagia and chronic heartburn. She was on proton pump inhibitors for heartburn but had minimal to no relief in symptoms. An abdomino-thoracic CT revealed mesenteroaxial rotation of the body of the stomach with the distal part of the stomach lying in thoracic cavity. After initial diagnostic evaluation accompanied with medical and anesthetic risk assessment patient was prepared for laparotomy. A midline laparotomy was performed with detorsion of the stomach and transhiatal hernia repair along with Hill Procedure. Patient remained stable post-operatively and was discharged on the 6th post-operative day. Patient had satisfactory postoperative outcomes.

KEY WORDS Volvulus of stomach, Hiatal hernia; Surgical Repair
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Case Report

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Gastric volvulus is defined as the rotation of more than 180° of the stomach along its mesentery as proposed by Singleton[1]. To classify the volvulus of the stomach, learning about the rotation of the stomach along a certain axis is crucial. Two axis have been described in the literature with the organoaxial axis constituting 59% of the reported cases of gastric volvulus and 29% to be along mesenteroaxial, with the remainder being a combined type where both organoaxial and mesenteroaxial components are presents and it usually presents as a chronic gastric volvulus. Early on the gastric volvulus was attributed to the obstructive element but recently, volvulus is described as a torsion of the stomach with the obstructive element not always present.

Presentation of the condition could be acute or chronic. Acute presentations can be described by the classical triad associated with it, as described by Borchardt[2]. Severe epigastric pain, retching without vomiting, inability to pass a nasogastric tube. Whereas as described by Carter[3] following findings are also suggestive of gastric volvulus: minimal abdominal findings when the stomach is in the thorax, gas-filled viscus in the lower chest or upper abdomen on chest radiograph, obstruction at the site of the volvulus on an upper gastrointestinal radiological examination. Some unusual symptoms could be hiccups[4] or haematemesis[5], whereas in the chronic cases presenting complaints mostly comprise intermittent epigastric pain and early satiety after meals.

A hiatal hernia is defined as the protrusion of the stomach mostly its upper part through the weakness or a defect in the diaphragm. The diaphragm is the muscle that separates the abdominal and mediastinal cavity. The defect is called hiatus hence the condition is termed as hiatal hernia. Four types of hiatal hernias are known. However, the sliding hiatal hernia (type 1) accounts for 95% of all hiatal hernias hence being the most common. Other three types are classified as true para-esophageal hernias (PEHs) and account for remaining 5% of hiatal hernias[6].

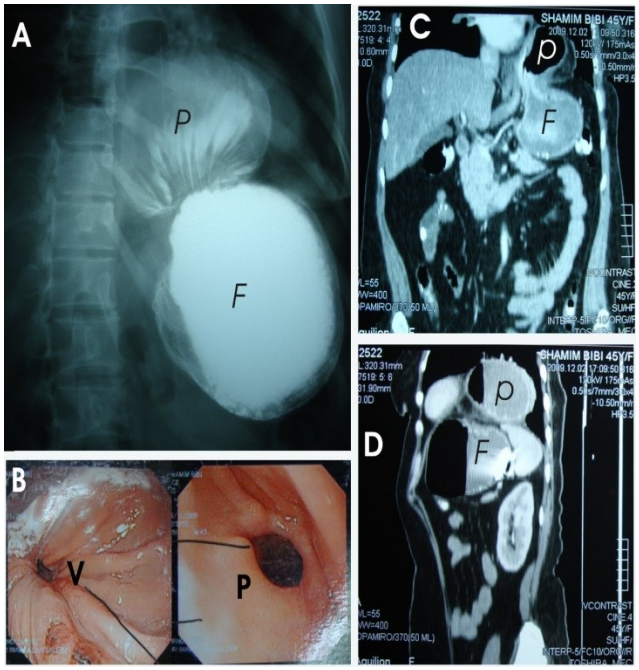
Here we present a classical case of gastric volvulus, secondary to para esophageal hiatal hernia resulting in bulging of the stomach into the mediastinal cavity complicated by volvulus.

CASE REPORT

A 45-year old frail lady presented with long-term heartburn and dysphagia starting with solids which gradually progressed to liquids. She was being treated at home with oral proton pump inhibitors for heartburn for almost 6 months but with minimal reduction in symptoms. She was admitted for further workup of progressive dysphagia and stubborn dyspepsia unresponsive to PPIs.

On clinical examination, no positive findings were present. Hematological workup was also unremarkable. She ingested barium meal which revealed obstruction at the level of the body of stomach due to a hiatal hernia. (Fig. A) An upper GI endoscopy was conducted which also confirmed rotation of the stomach precisely mesenteroaxial type (Fig B: note the rotated stomach with reduction of the

'outlet' diameter (left side); also compare the diameter with pyloric sphincter seen in the right panel). A CT abdomen was also ordered (Fig. C &D) suggesting type 3 transhiatal hernia. Coronal and sagittal sections through the upper abdomen and lower chest revealed mesenteroaxial rotation of the body of the stomach, with the distal part of stomach occupying thoracic hernial sac (Fig C & D, denoted as 'p') while fundus lying in the abdomen (Fig C & D, denoted as 'f'). The patient was successfully treated with transhiatal hernial repair and Hill's procedure.



DISCUSSION

Whenever encountering a patient with an abdominal complaint, a stomach volvulus is seldom thought of. Berti was the first person to have described the term gastric volvulus while performing an autopsy on a female patient in 1866. And it wasn't until 1896 when Berg performed surgery for this condition successfully.[7] Many patients end up being misdiagnosed as gastroesophageal reflux disease or peptic ulcer disease and further managed by proton pump inhibitors and/or antacids. Although it is a rare entity, its underdiagnosis may be consequential to grave complications like strangulation, necrosis, and eventually perforation. Hence a thorough knowledge of the condition is essential in early diagnosis and prompt management of the patient. There is no predilection towards any gender or race, although the incidence rises after the fifth decade.[8]

According to the etiology of gastric volvulus, it can be classified as Idiopathic, usually due to the laxity of the gastrosplenic, gastroduodenal ligaments which predisposes the individual towards hiatal hernia and inturn gastric volvulus. Another etiology is Acquired/Congenital conditions which cause excessive mobility of the stomach leading to this condition[9].

Hiatal hernias are the number one cause of gastric volvulus[10] mainly because of the negative intrathoracic pressure of the mediastinal cavity leading to the bulging of the stomach into the chest cavity, which further is complicated by volvulus of the stomach. Four types of hiatal hernias are known, type I "sliding hiatal hernias" being the most common where the gastroesophageal (GE) junction slides into the thoracic cavity due to a lax diaphragmatic opening. Type II to IV are termed as "paraoesphageal hernias" (PEHs) and are further classified upon the location of the GE junction and the organ or the part of the organ which has herniated into the chest cavity. Type II hiatal hernia refers to a condition when the GE junction lies in its normal anatomical position but a portion of the stomach herniates into the chest cavity. Type III is similar to Type II but involves the displacement of GE junction from its anatomical position. Type IV has similar features as I and III but the herniated organ is usually other than the stomach.

Among all diagnosed gastric volvulus 75% are associated with a paraoesophageal hiatal hernias, abdominal conditions, or diaphragmatic problems.[9] General physical examination and abdominal examination of the patients with gastric volvulus is usually non-specific although epigastric tenderness and abdominal distention may suggest a gastric volvulus. If complications develop signs of peritonitis like abdominal tenderness, rebound tenderness, guarding or rigidity, decrease in bowel sounds, maybe present. Laboratory tests are non-diagnostic, but the elevation in serum alkaline phosphatase and high amylase levels have been reported[11]. Many cases have been reported with a positive association between hyperamylasemia and gastric volvulus[12]. Such presentations might lead to a misdiagnosis of acute pancreatitis.

Imaging studies, such as radiography, a plain film chest x-ray revealed gas-filled viscus in the chest cavity, confirming the diagnosis. In erect abdominal x-ray, a distended viscus may be seen in the upper abdominal cavity usually horizontally oriented with one or more air-fluid levels. Whereas in contrast radiography like barium studies, the stomach may be visualized in a twisted state, making the study diagnostic for the condition.[13] [14]
Some authors consider CT abdomen to be the diagnostic modality for gastric volvulus.[15] [16] Contrast studies have been reported to have a diagnostic yield in 81-84% of patients.[14] [17] [18] [19]

For acute gastric volvulus, the management involves resuscitation, passing a nasogastric tube with intention of gastric decompression, and placing the patient in a prone position followed by medical optimization involving anti-emetics and analgesics for surgery, since emergency

surgery is still considered to be the gold-standard treatment for acute gastric volvulus[20]. For chronic gastric volvulus, emergency surgical treatment is not preferred unless the patient becomes symptomatic or any complication occurs.

The surgical procedure involves the reduction of the volvulus, assessment of the gastric tissue of viability, and if the gangrenous portion is present it is followed by resection of the gastric tissue by segmental, total, or subtotal gastrectomy. After devolvulation and reintegration of the stomach back into the abdominal cavity with the gastroesophageal junction at the anatomical position, it is necessary to treat the secondary causes which could predispose the patient to recurrent volvulus. Further prevention of reflux disease if present pre-operatively can be done through performing fundoplication, which also helps in the reduction of re-herniation[21]. Both laparoscopic and open techniques are used to operate on the gastric volvulus but open surgery is usually preferred since it broadens access to the abdominal cavity. Whereas for chronic gastric volvulus, the laparoscopic technique has shown its usefulness. Overall the choice of surgery depends on various factors as clinician's personal preference, patient characteristics, etc. Postoperatively gastric decompression is maintained until the return of bowel sounds.

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22.

Archives of Surgical Research | Feature Interview

Becoming Sir Khawaja: A Product of Model Mentorship and Menteeship

Zaitoon Zafar

IMPORTANCE "Mentoring is a brain to pick, an ear to listen, and a push in the right direction." — John Crosby

Prof Khwaja Azeem is one of the finest surgeons in the country who believes in quality of care and surgical education. We had the opportunity to interview him on the his 67th Birthday. This interview highlights on the impact of mentorship and role modeling in the life of a surgeon. This interview although gives personal account but has important lessons for the students and trainees are pursuing surgical career.

KEY WORDS Volvulus of stomach, Hiatal hernia; Surgical Repair
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Feature Interview

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The Great Sir Khwaja has - unbeknownst to me - scheduled his interview with me on his 67th birthday. As I enter his room 3 cakes adorn his table, his daughter on his left & his protege, Dr. Talat, on his right. Other spaces are taken up by students; all inspired & intimidated by him, in equal amounts. He is wearing his scrubs and answering professional calls, as others celebrate his birthday for him. I ask him later if he had considered today would be his birthday when we were scheduling, he replies, "today is a Wednesday, beta". In contrast to his domineering personality in operation theaters and lecture halls, he is an eager host and is worried whether everyone received an equal share of cake.

Sir Khwaja Mohammad Azim was born on the 2nd of September, 1953 in Kashmiri Bazar, an area within the Walled City of Lahore. Being the second child and the first son of his parents, becoming a doctor was expected of him, a task he took in stride. After graduating from GCU, Lahore in 1971, he enrolled at Nishtar Medical University (NMU), Multan. At Nishtar is where he met Professor Zafar Haider, the man who would direct the course of his life.

WHEN THE STUDENT IS READY, THE TEACHER WILL APPEAR

"One of the greatest values of mentors is the ability to see ahead what others cannot see and to help them navigate a course to their destination." — John C. Maxwell

Professor Zafar Haider was the Head of Department of Surgery at NMU, where he started mentoring Sir Khwaja, mainly during Sir's year as a House Officer, after which he offered Sir Khwaja the position of Senior Registrar at Nishtar Hospital in the year 1979. Professor Zafar Haider relocated to Lahore the same year, where he was appointed as Professor of Surgery at King Edward Medical University (KEMU). At Mayo Hospital, Professor Zafar Haider performed the first parathyroidectomy in Punjab. Following in his steps was a talented & promising student he had not forgotten. On the 17th of January, 1980, Sir Khwaja was appointed as a Registrar at Mayo Hospital, South Surgical Ward, under the patronage of the pioneer Professor.

After clearing his MCPS towards the end of 1980, Sir Khwaja was offered the job of Senior Registrar. During this time,

Professor Zafar Haider moved from the South to the East Surgical Ward (ESW), and naturally, Sir Khwaja followed. The Professor made the ESW the hub of thyroid surgery, performing over two thousand thyroidectomies. At his right-hand side learning and witnessing such trail blazing was our Sir Khwaja.

The Professor then tasked Sir Khwaja with pursuing a fellowship in surgery from the UK. Sir went to Edinburgh in 1983 to complete his Part One, but soon returned to Pakistan, only to be sent back by the Professor to gain work experience from the UK, "go and see how state-of-the-art institutes function".

Sir Khwaja obtained his Fellowship in October 1986 from Royal College of Physicians of Glasgow and worked in various hospitals around the UK, from Ireland to London. Sir returned to Lahore (and to his mentor) to be appointed Assistant Professor of Surgery in March 1987 at KEMU. Within 5 years he was offered the job of Associate Professor of Surgery and was finally appointed as a Professor of Surgery in 2005 at KEMU, a role he fulfilled until 2013. A day after his retirement from KEMU, he started working at Shalamar Institute of Health Services, a move also credited to Professor Zafar Haider, as he served as honorary consultant to Shalamar Hospital for ten years following his retirement, and encouraged Sir Khwaja to join the institute as it "served the poor and had diversity of pathology".

Sir lowers his voice and looks down solemnly as he talks extensively about his Professor, "he was my master, my mentor, my spiritual father. I have learned a lot from him. I only followed in the footsteps of my great teacher". He considers himself blessed to have received one-on-one training from him. He claims his interest in surgery also developed when he saw how committed and dedicated Professor Zafar Haider was to his job as a teacher, "he was the teacher of teachers. I have not seen a greater teacher in Pakistan".

THE STUDENT BECOMES THE MASTER

Sir Khwaja considers being a teacher one of his roles in life, a responsibility he appreciates in its fullness; "this is how nations are built". He has mentored multiple talented students throughout his life, from Prof Ashfaq Ahmad, Professor Ameer Afzal of KEMU, Professor Akram Dogar of Central Park Medical College, and numerous other consultant surgeons, assistant professors at KEMU, SIMS, Lahore General Hospital. "They are carrying on the candle I took from Professor Zafar Haider".

When it comes to his final relay, he is most proud, "I have tried to transfer all of my teacher's teachings on to Talat, he is superb. There is no one better than him in this town. This is my last and best protege". Sir considers his student a blessing to him.

Following interview, I sought a brief input by Sir Talat about Prof Khwaja Azim.

"I have worked with many great people like, Stanley W Ashley, Malcolm K Robinson, Edward Whang, Evan Matros, Mark Duxbury, Hiromichi Ito from Harvard Medical School, Paul Redmond from University of Cork and many great people, but found Prof Khwaja Azim best of them all! He is the most meticulous, passionate and self-efficacious of them all. His hard work, belief in perfection and his way of self-quality assurance are outstanding.

He truly believes in the idea of mentorship in surgery and it has worked for him and his disciples. His surgical skill is enormous, unmatched and exemplary." says Sir Talat, who then provides personal insights he has gathered over the years:

"He has certain important qualities, which make him who he is:

- He is a perfectionist and is clear in his objectives, he is happy when he achieves them and is NOT when he does not! He lands in operation theater every morning with one single thought, 'today I am going to do the best operation of my life'.
- He has an innate quality to rise again and again from a crisis, and very quickly. He rejuvenates in a very short time span following a surgical crisis and is soon filled with hope again. His self-efficacy is impeccable.
- He is daring and willing to take risks and has finessed the art of managing risks associated with the sequelae.
- He has tremendous energy and can work with passion for hours! Even at the age of 67.
- He knows his strengths very well and knows how to capitalize on them.

So, becoming Professor Khwaja Azim is not simple and easy. He is the product of obedience to his mentors, hard-work, belief in perfection, self-efficacy and a big dose of courage."

THE LINEAGE (AS TOLD BY SIR KHWAJA)

1. Professor Dr. Ameer Uddin: As the Professor of surgery at Mayo Hospital during Partition, Dr Ameer provided treatment services for those who got injured while migrating. He was also a philanthropist, and reportedly sold out his residence at Gulberg to contribute to the establishment of the Department of Pediatric Surgery at Mayo Hospital. The government awarded him with the title of Emeritus Professor of Surgery. He was considered to be one of the top 20 surgeons of the world, and recently a medical college was named after him.

2. Professor Dr. Zafar Haider: Graduate of King Edward Medical University,1950. He opted to become a surgeon after being influenced by his teacher and mentor, Professor Dr. Ameer-ud-din. He obtained his FRCS in 1957 & trained under the likes of Hamilton Stewart and John Charnley. He was a general surgeon in addition to being competent in cardiothoracic, orthopedic, urology & oncological surgery, he felt it was necessary to be trained in multiple fields for a recently established and young country, Pakistan. His main field, however, was endocrine, specifically the thyroid and parathyroid.

3. Professor Dr. Khwaja Azeem: Graduate of Nishtar Medical University, 1976, he was inspired by Professor Dr. Zafar Haider's discipline and commitment to his students to become a surgeon. Appointed Professor of Surgery at King Edward Medical University in 2005 until his retirement in 2013. Then started Professorship of Surgery at Shalamar Medical & Dental College till present.

4. Professor Dr. Ameer Afzal: Professor of Surgery at King Edward Medical University, a student of Sir Khwaja Azeem. He recently led the earthquake relief operation in Azad Jammu and Kashmir.

5. Dr. Talat Waseem: Current Associate Professor of Surgery at Shalamar Medical & Dental College, he is a Consultant Surgical Oncologist & Endocrine Surgeon, who completed his Postdoctoral Fellowship Surgical Research from Harvard Medical School.

THE TOOLS OF THE MASTER

"A person should be morally, professionally, financially incorruptible" Sir Khwaja exclaims, "this is what you need to be successful". His life's philosophy is of a simple and honest man, he does not believe in pride or ownership, "do not take pride in whatever is given, and do not cry over what is taken". With an unwavering faith in Allah, who he calls upon repeatedly, he believes he has cleared all obstacles. It is surprising to hear from Sir Khwaja himself that there were days he felt like running away, but he dismisses the possibility of that actually happening with "just keep busy. When tense, leave it to Allah, what else can a man do?"

He says he is fond of talking and holding discussions, and even uses it as an outlet when tired or bored. He believes one must not go to sleep without reading, "even if it is an Urdu digestive", and still continues to study and revise surgery lessons for at least 2 hours a day. Sir's morning routine consists of waking up early for Fajr, then going for a walk, and returning to recite the Holy Quran.

Sir Khwaja holds a strong belief in being steadfast and leaving the rest up to Allah, "do not get distracted, have clarity of mind, consult others, but stick with your decision once you make it. Allah will open all doors for the path you decide to take". He is also a strong proponent of merely trying, he says trying is what will determine whether you will achieve a goal or not.

"There is no substitute for hard work. Believe in your destiny, work hard and honestly in order to fulfill it". When asked if he has had to make any sacrifices to get to the position he is, "no, my wife has". She is the only other person apart from Professor Zafar Haider he credits with his success in life.

LAST WORD

When asked if reaching Sir Khwaja's level of success is possible without a stout mentor, he believes it is simply not possible; "you will be shooting aimlessly in life". He considers having a mentor one of fate's biggest blessings and equally influential as having parents. Recalling upon Professor Zafar Haider speaking of his own mentor, Professor Dr. Ameer-ud-din, "if I hadn't chanced upon Dr. Ameer-ud-din, I would have ended up a street vendor". Sir Khwaja holds the same belief in regards to his master.

"If I have seen further it is by standing on the shoulders of giants." — Isaac Newton

Author Guidelines

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- ASR-Consent Form of Case Reports (WORD FORMAT) (PDF FORMAT)
- ASR-Peer Reviewer Proforma (WORD FORMAT) (PDF FORMAT)
- ASR-Manuscript Submission Checklist (WORD FORMAT) (PDF FORMAT)
- ASR-Disclosure Form (WORD FORMAT) (PDF FORMAT)
- ASR-Title Page Sample (WORD FORMAT)

Authors are required to follow ICMJE Guidelines for reporting research work. Before submitting, kindly ensure that the following aspects are present. Please also review journal policies listed below in website especially about Ethical Publishing, Professional Misconduct about Scientific Reporting, Plagiarism, and Peer Review Process etc. before writing a manuscript.

For the correspondence author:

- E-mail address
- House address

Manuscript: The Manuscript files should be prepared in a manner to facilitate double blind peer review process. The title page containing author and institutional information should be submitted separately from the body of the manuscript. The manuscript should include:

- Cover Letter
- Title Page
- Article Body Text
- All figures (with relevant captions)
- All tables (including titles, description, references)
- Ensure all figure and table citations in the text match the files provided
- Supplemental files, if applicable
- Letter of Undertaking
- Ethical Compliance Undertaking
- Reviewer Suggestion Form (One Reviewer should preferably from outside Pakistan)
- Plagiarism Check Report (Optional)
- Relevant Consent Forms
- IRB Approval Letter
- Disclosure Form
- Proof of Submission of Article Processing Charges (APC) Contact Support Person

2. SUBMISSION CHECKLIST

(HIGH LEVEL OF COMPLIANCE IS REQUIRED; THE ARTICLES NOT IN COMPLIANCE WOULD BE RETURNED)

The authors must comply with these important checklist items prior to submitting their manuscript for publication as the non-compliant manuscripts would be returned without review: -

1. Manuscripts should be prepared following Uniform requirements for manuscripts submitted to Biomedical Journals as approved by the International Committee of Medical Journal Editors (www.icmje.org). The manuscript handling is done through Committee on Publication Ethics (COPE) guidelines.
2. The submission file is in Open Office, Microsoft Word, or RTF document file format. The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
3. All original manuscripts should have Abstract in structured format up to 350 words. It should mention Objective, Methodology, Results, Conclusions and appropriate Key Words.
4. Please strictly follow the author guidelines for writing your manuscript. Non-compliant manuscripts would be returned without review without any exception. Referencing should be done through Mendeley, Endnote or any other such referencing software. In text citation should be in form superscript. The manuscripts with improper citation would be retuned without review. A sample manuscript submission file may be downloaded from this website.
5. The submission files should have a. Cover Letter describing the value of research work being submitted, b. Title Page containing the Manuscript Title, Authors, affiliations, contributions—an example of title page can be downloaded from this website, c. Article Text File having body of the main manuscript, d. Images and Tables, e. IRB approval Letter, f. Signed Letter of Undertaking, g. Consent Form for Case Report h. Article Processing Charges Submission Proof, i. Ethical Undertaking. Make sure that quality of Images is according to specifications provided in author guidelines. j. Reviewer Suggestion Form. k, Disclosure Form
6. Title page should contain title of the write-up, Name of the author/co-authors, their qualifications, designation & institutions they are affiliated with and mailing address for future correspondence, E-mail address, Phone, Cell Phone number besides a short running title of the manuscript. Don't type the name of the author/s on other pages in the manuscript except the title page to ensure the double blinding of the review process.
7. Prior to submission the manuscript should be checked for plagiarism preferably through Turnitin or some other medium and the similarity index should exceed 19%.
8. You have the proof in PDF/ JPEG form of submission of Article Processing Charges (APC).
9. All submissions are received through online portal through www.archivessr.com.
10. All randomized control trials should be prepared according to CONSORT Guidelines. All Clinical Trials submitted for publication must be registered in a registry e.g. https://clinicaltrials.gov/. Provide registration number.
11. Disclosure regarding source of funding and conflict of interest if any besides approval of the study from respective Ethics Committee/Institution Review Board.
12. Manuscript must be submitted along with IRB/Ethics Committee Approval letter.
13. Case Reports should be submitted along with Consent Form wherever applicable.

Corresponding Author Name_____ Sig. _____

Date _____

Manuscript Title: _____

_____

Further Considerations:

- Manuscript has been checked for correct spelling and grammar
- All Reporting Guidelines have been met
- All references mentioned in the Reference List are cited in the text, and vice versa
- All figures and tables are cited in text
- Permission for use of copyrighted material from other sources has been obtained
- A conflict of interest statement is provided, even if the authors have no conflicting interests to declare
- All research and clinical trials are registered in a public registry
- Journal policies detailed in this guide have been reviewed
- Referees and reviewers suggested by author(s) comply with journal policies as well.

3. BEFORE INITIATING SUBMISSION PROCEDURE

Ethical Confines

The work detailed in the manuscript must be approved by the appropriate ethical committees related to the institution(s) in which it was performed, including verification that all subjects involved gave informed consent. Records of written consent must be kept by the author. Studies involving experiments with animals must follow institution guidelines for the care of animal subjects. Any identification markers of patients and volunteers – including names, initials, and hospital numbers – must NOT be used.

Declaration of Interest

All authors must disclose financial and personal relationships with individuals or organizations that could potentially introduce bias to their article. Examples of possible conflicting interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications or registrations, and grants or other funding. If there are no interests to declare, then please: 'Declaration of interest: none'. This summary statement will be published if the article is accepted.

Submission Declaration and Verification

Verify that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis), that it is not being considered for publication anywhere else, that its publication is approved by all authors, and by the responsible authorities/institutions where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form without the written consent of the copyright-holder. Verify that the work is original – all manuscripts are checked for plagiarism, and if found to be plagiarized above a certain degree, the author is liable to be blacklisted.

Use of Impartial and Inclusive Language

Inclusive language acknowledges diversity, conveys respect, is sensitive to differences, and promotes equality of opportunity. Content must not imply that one individual is superior to another on the basis of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition. Authors should ensure that writing is free from bias, stereotypes, slang, and references to dominant culture. Avoid using markers of identification – including age, gender, race, ethnicity, culture, sexual orientation, disability or health when referring to subjects unless absolutely necessary. Always use the gender-neutral 'they' when referring to singular subjects unless the gender of the subject has particular influence on the research matter.

Authorship and Author Rights

Manuscripts by multiple authors must be signed by all the authors and contain details of contribution of every individual author. All authors must fulfill criteria for authorship. Authorship credit should be based on:

- Significant contribution to formation or design of study, procurement of data, or analysis and interpretation of data (Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship)
- Drafting the article or revising it analytically
- Final approval of the version to be published
- Agreement to be responsible for all aspects of the work, and ensuring that the accuracy or integrity of any part of the work is maintained.

If a large, multi-center group has conducted the work, the group should identify the individuals who accept responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above and complete journal-specific author and conflict of interest disclosures. When submitting a group author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name. Other members of the group should be listed in the acknowledgements. In case of suspicion of gift authorship the journal may refuse further processing of the manuscript. Manuscripts with more than *Eight* authors will not be accepted for further processing and will be rejected. An author (or employer or institution) has certain rights to reuse work that this journal will not infringe upon.

Registration of Research and Clinical Trials

All types of research studies and clinical trials involving human participants should be preferably registered prior to submission, and proof of registration must be provided. Unregistered trials and studies may not be published.

Role of Funding Source

The funding source must be disclosed along with their degree of involvement with the research matter, if any, in the design, collection, analysis or interpretation of data; in the writing of the article, or in the decision to submit the article for publication. If the funding source had no involvement, then this should be stated. Any authors found guilty of scientific misconduct will be blacklisted from future publications.

4. PREPARATION

Reviewing Process

This journal is reviewed using a *double blind* method through OJS. The following categories the journal will accept, out of guest editorials, original articles, review articles, case reports, clinical updates, short communications, book reviews, case studies, clinical notes, Continuation of Medical Education (CME), obituaries , letters, Knowledge-Attitude-Practice (KAP) studies, routine surveys and cross sectional studies. The authors are required to suggest potential refrees for the review process. The journal however would have to discretion to get the article reviewed by the suggested faculty or not.

Reporting Guidelines

Compliance with the relevant reporting guideline is mandatory for submission of the following guidelines:

1. Submit a completed checklist, indicating the page numbers where compliance to the guidelines was ensured.
2. Mention in the 'Methods' section that the research is being reported in line with the relevant guideline, which should be named and cited.

Randomized Controlled Trials

All randomized controlled trials submitted for publication in Archives of Surgical Research must include a completed

Consolidated Standards of Reporting Trials (CONSORT) flow-chart and ensure that all features of the CONSORT checklist are present. A copy of the CONSORT checklist must be uploaded in supplemental material. Refer to the CONSORT statement website here.

Systematic Reviews

Systematic reviews are to be reported in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines and must include the flow-chart as a figure and the checklist as a supplemental material. Please download a PRISMA Flowchart and a PRISMA Checklist here. To aid and improve the methodological quality of your article, include an AMSTAR 2 checklist as well, which is available here.

Cohort, Case-control and Cross-sectional studies

Cohort, Case-control and Cross-sectional studies must be compliant with the STROCSS criteria (Strengthening the reporting of cohort studies in surgery), which is available here. Cite the following paper: Agha RA, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, for the STROCSS Group. STROCSS 2019 Guideline: Strengthening The Reporting Of Cohort Studies in Surgery. Each study type has its own checklist which must be uploaded as supplemental material.

Diagnostic, Quality Improvement and Qualitative studies

Diagnostic studies should be reported according to the STARD statement criteria (Standards for the Reporting of Diagnostic Accuracy studies). The flow-chart should be a figure and checklist should be uploaded as supplementary material. Quality Improvement studies must comply with the Standards for Quality Improvement Reporting Excellence (SQUIRE) criteria, which is available here. Qualitative studies require the Consolidated criteria for Reporting Qualitative Research (COREQ) checklist, available here.

Health Economic Evaluation

Health Economic Evaluation studies should conform to the CHEERS statement, available here.

Tumour Marker Prognostic Study

Tumor Marker Prognostic studies should be reported according to the REMARK criteria.

Before and After Studies

Before and After studies measure specific characteristics of a population or group of individuals after an event or intervention, compare them with those characteristics before the event or intervention, then measure the effects of the event or intervention. These studies should conform to the STROCSS statement.

Experimental Animal Studies

Animal studies must be reported according to the ARRIVE guidelines (Animals in Research: Reporting In Vivo Experiments) and must include the checklist as supplemental material. An example of a completed checklist can be found here. The institutional protocol number must be included at the end of the abstract.

Qualitative Surveys

Qualitative Surveys should be reported according to the criteria detailed in the SRQR Guidelines. Guidelines for synthesis of qualitative research can be found here. Guidelines for interviews and focus groups are available here.

Case Series

Ensure that the case series is compliant with the PROCESS Guidelines and submit a completed PROCESS checklist. State that the work has been reported in line with the PROCESS criteria and cite the following paper: Riaz A. Agha, Mimi R.Borrelli, Reem Farwana, Kiron Koshy, Alex Fowler, Dennis P. Orgill, for the PROCESS Group. The PROCESS 2018 Statement: Updating Consensus Preferred Reporting Of CasE Series in Surgery (PROCESS) Guidelines.

Article Structure

Title Page

The title page should give the title in capital letters and a shorter running title. Avoid abbreviations and formulae if possible. In addition, the title page should also include:

- Correctly spelled names of all authors, and their affiliation addresses where the actual work was done. Include the e-mail address of each author.
- Signpost clearly the correspondence author who will maintain contact at all steps of reviewing and publication, and post-publication, and answer any questions about the research. All information must be updated in case of any changes.
- Present/permanent address of every author.
- The source of funding of the research.
- The number of figures and tables, the total word count and the total number of pages of the manuscript.
- A sample Title Page has been uploaded on this page above.

Abstract

All original articles must accompany a structured abstract of up *to 250-350* words. It should state aims of the study, methodology and materials used, results obtained, and conclusions reached. Specify how the sample selection of study subjects or experimental animals was carried out, specify the observational and analytical methods, and give specific data and its statistical significance, where possible. Highlight novel and significant aspects of the study. Avoid references, but if necessary, cite the author(s) and year(s). Avoid non-standard or uncommon abbreviations, but if necessary they must be defined at their first mention in the abstract. This page should constitute of the abstract and keywords only.

Keywords

Right after the abstract, provide a maximum of *6* keywords, using British spelling. Avoid general and plural terms and

multiple concepts (avoid, for example, 'and', 'of'). Only abbreviations firmly established in the field may be appropriate. These keywords will be used to aid the indexing process of the journal.

Introduction

Outline the aims of the work and provide sufficient background information, avoiding a lengthy literature review or a summary of the results.

Methodology

Provide adequate details to allow the research to be reproduced by an independent researcher. If experimental apparatus is used, the manufacturer's name and address should be included in parentheses. Methods that have previously been published should be summarized, and signposted by a reference. If quoting directly from a previously published method, use quotation marks and cite the source. Any alterations to existing methods should also be described. If a drug is used, its common name, dose and route of administration must be included. For patients, age and sex with mean age ± standard deviation must be given where relevant to the data. Statistical methods employed for comparisons of data sets must be mentioned and any computer programs used for calculations must be specified.

Results

Results should be clear and succinct. They must be presented in the form of text, tables and illustrations. The content of the tables should not be repeated in the text; the tables should be numbered and identified and referenced to as their number. A conclusion that either supports or negates the hypothesis should be included. If the data is inconclusive, that should also be noted.

Discussions

This should emphasize present findings of the research, and the differences and similarities with prior work done in the field by other researchers. Data must not be repeated in the discussion, and lengthy citations and reviews must be avoided. Highlight the original and central aspects of the study and the conclusions that they lead to.

References

Please make sure that Mendley or some other software is used for referencing. The articles without compliance in this area would be sent back. **American Medical Association (AMA Referencing Style) should be used.** References should be typed in sequential numbers in superscript for in-text citations, and numbered sequentially in the Reference List provided at the end. Maximum references for original article should not exceed 40; they should not exceed 10 for case reports, and 80 for reviews. Authors should ensure that locally published studies are given precedence. Add DOI number of documents where it is available.

References from books should include author, title, publisher, and year of publication. Example:

Das JC. *Power System Harmonics and Passive Filter Designs*. John Wiley & Sons, Inc; 2015.

For articles in journals, the authors, title of article, name of journal, year of publication, and an article identifier and page range (where available) must be included. See the following example:

Zhu Z, Hoffman JE. Condensed-matter physics: Catching relativistic electrons. *Nature.* 2014;513(7518):319-320.

Websites that are blogs and subject to changes by the author must be used as sparingly as possible, and when included, the author's name, the title, the name of website, date of publication, date on which the website was accessed, and a link to the website must all be included. Example:

Andrew E. After Years Of Conflict, Huge Project Could Help Scientists Decipher The Brain. IFLScience. Published June 18, 2015. Accessed October 30, 2018. https://www.iflscience.com/brain/after-years-conflict-huge-project-could-help-scientists-decipher-brain/

For government reports, technical reports, and scientific reports, if the report number is unavailable, then cite the report as a book. For reports it is usually not individual people that are credited as authors, but a governmental department or agency. Include the name of the agency, the title of the report, the publisher, and the year of publication. An example is as follows:

Government Accountability Office. *The Manager, the Government, and the Accounting Profession*. U.S. Government Printing Office; 1968.

References to Ph.D. dissertations, Master's theses or Bachelor theses follow the format outlined below, and must include author, title, publication detail if applicable, and year of publication.

Campbell AJ. History transformed: Sengoku Daimyo in Japanese popular media. Published online 2012.

For newspaper articles, citation must include the author, title, name of newspaper, full date and page number. The example is as follows:

Kinsley M. Paid Leave Counts as Progress. *New York Times*. May 27, 2017:SR3

Avoid referencing personal communications and unpublished observations, but they must be presented in parentheses in the text if included, and not in the list of references in the appendix. A research article may not be cited as "Under Publication" or "In Press" unless it has been accepted for publication. In such a case, the name of the journal must be given.

Acknowledgements

All contributors who do not meet the criteria for authorship should be credited in this section. It should include persons who provided technical help, writing assistance and general support or supervision. Financial and material assistance must also be credited. Persons who have added to the material but do not justify authorship can be listed as "clinical investigators", "participating investigators", "scientific advisors", "reviewers', or "data collectors."

5. FURTHER CONSIDERATIONS

World Limits

Maximum length of the original manuscript should not exceed *4000* words including title page, table and references. For review articles, the maximum word count is *3500,* however considering the demand of the subject it can be up to 8000 words. Maximum number of tables & illustrations should not exceed 5. Short reports of cases, clinical experience, drug trials and their adverse effects can be submitted. Maximum length of these case reports should not exceed *800* words, *5* maximum number of references, and *2* table or illustrations. For letters, maximum words are *600* with *5* references. Extra charges will be applicable for lengthy manuscripts.

Units, Abbreviations and Formulae

Système Internationale (SI) units should be used, with the traditional equivalent in parentheses where appropriate. Avoid non-standard or uncommon abbreviations, but if necessary they must be defined at their first mention. Submit math equations as editable text. Add simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. Variables are to be written in italics. Powers of e should be denoted by exp. Any equations that have been presented separately from the text (if referred to explicitly) must be numbered consecutively.

Artwork

Make sure to use uniform lettering and sizing of original artwork. For original illustrations, use Arial, Courier, Times New Roman, Symbol, or a font that looks similar. Number the illustrations according to their order in the text with a logical naming convention for the artwork files. Provide captions to illustrations separately. Size the illustrations close to the desired dimensions of the published version, avoiding any files that are disproportionately large. Submit each illustration as a separate file. If the electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply in the native document format without alterations or conversions. If the application used is not part of Microsoft Office, convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

- EPS (or PDF): Vector drawings, make sure to embed fonts.
- TIFF (or JPEG): Color or gray-scale photographs (halftones); ensure a minimum of 300 dpi.
- TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings; ensure a minimum of 1000 dpi.
- TIFF (or JPEG): For combinations of bitmapped line/half-tone (color or gray-scale), ensure a minimum of 500 dpi.

Do not supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors. Do not supply files that are too low in resolution. Ensure that each illustration has a separate caption that is not attached to the figure. A caption should comprise of a short title and a brief description of the illustration. Avoid text in the illustrations themselves but explain the symbols and abbreviations used.

Tables

Submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or separately at the end in an appendix. Number tables consecutively according to their sequence in the text and present any table notes below the table body. Keep the use of tables to a minimum and ensure that the data included in them is not repeated in results described elsewhere in the article. Avoid using vertical rules and shading in table cells.

Supplementary Material, Research Data, and Video

Supplementary material such as applications, images, and sound clips, can be published with the article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Submit this material with the manuscript and supply a concise, descriptive caption for each file. If you want share data that supports your research publication, where appropriate, interlink the data with the article. Research data refers to the results of experimentation that validate research results. To enable reproducibility and data reuse, share the software, code, models, algorithms, protocols, methods and other useful materials related to the project. If you have made your research data available in a public data repository, link the dataset directly into your article. To enable transparency, we require you to state the availability of data in your submission if your data is unavailable to access or unsuitable to post. Authors who wish to submit video files with their article are encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed, or separately at the end. Keep the file in one of the recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total.

6. AFTER COMPLETION

Proofreading

Final version of the article is sent to corresponding author for proof reading before publication. In case of changes, corrections should be sent to the editor by email.

Processing & Publication Charges

This is open access journal and journal charges Article Processing Charges (APC) of Rs 5000/- for local manuscripts and $US 100 for foreign manuscripts. Article Processing Charges are deposited at the time of submission and are non-refundable. Moreover, please also note that once accepted minimum publication charges for articles, manuscripts are Rs.4,000/- per page (in case of overseas US$ 50/- per page; Overseas US$ 50/- per page). Charges for photograph, films and illustrations are additional. Publication charges are payable in advance once the manuscript has been accepted for publication.

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Those who cannot pay for processing and publication can apply for waiver at the time of the submission of their article.

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All manuscripts involving human subjects must be accompanied with certificate of approval by the relevant institutional review body or ethics committee.

Informed Consent

While the actual signed consent forms need not be sent to the journal, all manuscripts reporting the results of experiments involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after the experimental protocol is approved by relevant institutional body or ethics committee.

Letter of Undertaking

Manuscripts must be accompanied by letter of undertaking signed by all the authors

Printed Copy

One printed copy will be sent to the correspondence author. Authors can order additional copies at the rate of *cost*. Payment for additional copies should be sent in with the publication charges.

Submission

All manuscripts must be Word documents.

Ombudsperson

The journal's managing Editor can be contacted by authors and other personnel in case any grievances should arise by e-mail.

7. PRIVACY POLICY

Archives of Surgical Research is committed to the protection of your personal information. The privacy policy outlined here applies only to information collected by Archives of Surgical Research through the http://www.archivessr.com/.

Information We Collect

We will request personal data from you to ascertain your individual user profile that may support all online activities allotted as an author, editorial member, or other connected role. Data like your name, postal address, e-mail address, telephone number and geographic locale are used as identifiers to permit access to certain content or to a secure website. All personal information is treated by Archives of Surgical Research as strictly personal and confidential. Archives of Surgical Research won't disclose any personal information to third parties without your permission, unless required by law

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Cookies and log files are automatically recorded when you visit our site. These data includes some of the following information: IP address, host name, domain name, browser version and platform, date and time of requests, and downloaded or viewed files. This information is used to measure and analyze traffic and usage of the www.archivessr.com website and our digital products.

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When you have created an account on the http://archivessr.com, you can update your private information at any time through your account settings.

This statement may be periodically updated.

If you are concerned about how your information is stored, please contact us by email at editor@archivessr.com

8. PUBLISHING ETHICS

Archives of Surgical Research follows the COPE Core Practices and ICMJE's *Recommendations to conduct, report, edit and publish Scholarly Work in Medical Journals*, and expected an ethical behavior from authors, reviewers and editors to follow guidelines. We also follow the Principles of Transparency circulated through WAME.

Allegations of Misconduct

Archives of Surgical Research (ASR) defines research & publication misconduct as follows:

- Plagiarism: the practice of taking someone else's work or ideas and passing them off as one's own.
- Citation manipulation: a problem when references do not contribute to the scholarly content of the article, and are included solely to increase citations.
- Data falsification/fabrication : intentional misrepresentation of research results
- Conflict of interest: a conflict of interest exists when a manuscript's or journal's author, editor, reviewer have a financial or personal relationship that may influence their intentions or bias.
- Redundant publication : when a published work (or substantial sections from a published work) is/are published more than once (in the same or another language) without adequate acknowledgment of the source/cross-referencing/justification (https://publicationethics.org/category/keywords/redundant-publication)

Any allegations of misconduct brought to the journal's attention will be dealt with immediately and seriously. ASR

will not accept articles that violate research & publication ethics, any manuscript not in compliance will be rejected.

ASR utilizes Turnitin to assess all submitted manuscripts, a plagiarism percentage upwards of 24% is unacceptable and articles not in accordance with this rule will be rejected.

In cases of citation manipulation, relevant COPE guidelines will be followed.

In case of suspected data falsification/fabrication, respective authors will be asked to clarify and explain their methods. Failure to do so will result in:

1. rejection of their submitted manuscript
2. communication of the authors' misconduct will be made to relevant institutions and regulatory bodies
3. black-listing of the authors from ASR for all future submissions

This is in accordance with COPE guidelines.

We follow the COPE Guidelines for sharing information regarding any misconduct with other journals. We also follow the COPE Retraction Guideline. We as a journal have policy to refer such cases to COPE if required.

In case of suspicion of image manipulation in a manuscript, COPE flowchart will be followed.

In cases of redundant publications, COPE flowchart will be followed.

Disclosures

All authors are required to submit a Disclosure of Interest form, which can be found here: http://www.icmje.org/disclosure-of-interest/. In case of an undisclosed conflict of interest, COPE guidelines will be followed.

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Archives of Surgical Research (ASR) follows the COPE flowchart to recognize potential authorship problems. Ghost, guest, and gifted authorship will result in rejection of submitted manuscript, in accordance with COPE guidelines.

ASR implements ICJME recommendations for what constitutes authorship of a manuscript.

If a contributor does not fulfill the authorship criteria, ASR encourages listing them in the acknowledgements section. **All** authors are required to submit a Disclosure of Interest form, which can be found here: http://www.icmje.org/disclosure-of-interest/. In addition to submitting a disclosure of interest form, the manuscript must outline the specific contribution of each author. ASR Authors are also encouraged to link their ORCiD profiles.

Authorship disputes should be brought to light via email to relevant editors. They are handled through COPE Guidelines.

ICMJE Authorship Criteria

As per ICMJE guidelines the authorship should be based on the following criteria:

1. Substantial contributions to conception & design, or acquisition of data, or analysis & interpretation of data.
2. We do not allow ghost, guest and gift authorships and if found so we follow COPE guidelines to handle such cases.
3. Drafting the article or revising it critically for important intellectual content.
4. Final approval of the version to be published. All those who meet the above three conditions are eligible to be included as Authors in the manuscript
5. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
6. When a large multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, general supervision of the research group does not qualify any one to be an author. All contributors who do not meet the criteria for authorship should be listed in the acknowledgment section. Those who provide technical support, writing assistance, or department chair who provided just general support should also be mentioned in acknowledgment. It is also important that all those whose names appear in acknowledgement must have given permission to be acknowledged.

ICMJE http://www.icmje.org

Complaints and Appeals

Archives of Surgical Research (ASR) follows COPE guidelines in case of appeals to the journal's editor's decisions and complaints about ASR's journal management of the peer review process.

If authors wish to file a complaint or appeal against an editorial decision, they are encouraged to email: editorial@archivessr.com, with the subject heading mentioning "COMPLAINT" or "APPEAL". We have dedicated Ombudsperson for handling such appeals.

Furthermore, Archives of Surgical Research (ASR) consults COPE guidelines if a reviewer is suspected of appropriating or mismanaging author material and may refer such cases to COPE if required.

Data and reproducibility

Archives of Surgical Research (ASR) follows ICMJE data sharing guidelines.

In case of suspected data falsification/fabrication, respective authors will be asked to clarify and explain their methods.

To Improve transparency, we encourage use of and link to international standard reporting guidelines such as those listed in the EQUATOR Network. We encourage pre-registration of clinical trials (and other study designs) in an online clinical study database before data are collected (eg, ClinicalTrials.gov). We encourage journal pre-registration and peer review of study protocols before data are collected (eg, as promoted by the Center for Open Science).

We have system of scruitiny to find such data manipulations, if found may result in:

1. Rejection of their submitted manuscript
2. Communication of the authors' misconduct will be made to relevant institutions and regulatory bodies
3. Black-listing of the authors from ASR for all future submissions

This is in accordance with COPE guidelines.

In case of suspicion of image manipulation in a manuscript, COPE flowchart will be followed.

Ethical Oversight

Archives of Surgical Research (ASR) follows COPE guidelines for ethical oversight, wherever applicable. ASR has it's own consent form for case reports, which is mandatory along with the submission of the manuscript. The consent form is adapted from BMJ Case Reports and is in line with COPE guidelines. To determine whether a study requires ethical approval or not, ASR looks to COPE guidelines.

Furthermore, ASR requires a transparency declaration from the lead author of an original study guaranteeing honesty and accuracy (as published & implemented by the BMJ and endorsed by the EQUATOR network).

Post-publication Review and Audit

If authors whose work has been accepted and/or published wish to retract/correct/revise their articles, please email: editorial@archivessr.com, with the subject heading mentioning "RETRACTION" or "CORRECTION" or "REVISION".

Conflict of Interest Policy

Adopted from Conflict of Interest in Peer-Reviewed Medical Journals which is prepared by WAME Editorial Policy and Publication Ethics Committees.

Articles would be published with statements or supporting documents declaring:

Authors' conflicts of interest

Sources of support for the work, including sponsor names along with explanations of the role of those sources if any in study design; collection, analysis, and interpretation of data; writing of the report; the decision to submit the report for publication; or a statement declaring that the supporting source had no such involvement; and Whether the authors had access to the study data, with an explanation of the nature and extent of access, including whether access is on-going.

To support the above statements, editors may request that authors of a study sponsored by a funder with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

Disclosure form is available from the website, which has been adapted from ICMJE Disclosure Form and should be filled at the time of acceptance of manuscript. Disclosures are also obtained whenever deemed necessary at the time of review and editorial tasks.

9. EDITORIAL POLICIES

Principles of Transparency and Best Practice in Scholarly Publishing are followed as per ICMJE guidelines. This Journal strives to adhere to the ***Principles of Transparency and Best Practice in Scholarly Publishing*** which could be found in the **DOAJ** Web site completely,

This Journal has established a guideline for editorial independence as delineated below. The guideline generally follows that created by the World Association of Medical Editors.

1. This Journal is operated by Pakistan Endocrine & Thyroid Surgeons Association (PETSA), which is publishing organization.
2. The Chief Editor is responsible for independent leadership of This Journal editorial operations. The General Publishing Editor reports to the Editor-in-Chief for all editorial matters.
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4. Content-related decisions are based on quality, importance, and value to the users of this Journal. Contributing authors, editors, This Journal staff are free to express responsible positions -even if these views are not in agreement with interests, policies or published research, editorial or commentary of PETSA.
5. This Journal actively seeks input regarding editorial matters from the physician Editors-in-Chief in an advisory capacity, as well as from the other editorial board members, internal editorial staff, and readers.
6. Editors-in-Chief of this Journal is empowered to create content and commentary free of commercial and organizational influence. All authors and editors operate without conflict of interest and all potential conflicts are disclosed (please also see Conflict of Interest Policy).

10. PEER REVIEW POLICY

We follow ICMJE recommendations on the manuscript handling. The practice of peer review is to ensure that only good science is published. It is an objective process at the heart of good scholarly publishing and is carried out by all reputable scientific journals. Our referees play a vital role in maintaining the high standards Review Policy and all manuscripts are peer reviewed following the procedure outlined below:

Initial manuscript evaluation

The Editor first evaluates all manuscripts. It is rare, but it is possible for an exceptional manuscript to be accepted at this stage. Manuscripts rejected at this stage are insufficiently original, have serious scientific flaws, have poor grammar or English language, or are outside the aims and scope of the journal. Those that meet the minimum criteria are normally passed on to at least 2 experts for review. Most of the submitted manuscripts are reviewed except few invited or editorial content.

Type of Peer Review

Policy employs double blind reviewing, where both the referee and author remain anonymous throughout the process.

How the Referee is selected

Whenever possible, referees are matched to the paper according to their expertise and our database is constantly being updated. The referee is selected both from the editorial team and outside and depending on the author suggestions.

Referee Reports

Referees are asked to evaluate whether the manuscript: - Is original - Is methodologically sound - Follows appropriate ethical guidelines - Has results which are clearly presented and support the conclusions - Correctly references previous relevant work. This is a systematic process and works on the well-designed Peer Review Proforma. The confidentiality of the peer review is ensured. Reviewers are encouraged to report conflict of interest, ethical misconduct etc.

Language correction is not part of the peer review process, but referees may, if so wish, suggest corrections to the manuscript.

How long does the review process take?

The time required for the review process is dependent on the response of the referees. Should the referee's reports contradict one another or a report is unnecessarily delayed, a further expert opinion will be sought. The Editor's decision will be sent to the author with recommendations made by the referees, which usually includes verbatim comments by the referees. Revised manuscripts might be returned to the initial referees who may then request another revision of a manuscript.

Final Report

A final decision to accept or reject the manuscript will be sent to the author along with any recommendations made by the referees, and may include verbatim comments by the referees.

Editor's Decision is Final

Referees advise the editor, who is responsible for the final decision to accept or reject the article.

Conflict of Interest

All reviewers and editors have to declare any potential conflicts of interest if any. We follow COPE and ICMJE guidelines in this regard.

Editorial and Peer Review Processes Generally Follow these Steps:

We follow and request from authors, reviewers and editors the "ICJME Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals". Editorial reviewer policy is independent of any financial, academic or any other interest.

- When an article is submitted to Archives of Surgical Research, Editor makes the first check of submitted articles (structure, plagiarism, scientific quality).
- Article may be rejected, sent back for structural revision, or sent to at least two reviewers for peer review.
- After peer review process, articles may be rejected, sent back for revision requested by reviewers or accepted for publication.
- Revised articles by authors may be accepted, resent to reviewers, resent to authors for additional corrections/revision or rejected.
- Authors could not see reviewers' information. Editor may make authors' information available to reviewers or not.
- Accepted articles are forwarded to publishing process.
- Editor(s) may require additional materials or changes from authors during copy editing, composing, grammatical editing and/or proof reading steps.
- A fast track review system is in place upon deposition of additional processing fee (Rs. 20,000), however we do not encourage such route and should be employed only in significant circumstances. Moreover, this does not ensure that manuscript if accepted would be published on priority.
- Post-publication review and peer review is encouraged and is managed through letter to the editors.

11. STATEMENT OF INFORMED CONSENT

We follow ICMJE and COPE Guidelines for appropriate consenting. Patient's privacy should not be breached without taking consent. In written descriptions there should not be any specifications regarding patients including names, hospital numbers, photographs or pedigrees unless the information is needed for scientific purposes and the patient

allows for publication with written informed consent. It should be disclosed by authors to the patients that any identifiable material could be available on the Internet or in printed form after publication. Patient consent ought to be written and archived with the journal, the authors, or both, as settled by local rules and regulations. Applicable laws vary from territory to territory, and journals should make their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are de-identified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

- International Committee of Medical Journal Editors ("Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals")

12. GUIDELINE FOR REVIEWERS

Peer review in all its forms plays an important role in ensuring the integrity of the scholarly record. The process depends to a large extent on trust, and requires that everyone involved behaves responsibly and ethically. Peer reviewers play a central and critical part in the peer-review process, but too often come to the role without any guidance and unaware of their ethical obligations.

Archives of Surgical Research follows COPE Guidelines for educating the reviewers for the review process.

13. ETHICAL EDITING FOR EDITORS

Becoming an editor of Archives of Surgical Research is an exciting but daunting task, especially if you are working alone without day to day contact with editorial colleagues. This short guide aims to summarize key issues and to provide links to relevant pages of the COPE website as well as those of other organizations. We encourage the editorial team to consult COPE and ICMJE resources frequently for their training and handling of the manuscript and various editorial issues.

14. GUIDELINES FOR JOURNAL MANAGEMENT

We believe that Archives of Surgical Research serves as an important part of the scientific literature. Hence, its management should be of the highest quality and ethically sound. We follow COPE Guidelines to manage the top hierarchy in terms of conflicts of interest and ethical considerations. We also following COPE Guidelines for maintaining relationship of journal management to the Pakistan Endocrine & Thyroid Surgeons Association to ensure editorial independence. The journal editorial teams meets periodically at least biannually. The editorial team is independent of the society and is managed by a transparent process two yearly as per the ethical confines suggested by COPE, ICMJE and local guidelines.

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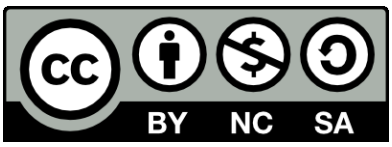

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