Difficult Decisions in Surgery:
An Evidence-Based Approach

Peter Angelos · Raymon H. Grogan
Editors

Difficult Decisions in Endocrine Surgery

An Evidence-Based Approach

Springer

Difficult Decisions in Surgery: An Evidence-Based Approach

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The complexity of decision making in any kind of surgery is growing exponentially. As new technology is introduced, physicians from nonsurgical specialties offer alternative and competing therapies for what was once the exclusive province of the surgeon. In addition, there is increasing knowledge regarding the efficacy of traditional surgical therapies. How to select among these varied and complex approaches is becoming increasingly difficult. These multi-authored books will contain brief chapters, each of which will be devoted to one or two specific questions or decisions that are difficult or controversial. They are intended as current and timely reference sources for practicing surgeons, surgeons in training, and educators that describe the recommended ideal approach, rather than customary care, in selected clinical situations.

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ISSN 2198-7750 ISSN 2198-7769 (electronic)
Difficult Decisions in Surgery: An Evidence-Based Approach
ISBN 978-3-319-92858-6 ISBN 978-3-319-92860-9 (eBook)
https://doi.org/10.1007/978-3-319-92860-9

Library of Congress Control Number: 2018950569

This Springer imprint is published by Springer Nature, under the registered company Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Dr. Grogan:
I dedicate this book to my wife Yuemi and my two beautiful girls Ivy and Emery. Thank you Yuemi for supporting me day in and day out even though I spend so many hours away from home. And thank you Ivy and Emery for being my own personal "Fountain of Youth." You truly are a joy, an inspiration, and a daily source of pride and motivation.

Dr. Angelos:
I dedicate this book to my wife Grace without whose support none of my efforts would have been possible and to my children. Without Audrey, Christian, Meghan, and son-in-law Zach, life would not be nearly as exciting nor as much fun. Thank you all for your understanding and support.

Acknowledgements

There are several people who helped make this book possible. First and foremost, we would like to say thank you to our friend and colleague Dr. Edwin Kaplan. We both have benefited tremendously from the wisdom, knowledge, and camaraderie of working next to Dr. Kaplan on a daily basis. His inquisitive nature and seemingly bottomless wealth of knowledge on the subject of endocrine surgery has certainly changed the way we (and many people throughout the world) practice. Without his friendship over the years it is safe to say that we would not be the same surgeons we are today, and thus, this book would be a different book.

We would also like to thank the unseen heroes who work hard day in and day out taking care of our patients and practice, because without them we truly would not have the time or energy to pursue an academic endeavor such as this book. Ms. Pat Schaddelee our administrative assistant who basically does everything for us, Mrs. Sandra Frausto our RN and practice manager who is the face of our practice for our patients, and Mrs. Joly Raju our nurse practitioner who knows more about endocrine surgery than many endocrinologists we know.

Finally, we would also like to say thank you to all the endocrine surgery fellows and research fellows we have worked with over the years, because again it is their hard work and dedication that help to make academic pursuits like this possible. But more than that it is the fellows that help shape the way we perceive and think of the future of endocrine surgery as a specialty, and their influence has helped shape the content of this book.

Introduction

> The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research—From "Evidence based medicine, what it is and what it isn't" BMJ Jan 13 1996 Volume 312

What Is a Difficult Decision?

Life is a constant stream of decision making. From the time we wake up until the time we go to bed, we are continually making decisions. Every action taken, every movement, every thought has derived in some way from the decision-making process. Decision making is so essential to everyday function that it seems like much of it happens without our consciously thinking about it. But have you ever stopped to think about what a decision is and how it is derived? When you stop to consider this for a moment, you realize that what seems like something simple and mundane, the act of making a choice, is actually quite complex. So complex that there are entire psychology departments, societies, and scientific journals dedicated to studying and understanding human decision making. For the context of this book, however, let us consider a simple definition. In essence, decision making is the process of selecting a course of action from among multiple alternative possibilities. The final result of this process being a choice that will ultimately lead to future consequences. In medical decision making, it is these future consequences that we are consciously and subconsciously weighing every time we give our advice or opinion to our patients. Decision making becomes difficult when there is uncertainty regarding the type or magnitude of the consequences of each alternative being weighed. The more uncertainty, or the bigger the possible consequence, the more difficult the decision. Uncertainty is inherent in the medical decision-making process. We as physicians expect that our tests are not perfect, good outcomes are not always guaranteed, and the risks and benefits of our interventions vary based on circumstance. After all, it often seems as if the whole point of learning about sensitivity, specificity, and receiver operator curves in medical school is to remind us of the fact that there is still a certain amount of "art" in the science of medicine.

What Is This Book About Anyway?

It is from this idea that a lack of information leads to difficult decisions that this book *Difficult Decisions in Endocrine Surgery* was created. We started with a simple premise, to identify clinical scenarios that we see in our academic endocrine surgery practice that made us pause for a minute and think "what in the world *are* the evidence-based data on *that*?" Fortunately for us as editors of this book, there is no paucity of unusual, rare, and interesting cases that come through a busy academic endocrine surgery practice. That aspect of endocrine surgery is in part what makes it such an interesting clinical practice and what drives so many interesting research questions. Aside from the rare and unusual we also felt that to keep the book contemporary and useful on a broader level it was important to include chapters on things that might be more common, but are still controversial. Once the questions were identified, we looked through available literature as well as past meetings of the American Association of Endocrine Surgeons to find our expert chapter authors. We asked these authors to use a strict set of guidelines to write evidence-based medicine chapters on each topic. The goal being to provide the reader with the highest level of evidence possible to allow for clinical decision making. You can think of this book almost as a premade literature search combined with an expert mentor giving his or her own take on that literature. At the time of the writing of this book, there really is no additional scientific evidence available on most of these topics outside of what you will find synthesized here.

What Is Evidence-Based Medicine Really?

A common theme you will see throughout this book is a lack of good, objective level 1 evidence for many of the topics being discussed. Using the definition of a "Difficult Decision" that we outlined above, it was inevitable that we would come up with a set of clinical scenarios that did not have much evidence to support their treatment or care. So you might reasonably ask, is this book then an evidence-based book? We would argue that yes, in fact, this is an evidence-based book of a high quality. We believe this to be the case because the meaning and purpose behind the idea of "evidence-based medicine" is often misunderstood. Evidence-based medicine is not a mechanical following of practice guidelines. As explained in an editorial by Dr. David Sackett, one of the pioneers and founders of the evidence-based medicine movement, "The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." In endocrine surgery, because there are many things that are unusual and rare we deal daily with cases and scenarios that do not have high levels of research-based evidence. In these cases, we can still practice evidence-based medicine, but we do this by integrating what little evidence is known with our own clinical experience along with the clinical expertise of those among us who have the most experience dealing with these situations. In this way, we learn and grow as individual practitioners and expand the broader field of endocrine surgery. We hope

you find this book informative and useful, as well as helpful for your patients. We also hope that you take the lack of evidence presented in this book not as a negative but as a positive motivator to continue to expand your own personal research endeavors, as well as those of the entire endocrine surgery community. It is the basic inquisitive nature that is at the core of what drives so many of the most important clinical research studies. If this book leaves you with more questions than answers, then perhaps, counterintuitively, we have done our job.

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Abbreviations

Misc

3HPT	Tertiary hyperparathyroidism
4DCT	Four-dimensional computed tomography
5-FU	Fluorouracil

A

AACE	American Association of Clinical Endocrinologists
AAES	American Association of Endocrine Surgeons
ACC	Adrenocortical carcinoma
ACS-NSQIP	American College of Surgeons' National Surgical Quality Improvement Program
ACTH	Adrenocorticotropic hormone
AIMAH	ACTH-independent macronodular adrenal hyperplasia
APA	Aldosterone-producing adenoma
ARR	Aldosterone-to-renin ratio
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the curve
AUS	Atypia of undetermined significance
AVS	Adrenal vein sampling or adrenal venous sampling

B

BAH	Bilateral adrenal hyperplasia
BMAH	Bilateral macronodular adrenal hyperplasia
BMD	Bone mineral density
BNE	Bilateral neck exploration

C

CaSR	Calcium-sensing receptor
CDA	Clinical decision analysis
CgA	Chromogranin A
CHPA	Cryopreserved heterotopic parathyroid autotransplantation
CT	Completion thyroidectomy
CT	Computed tomography

D

DFI	Disease-free interval
DFS	Disease-free survival
DXA	Dual-energy X-ray absorptiometry

E

EBM	Evidence-based medicine
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetra-acetic acid
EGFR	Epidermal growth factor receptor (EGFR)
ENSAT	European Network for the Study of Adrenal Tumor
ESMO	European Society of Medical Oncology
EUS	Endoscopic ultrasound

F

FHH	Familial hypocalciuric hypercalcemia
FIHP	Familial isolated hyperparathyroidism
FIRM-ACT	First international randomized trial in locally advanced and metastatic adrenocortical carcinoma reatment
FLUS	Follicular lesion of undetermined significance
FN	False-negative
FNA	Fine-needle aspiration
FNMTC	Familial non-medullary thyroid cancer
FP	False-positive
FTC	Follicular thyroid carcinoma

G

GAN	Greater auricular nerve
GEC	Gene-expression classifier
GLP-1	Glucagon-like peptide 1 analog
GRADE	Grades of recommendation, assessment, development, and evaluation
GRBAS	Grade, roughness, breathiness, asthenia, and strain
GY	Gray

H

HNR	Harmonics-to-noise ratio
HPF	High-power field
HPT	Primary hyperparathyroidism
HPT-JT	Hyperparathyroidism jaw tumor
HTC	Oncocytic or Hurthle cell variant of FTC
HTN	Hypertension
HypoCa	Hypocalcemia

I

IA	Interarytenoid
ICU	Intensive care unit
IDLE	Indolent lesions of epithelial origin
IHA	Idiopathic aldosteronism
IMRT	Intensity-modulated radiotherapy
IOPTH/IoPTH	Intraoperative parathyroid hormone
IOUS	Intraoperative ultrasound
^{131}I-MIBG	Iodine meta-iodobenzylguanidine
iPTH	Intact PTH
IRI	Immunoreactive insulin
IVC	Inferior vena cava

L

LA	Laparoscopic adrenalectomy
LCA	Lateral cricoarytenoid
LN	Lymph node
LOS	Length of stay
LSP	Less than subtotal parathyroidectomy
LTA	Laparoscopic transperitoneal adrenalectomy

M

MDCT	Multidetector CT
MEN 1	Multiple endocrine neoplasia type 1
MeSH	Medical subject headings
MGD	Multiple gland disease
MIBI	99mTc-sestamibi
MIP	Minimally invasive parathyroidectomy
MR	Mineralocorticoid receptor
MRI	Magnetic resonance imaging
MTC	Medullary thyroid carcinoma
mTOR	Mammalian target of rapamycin
MTNS	McGill thyroid nodule score
MWA	Microwave ablation

N

NANETS	North American Neuroendocrine Tumor Society
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NED	No evidence of disease
NGS	Next-generation sequencing
NIFT-P	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features
NIH	National Institutes of Health
NIS	Nationwide Inpatient Specimen
NPV	Negative predictive value
NR	Not reported
Ns	Not specified

P

PA	Primary aldosteronism
PAF1	Polymerase II–associated factor 1
PCA	Posterior cricoarytenoid
PCR	Polymerase chain reaction
PDC	Poorly differentiated thyroid carcinoma
PDGF	Platelet-derived growth factor
PDNET	Pancreaticoduodenal neuroendocrine tumors
PEI	Phonation efficiency index
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PHP	Primary (chief cell) hyperplasia

pHPT	Persistent hyperparathyroidism
PICO	Population, intervention, comparator, and outcome
PNET	Pancreatic neuroendocrine tumor
PPAR	Peroxisome proliferator-activated receptor
PPNAD	Primary pigmented nodular adrenocortical disease
PPV	Positive predictive value
PRA	Posterior retroperitoneal adrenalectomy
PRO	Patient-reported outcomes
PTC	Papillary thyroid cancer
PTC-FV	Follicular variant of PTC
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related peptide
PTMC	Papillary thyroid microcarcinomas
PTX	Parathyroidectomy
PV/SMV	Portal vein/superior mesenteric vein

Q

QALY	Quality-adjusted life years
QOL	Quality of life

R

R	Retrospective
RCT	Randomized controlled trials
RFA	Radiofrequency ablation
RH	Resistant hypertension
rHPT	Recurrent hyperparathyroidism
RLN	Recurrent laryngeal nerve
RPMI	Roswell Park Memorial Institute
RPT	Randomized, prospective trial
RTOG	Radiation Therapy Oncology Group

S

SABR	Stereotactic ablative body radiotherapy
SCIP	Surgical Care Improvement Project
SEER	Surveillance, epidemiology, and end results
SeS	Sestamibi
SF-36	Short form 36
SP	Subtotal parathyroidectomy
SPECT	Single-photon emission computed tomography

SRI	Surgically remediable aldosteronism
SSA	Somatostatin analogue
SSI	Surgical site infections
SSTR	Somatostatin receptors
SUS	Surgeon-performed ultrasound
SV	Splenic vein
SVS	Selective venous sampling

T

TA	Thyroarytenoid
TP/AT	Total parathyroidectomy and autotransplantation
TSH	Thyroid-stimulating hormone
TT	Total thyroidectomies

U

UFC	Urinary free cortisol
UICC	Union for International Cancer Control
US	Ultrasonographic
US FDA	United States Food and Drug Administration
USG	Ultrasonography
USG-FNAC	USG-guided fine-needle aspiration cytology
UTC	Undifferentiated or anaplastic thyroid carcinoma
UTI	Urinary tract infection

V

VEGF	Vascular endothelial growth factor
VFA	Vertebral fracture assessment
VHI	Voice handicap index
VHL	von Hippel-Lindau type 1

W

WHO	World Health Organization

Evidence-Based Medicine and the GRADE Approach

1

Sadeesh K. Srinathan

Abstract

Evidence-based medicine (EBM) is a term which entered the lexicon of medical practice in 1992. It can be defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients". In this chapter we illustrate how to practice EBM using a sequence of straight forward steps moving from phrasing a clinical question to making a judgment of the risk of bias in the evidence we encounter. We will then introduce and use the GRADE system of determining the quality of evidence to allow the surgeon a means of determining their confidence in the evidence that they use to guide their clinical practice.

Keywords

EBM · Evidence based medicine · GRADE · Bias · Study design · Systematic reviews · Trials

Introduction

Surgeons routinely make difficult decisions. In many cases, the difficulty lies in the need to make these decisions in the face of incomplete or unreliable information. An example of this in an individual patient is deciding to perform an exploratory laparotomy for an acute abdomen where the evidence from diagnostic studies may be

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P. Angelos, R. H. Grogan (eds.), *Difficult Decisions in Endocrine Surgery*, Difficult Decisions in Surgery: An Evidence-Based Approach,
https://doi.org/10.1007/978-3-319-92860-9_1

incomplete or contradictory. Another example, in terms of policy, would be to decide on the appropriateness of screening for occult malignancies where the evidence for early detection may be closely matched by evidence for undesirable events such as overtreatment.

In this book, difficult scenarios commonly encountered by the endocrine surgeon are presented. The authors of each chapter lay out the available evidence and make a recommendation as to the appropriate responses in these scenarios. They have followed the principles of evidence-based medicine to come to their recommendations and the purpose of this chapter is to present an overview of the process which led to their recommendations.

The phrase Evidence Based Medicine (EBM) came into widespread use after 1992 following a publication by Guyatt et al. [1], and is now commonly agreed to mean: '…the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" it also means that "… thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decision…" [2].

The practice of EBM can be carried out by using the following principles: (1) ask a clinical question, (2) locate the evidence, (3) appraise and synthesize the evidence, and (4) apply the evidence [3].

Asking the Clinical Question

On the face of it, asking the clinical question is straightforward. A patient problem is presented, and a question arises. For example, Mrs. Smith is presenting with a multinodular goiter. Should this patient undergo a total thyroidectomy or a subtotal thyroidectomy?

Going directly to Google with the key words "thyroidectomy for goitre", we obtain 250,000 hits, while Wikipedia results in 17 hits. Clearly, neither of these extremes is satisfactory in helping us to determine a surgical approach. A useful step is to convert this specific clinical question about Mrs. Smith to a form that will allow us to search for the relevant evidence. The *PICO* format, which is used throughout this book, is a useful tool for this purpose.

The *P* stands for Patient or Population and specifies the patient group to which the question refers, in this case it may be: (a) all patients with a multinodular goitre, (b) adult patients with a multinodular goiter, (c) adult patients with a non-toxic multinodular goiter (d) adult patients with a non-toxic multinodular goiter who have had a previous operation in the neck. It is apparent that each iteration of the definition of the population is more and more specific. These details are important, but we may limit the information available to us if we define our population of interest too narrowly.

The *I* is for the Intervention or exposure of interest and specifies what has happened to a group of patients such as an operation, or a diagnostic test. In our example

the intervention we are considering is a total thyroidectomy. However, there could also be specific issues that are considered important such as the use of drains.

The *C* refers to the comparator that we are interested in. In this case it is a subtotal total thyroidectomy, but again we should be mindful of specific details of the standard procedure that may be important for our specific question.

O stands for the Outcome of interest. It is very important to be specific about the outcome of interest as it is likely that various studies may have used different outcomes in the study design than the one you are interested. One study may have been focused on goiter recurrence, whereas another may have been focused on incidence of major complications. It is worthwhile to identify each outcome of interest in the specific clinical scenario and to order them in order of importance to the patient and surgeon so that an overall assessment of the utility of an intervention can be made.

Taking these features of the clinical question into account, we can frame the scenario for Mrs. Smith in the following PICO question:

> In an adult patient with a non-toxic goiter, does a total thyroidectomy result in 1) decreased mortality 2) lower or same goiter recurrence 3) fewer complications than a subtotal thyroidectomy?

P: Adults with a non-toxic multinodular goiter
I: total thyroidectomy
C: subtotal thyroidectomy
O: (1) operative mortality, (2) goiter recurrence, and (3) complications

It is worth considering when reviewing the chapters in this book, whether the PICO questions chosen by the authors are *sufficiently* similar to your own formulation of the question for their findings and recommendations to apply to your specific case.

Finding the Evidence

Often the first step in a literature search is to go to PubMed, the interface to access the Medline database of citations in the National Library of Medicine in the United States. However, a search of "total subtotal thyroidectomy" produces 776 citations. This is more than we can reasonably go through for the purposes of answering a specific question for a patient. But, if we use the Clinical Queries page in PubMed which uses an algorithm to deliver focused studies relevant to clinical practice [4], we obtain citations for 26 systematic reviews and 313 clinical studies, much better. Alternative search engines include TRIP database (http://www.tripdatabase.com/) and SUMsearch (http://sumsearch.org/), which use multiple databases including Medline, EMBASE, and databases of guidelines and technology may also be used. Last, but certainly not least is the expertise available through your local medical librarian who will be well versed in the methods of constructing a PICO question and finding the relevant information from the medical literature.

Appraising the Studies

Once we have found the studies of interest, the next step is to identify the "best evidence". The concept of "best evidence" assumes a hierarchy of evidence. But to apply a hierarchy, it is important to understand the types of study designs and their use in answering specific types of clinical questions. Grimes and Schulz [5] provide a useful taxonomy of study designs (Fig. 1.1). In general, questions related to the superiority of one intervention over another (or no intervention) are best answered by experimental studies where one group of patients are assigned to the intervention by a bias free method, while another receive a comparison intervention. The gold standard for the experimental study is a well-designed randomized trial. Other types of clinical questions such as that of prognosis are appropriately answered using cohort studies, while questions of diagnosis rely on comparing the performance of a diagnostic test to a gold standard.

All study types have the potential for any number of biases which may lead to a finding which deviates from the "truth" [6]. The tools of critical appraisal are used determine the type and extent of these biases in the design and conduct of the study and make a judgment of how it may have affected the findings of the study and the extent to which it undermines our confidence in the validity of the findings.

There are many excellent resources and tools to guide us in the specifics of appraising the medical literature and practicing EBM and these are listed in the recommended readings.

What happens when despite the best formulation of a question and literature search we are unable to find the high quality systematic review or randomized trial to guide us? Do we abandon the principles of EBM? Again from Sackett: "Evidence based medicine is not restricted to randomized trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions…. However, some questions about therapy do not require randomized trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomized trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there." [3].

Although we can approach each problem we face by formulating a question and finding the best available evidence, individual clinicians are unlikely to have the time or resources to do this for all possible scenarios. To illustrate: our example PICO question generated 85 results using PubMed. To identify and read through the abstracts or articles for this one question can take a considerable amount of time. To then appraise each study for its quality and relevance will add more.

The alternative to searching for each question has been standard textbooks, which seek to distill the evidence and guide clinical practice. The authors of these textbooks have always made decisions about which studies to consider and judgments about their confidence in making recommendation based on this evidence. However, these judgments and decisions have not been transparent. And although there are many schemes in use which grade the level of evidence and have been increasingly used in textbooks, it is not clear on what basis these decisions of grade

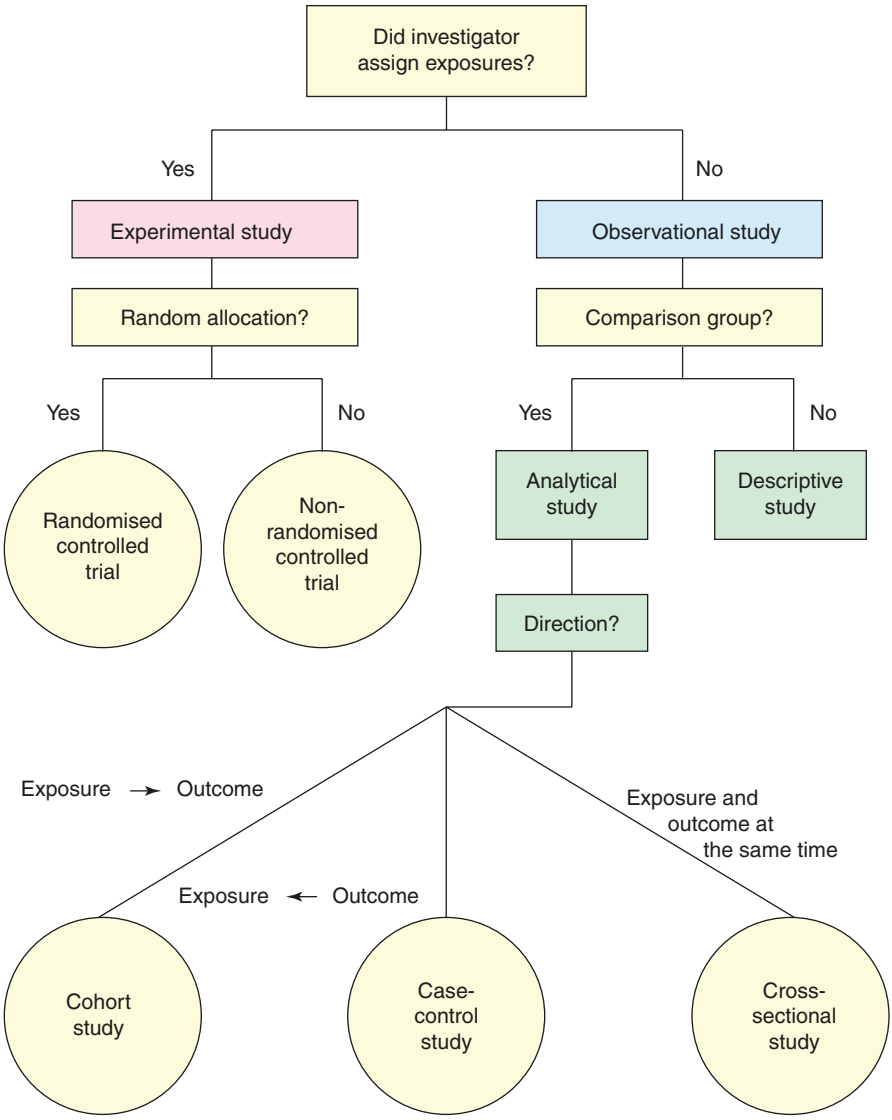

Fig. 1.1 Algorithm for classification of types of clinical research. From Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet. 2002; 359(9300):57–61; with permission

were specifically arrived at [7]. A good systematic review makes transparent the question, the search strategy, and the rules for inclusion of studies and on what basis the quality of the study is determined. However, the final assessment of the overall quality of evidence and the subsequent recommendation arising from this evidence is often obscure.