Evidence based medicine (surgery)

One of the key elements of improving the health care system in the world is to respect the recommendations resulting from the so-called evidence-based medicine (EBM). Improvement considering clinical decision-making in medicine, including surgery may be attained when best evidence based medicine (EBM) will be combined with the following:

– clinical experience,
– medical knowledge in the field of surgery supplemented by constant access to medical databases,
– communication skills in order to engage the patient and his social environment,
– proper assessment of the clinical situation in surgery.

According to Rothenberger, such understanding of the functioning of the health care system based on the above-mentioned principles forms the basis for the application of evidence based surgery in everyday clinical practice (1). Defining the problem of surgery, followed by systematic exploration and evaluation of the level of the investigated surgical problem, possibility of applying individual medical solutions based on EBM and evidence-based surgery (EBS) in a patient and in accordance with the highest level of evidence, and finally systematic evaluation of therapeutic results are essential stages of creating surgery fulfilling the highest criteria of quality (2).

This problem seems to be simple and obvious in assumption, but in practice, it is difficult to achieve by the surgeon. In comparison to other non-interventional medical specialties, surgical disciplines including surgery, create special conditions that clearly define and limit the ability to conduct and apply evidence based medicine. The above-mentioned is influenced by many objective conditions and numerous problems resulting from the specificity of being a surgeon.

In order to follow progress in medicine one should read 19 articles everyday, 362 days a year. Every year one may observe the doubling of the number of medical publications (3). It is well-known that in 40% of patients evidence based medicine is not applied. Additionally, the surgeon’s personality (self-confidence, impatience, need to take fast and responsible decisions) is not conducive to adopting all medical facts. What’s more, only approximately 60% of surgeons are aware of the functioning of EBM principles: the above-mentioned percentage is higher amongst surgeons practicing in university reference centers, and conducting research. Considering the aspect of age, young surgeons, resident and specialty surgeons are more willing to introduce EBM principles into surgery (3).

Therefore, for the surgeon a major challenge is to find the best documented medical data associated with his clinical practice. Thus was born the need to create understandable, easy-accessible, and easy-to-analyze databases. Such databases would be, or already are, the basis for the novel pursuit of education, identifying research problems, or establishing surgical guidelines at the highest level of evidence (2).

Another problem is the ability to use these databases. In Western countries the applica-
tion of EBM principles in surgery has been solved for many years. In Poland, it is a relatively new issue, and the overall knowledge of physicians concerning EBM (including surgeons in EBS) appears to be at a very low level. One solution is the use of diagnostics and therapeutic standards, and methods of objective evaluation concerning surgical results, based on scientific society and central institution recommendations dealing with the health care system in the United States, Canada, Great Britain, and the European Union.

In addition to publications analyzing clinical trial results, the above-mentioned countries conduct educational campaigns on the principles of EBM, including the training of medical students (4-6). In 2000, the American College of Surgeons and Canadian Association of General Surgeons came out with an initiative to create a journal dealing with publications based on EBM. Since 2005, the electronic version of the journal is available (Evidence Based Reviews in Surgery – EBRS) publishing prospective, randomized controlled trials (RCT) in the field of surgery, as well as review articles teaching proper use of the methodology of clinical trials. The need to record health care system principles has already been recognized in the seventies of the past century. The English epidemiologist Archie Cochrane and Canadian physician David Sackett developed the principles of objectivization of facts and postulated the need to create a database, which would be able to document medical evidence. Cochrane’s publication from 1972: „Effectiveness and efficiency: random reflections on health services” contains the following conclusion: „the health care system in Great Britain was not always based on evidence data. Its effectiveness and efficiency were entirely incidental” (2). On the other hand, Sackett was the first who postulated for a systematic approach to the analysis of published scientific data as the ground for clinical decisions. He underlined the significant importance to conduct RCT’s in clinical practice (7).

Evidence based trials and recommendation levels

One of the main objections against clinical trials were and still are reservations concerning their quality. Initially, one observed clinical case reports followed by retrospective investigations. The above-mentioned continues to be the most common in surgery. In accordance with the intentions of Cochrane and Sackett, at the initiative of American and British Medical Societies, Cochrane’s Collaboration database was established, which contains publications in the field of clinical medicine, including surgery.

Since the nineties of the twentieth century, based on Sackett’s propositions, publications were catalogued according to the so-called “levels of scientific evidence”. Level I contains publications obtained from meta-analysis, randomized, multicenter trials, properly planned controlled clinical investigations. Level II contains publications obtained from objectively controlled clinical trials without randomization, cohort surgical trials, and retrospective, uncontrolled trials. The lowest III level of evidence concerned clinical observations and opinions of panel experts in the field of surgery (7). Independently of the level of evidence, conclusions drawn from the clinical trial results also possess appropriate levels of evidence. Level A – high level of recommendation (I, II evidence levels) with an unambiguous interpretation of results by the panel of experts. Level B corresponds to a high level of recommendation with an unambiguous interpretation of results and conclusions by the panel of experts. Level C is characterized by a low level of recommendation (II and III level evidence) and incompatible interpretation of results and conclusions by a panel of experts. In case of level D the recommendation is lowest without empirical evidence. Some of the so-called “surgical experts”, for years regarded as indisputable and irrefutable medical authorities, do not agree with the modern doctrine, according to which one accesses the quality of clinical research and surgical treatment. Their role has been finally verified and the presented position is the lowest, considering recommendation ratings (7).

In addition to the Cochrane Collaboration (approximately 30000 titles to analyze, considering evidence IA) new databases are created on different research problems or scientific specialties, such as the National Library of Medicine – MEDLINE, CONSORT, which deals with the standardization of randomized investigations, or publications considering prospective studies: Evidence-Based Medicine
Limitations of clinical trials in surgery

Reviews – Journal of Evidence-Based Medicine, and Evidence-Based Reviews in Surgery. There is no doubt that the best way to assess treatment results or surgical intervention is to perform prospective randomized clinical trials (PRCT) – evidence level I, especially meta-analysis on the basis of such investigations – recommendation A.

It should be noted that the quality of evidence in surgical literature is rather mediocre. The brief review of surgical journals points to the fact that evidence level I in case of surgery is rarely observed. Prospective, randomized trials constitute only 5-10% of surgical journal articles, the remaining include case reports: >50%. The simple summary of the number of IA articles in the most respected surgical journals during the period between 2002-2003, such as Annals of Surgery, Archives of Surgery, British Journal of Surgery or Surgery enabled to identify only 113 such publications with randomization. While in reputable medical journals (during the same period): British Medical Journal, JAMA, Lancet, New England Journal of Medicine, 551 such publications were observed. In the last two years the number of publications in the above-mentioned surgical journals with recommendation IA increased to 185, while in case of medical journals amounted to 566 (8).

Detailed analysis of Cochrane’s database performed by Slim in 2005 confirmed the unsatisfactory situation considering the quality of clinical investigations in surgery. Of the 3181 meta-analysis with the highest level of evidence and recommendation only 169 (5.3%) concerned problems of surgery. Similarly, amongst the 378160 controlled, clinical trials, only 13200 (3.4%) were related to surgery (3).

Taking into account all the issues presented in surgical journals, one may specify some 260 research problems. According to experts approximately 40-60% of the above-mentioned could be solved by means of PRCT trials with EBM principles. However, in practice only 6% of the articles were based on RCTs. Publications with the highest level of evidence and recommendation IA concerning abdominal cavity tumors constitute only 6.7% of all publications on the subject (9). The MEDLINE database contains more than 11 million articles concerning solid abdominal tumors, however, only 0.03% are prospective, randomized trials (9).

Definitely, one may observe the domination of articles with an undetermined level of EBM, not having the nature of a medical experiment (non-randomized, observational, population-based), quantitative rather than qualitative.

The reasons for this are believed to be associated with the continuously changing methodological principles, which are currently used in clinical investigations. Furthermore, attention is paid to the problem of the possible interest of advisers concerning specific recommendations. Some authors dealing with the quality of trials in surgery point to the mediocre ability of surgeons to the methodological assessment of articles, and their use.

Clinical study problems in surgery

Difficulties considering the use of clinical trials in surgery are demonstrated by the fact that even in highly developed countries, standard recommendations concerning evidence levels in case of diagnostics and surgical treatment are highly unsatisfactory. In case of the British recommendations <20% constitute A recommendations, nearly 50% - B recommendations, and 30% - C recommendations. According to American recommendations evidence level IIA is the standard (10).

One of the reasons for the low level of clinical trials in surgery includes methodological errors. Nearly 56% of RCT trials in oncological surgery were poorly planned. Only 58% were properly randomized, and in only a few, statistically significant differences were obtained, most likely being associated with type II statistical error (11).

Hall conducted a review of 364 randomized trials from 10 leading surgical journals during the period between 1988 and 1994 (12). Considering 8 methodological features, such as the clear description of the surgical intervention, proper control group, inclusion criteria, randomization method, sample size calculation, definition of endpoints, undisturbed evaluation of results, and documented adverse effects, he claimed that none of the articles met the criteria of 100% correctness. Most objections related to the selection of the randomization method (27% of articles fulfilled the criteria) and determination of the sample size - number of patients required to obtain a statistically significant result (only 19%).
Results of the above-mentioned analysis were so surprising that Horton in the pages of the *Lancet* posed the thesis of the shortcomings of clinical trials in surgery (13). Indeed, many questions arise, unfortunately, thus far, there is no response in regards to the difficulties in planning and conducting clinical trials in surgery. Traditionally, surgical practice was based on the understanding of the pathophysiology of diseases, introduction of novel surgical techniques, and evaluation of treatment results in retrospective analyses. New conditions of conducting clinical trials, being in accordance with EBM principles forced surgeons to comply with the random selection of patients, that is to use proper randomization methods. Problems with randomization in case of surgical trials are unable to take into account the ethical issues, emergency indications, palliative treatment, the learning curve, standardization of surgical techniques, and others. When choosing between surgical and conservative treatment randomization may not always be observed, since the patient directed to a surgeon is always considered as a surgical candidate. Additionally, randomization does not consider patient preferences, which might significantly affect the rate of recruitment in case of RCTs. The patient will usually choose between treatment methods, rather than be randomly assigned to one of the methods (13, 14). In case of surgical RCTs compliance with the protocol in a larger manner affects the freedom of the patient, as compared to pharmacological studies. The basic principle in clinical pharmacology- double-blind study is virtually impossible in surgery. The term *sham surgery* raises major ethical resistance (15).

The introduction of patients into randomized, clinical trials might be perceived by the surgeon as loss of professional autonomy, as often without violating the study protocol, surgeons cannot undertake decisions, being specific for individual patients. The above-mentioned problem may be humorously presented: the surgeon as opposed to a pill is continuously learning, while the pill is not. This affects the different results obtained from many centers, and between the early and late period of the study. The clinical studies in the field of surgery do not consider the “learning curve” of a given therapeutic procedure. Most authors, regardless the surgical specialty considered the surgeon as an independent prog-

nastic factor, possibly influencing the percentage of complications, perioperative mortality, and distant results. The *high volume hospital* and *high volume surgeon* principle is commonly known. Therapeutic results, in contrast to results obtained in case of a given dose of a particular drug, in case of clinical studies in surgery depend on the experience of the center, as well as experience of the surgeon and number of performed operations (15).

Difficulties in conducting RCT studies in the filed of surgery might be associated with the specific condition of a given patient: concomitant diseases, social and economic condition. Additionally, in case of most surgical studies elderly patients are not usually the subject of interest (3, 15). One should also consider the financial implications for the surgeon, patient, and study center involved in the RCT study, which might influence the course of the clinical trial. The general opinion shows that equipment and diagnostic companies are most interested in conducting clinical trials in surgery. The above-mentioned might affect the results obtained in the study. Thus, many surgical interventions may be beyond the reach of RCT type studies.

Another factor limiting the availability of clinical trials in surgery is the possibility of recruiting patients for the study. The recruitment index in case of surgical studies is usually low, and achieving the planned sample size is generally more difficult. The greatest threat to the success of RCT studies in surgery is the difficulty in recruiting a sufficient number of patients. The understanding of the parameters affecting the size of the study group, very valuable when planning clinical trials is basis for the critical evaluation of scientific results, and their use in clinical practice (16).

Similarly important is the choice of the research hypothesis, either zero or alternative. The selection of the unilateral alternative hypothesis enables to show that one therapeutic method is better than another. In case of the bilateral option of the alternative hypothesis one therapeutic method is potentially better than the other. Generally, one should choose the bilateral alternative hypothesis, unless it is certain that the difference between both surgical interventions is aimed in only one direction (16). The assumption of different threshold variants determined the effective-
ness of therapy and might be associated with the need for random recruitment (30 patients with a 40% difference efficiency or 3000 patients with a 5% difference efficiency, considering both therapeutic variants). Only a few clinical studies in surgery can be carried out with such a large number of patients. The verification of a given hypothesis may be associated with the need to conduct multicenter, coordinated, prospective, randomized trials with absolute compliance for the quality of care, proper documentation maintenance, etc... Certainly, the size of the study group should be chosen in such a way as to minimize the probability of obtaining a false-negative or false-positive result (type I and II errors).

Their is a general belief that significant changes and progress in surgical treatment should be rather based on scientific evidence. In this context, the availability of data from completed clinical trials in surgery seems essential. Generating statistically significant and reliable evidence concerning the efficiency and safety of novel surgical procedures remains a challenge for the future. One way to achieve progress in surgery is to implement pre-clinical and clinical trial concepts into novel surgical research. For this purpose, one may create panels to discuss research projects, its implementation, and analysis of clinical trial results. It is also very important to systematically review data and conduct meta-analyses, which are effective methods to gather available clinical practice data. Additionally, they provide valuable means for proper topic selection, study protocol planning, and execution of the randomized, clinical study. An example illustrating the contemporary issues associated with the introduction of a new surgical technique may be the position of the surgical environment concerning endoscopic procedures through natural orifices – NOTES (Natural Orifice Transluminal Endoscopic Surgery). In February 2005, New York was host to a conference, which was attended by 14 leading representatives of scientific societies: American Society of Gastrointestinal Endoscopy (ASGE) and Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). The participants of the conference expressed their belief that the introduction of NOTES into clinical practice might prove beneficial for the patient: reduction of pain, faster recovery, and better cosmetic effect, as compared to current laparoscopic techniques. Experts also determined the limitations, which prevent further development of the NOTES technique, and formulated a list of further actions and recommendations for all those who subscribe to the so-called NOSCAR (Natural Orifice Surgery Consortium for Assessment and Research) platform, and will be involved in research and NOTES evaluation for further progress. It was established that the team should be interdisciplinary, comprising an experienced interventional endoscopist and laparoscopic surgeon. The participants of the platform should be members of SAGES and/or ASGE, and the center should comprise laboratory facilities enabling research and training on animals. All participants agreed to release the study results to other centers taking part in the joint meetings of NOSCAR every six months. Additionally, all procedures performed on human beings should be accepted by the local committee-Institutional Review Board (IRB). The first procedures performed on humans should be officially registered, and the preliminary results even if they turn out unfavorable, should be reported and discussed at National Society conferences and study trials. In the event of the availability of a new method the next step will include the beginning of early investigations comparing NOTES with alternative laparoscopic procedures. The head of the SAGES and ASGE societies remain full of hope and enthusiasm for this new technique and the safety of its development and introduction into clinical practice, which might in the future prove beneficial for the patient, as a new minimally invasive procedure (17).

Among the arguments against RCT type clinical studies in surgery, one must point to the fact that they do not bring anything new into surgical practice, announce the end of “surgical art”, ignore the importance of the patient, present the approach of a “cookbook” (3). The dissemination of recommendations, according to EBM and EBS principles did not improve, as expected, the clinical and surgical practice. In addition, the above-mentioned compels every surgeon to possess proper software facilitating decision taking in surgery, requires assess to useful surgical data by means of professional internet pages. The whole requires the introduction of organizational improvements facilitating the use of evidence based surgery.
The ideal physician should fulfill all criteria and principles of EBM, EBS, or GCP, regardless his health condition, time spent at work, costs, loaded with databases knowledge, being a great diagnostician, clinician, and therapist. Will it be possible that such a super evidence-based surgeon function? We do not know for sure but we are determined to comply with the words of a surgical authority from one of the best oncology centers in the world: "The basic element in clinical practice is to understand the rationale of our decisions in terms of diagnosis and planned treatment. The above-mentioned requires medical knowledge based on EBM principles". Ari Brooks – Memorial Sloan-Kettering Cancer Center, New York (9).

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