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Alternative methodological approach to randomized trial for surgical procedures routinely used

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ABSTRACT

Background: In medical oncology, changes in practices are almost always based on randomized trials but medical history shows that it is different in surgical oncology. In the past, many surgical procedures were routinely performed without a rigorous evaluation of the risk-benefit. To highlight the complexity of developing randomized surgical trials, disquisitions on methodology presented in the medical literature. This is particularly true when we consider breast reconstruction after surgical treatment for breast cancer. It is illusory to perform and conduct a randomized clinical trial (RCT) when a surgical procedure is routinely used by most surgeons.
Methods: As a case study, we present the scientific rationale and the design of the MAPAM01 trial which evaluates the security of the nipple sparing mastectomy. Other alternative approaches, such as propensity score and CUSUM, are presented.
Results: In this situation, to design surgical trials using alternative methodological approaches present a particularly important challenge both for surgeons and methodologists. Alternative approach to randomized trials can be useful to evaluate surgical procedures routinely used.
Conclusion: Close collaboration between surgeons and methodologists is needed to propose appropriate and well-designed surgical trials.

1. Introduction

In medical oncology, changes in practices are almost always based on randomized trials but medical history shows that it is different in surgical oncology [1]. Indeed, in the past, many surgical procedures were institutionalized into practice before systematic demonstration of a favorable risk-benefit ratio, a cost-effectiveness and quality of life evaluation by comparative prospective trials. For example, Halsted presented in 1898 a case series of patients which underwent Halsted's radical mastectomies [2]. After this presentation, Halsted's radical mastectomy became the standard treatment even for small breast cancers. This procedure saved the life of high number patients, but in the 50's different randomized trials questioned the uselessness of this procedure. In fact, there was no survival benefit for patients who underwent Halsted mastectomy compared to those who underwent conservative surgical procedures [3].

Undoubtedly surgical randomized trials were difficulty to conduct. In Section 3, the different barriers and specific challenges of randomized surgical trials will be reviewed. After presenting the example of the MAPAM-01 trial (Section 3), different alternative approaches will also be discussed in Section 4.

2. Challenge of randomized surgical trials

Designing, conducting and analyzing a randomized trial present practical and methodological challenges, particularly in surgical procedures. The unique nature of surgical trials is commonly cited in the literature as a barrier to perform clinical trials for surgical procedures. The different barriers to perform randomized surgical trials are well reported in the medical literature (Table 1) [4–6]. Generally, surgical strategies are developed by a single surgeon or a small group, and ensuring standardization of surgical procedure is a difficult task. One source of variability is the surgeon who can propose technical variation of the same procedure. Another source of variability are preoperative, post-operative care and experiences of operative teams (anesthetist, nurse, …). To limit variability, participation in the trial may be limited to a certain number of centers and surgeons. This strategy increases the likelihood to observed treatment effect, but reduces the trial feasibility.

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Table 1
Barriers for randomized surgical trials.

Barriers for randomized surgical trials
– Standardization of the surgical procedure
– Timing of trials
– Blinding of subjects and investigators
– Randomization for primary surgical treatment
– Patients and surgeons preference
– Difficulties in recruitments
– Ethics and legality consents

Another strategy to avoid between-group imbalance is to stratify randomization by surgeon or center.

Another critical issue in the design of surgical trial is the timing proposed in randomized trials. In fact, there is a learning curve for any surgical procedure. If the Randomized Clinical Trial (RCT) is proposed early, the trial will reflect the results of the learning curve and not the real results of the procedure. In fact, false conclusion against the novel procedure may be associated to the imbalance in the surgical expertise between control and experimental intervention. To minimize the effect of learning curve, several approaches were proposed in the literature [7]: the recommended annual surgical volume, outcome consistent with good clinical practice, training for participating surgeons… On the contrary, if the RCT is performed later, patient recruitment is difficult due to widely acceptance of the technique by the surgical community. In this context, there is; rightly or wrongly; equipoise lost which is the central principle of randomized trial. The concept of equipoise (or uncertainty principle), which requires that there is no decisive evidence that the experimental strategy being studied is superior or inferior to the standard strategy, is crucial for randomized clinical trials. In the NSABP B-06 trial (1803 patients), which compared lumpectomy to mastectomy, patients were enrolled between 1976 and 1984 [8]. One reason advocated by the investigators for not entering all eligible patients, was linked to surgeons and patients preferences [9]. This reason is particularly true in terms of breast reconstruction after breast carcinoma [10]. In this setting, there are multiple possible interventions (simple implant-based reconstruction, pedicled flap, free flap) which may influence the inclusion or not in randomized trials because of patients and/or surgeons preference. Between 1995 and 2014, only 13 breast reconstruction randomized trials were performed [11]. The two trials, which aimed to evaluate major questions (timing and type of breast reconstruction), were monocentric and stopped prematurely due to insufficient recruitment [12]. Moreover, accrual rate is often overestimated. In fact, only 10 to 50% of patient potentially eligible patients consent to participate in a surgical trial [13]. To perform a randomized trial, it is primordial that surgeon and patient equipoise exist for at least as many pairs (Patients/surgeon) to complete accrual. The randomized trial ACOZOG Z0011, which compared axillary lymph node dissection to no further axillary specific treatment in patients with clinical T1-2 N0 M0 breast cancer who had a positive sentinel node, was closed due to low accrual [14]. With a planned accrual of 1900 patients, only 891 patients were randomized between May 1999 and December 2004. Despite the small sample size and limited statistical power (only 29 loco-regional recurrence observed), treatment paradigm changed based on the results of this trial and many breast cancer teams limited axillary treatment to sentinel lymph node dissection in this patient population [15]. However, there is no consensus for axillary lymph node dissection between scientific societies for patients with one or two sentinel nodes with macro-metastasis [16]. The National Institute for Health and Care Excellence recommends axillary treatment. By contrast, the American Society of Clinical Oncology should not recommend axillary lymph node dissection for patients receiving breast-conserving surgery with conventionally fractionated whole-breast radiotherapy [17]. For the European Society for Medical Oncology, the results of the ACOZOG Z0011 need to be confirmed [18]. At the Axillary management consensus meeting (Association of Breast Surgery Conference, 2012), it was shown there are currently an equipoise in terms of effective axillary treatment. Voting results showed than 68.2% of the participants were agreed to randomize patients. Following this consensus, the POSTNOC trial (NCT02401685) is actually ongoing to address the weaknesses of the ACOZOG Z0011 study. Main objective of this randomized non-inferiority trial is to assess whether adjuvant therapy alone is no worse than adjuvant therapy plus axillary treatment, in terms of axillary recurrence within 5 years for breast-conserving surgery and mastectomy patients with one or two sentinel nodes macro-metastases. One thousand nine hundred participants need to be randomized in this international multicenter phase III trial, which is open to accrual in > 50 centers since July 2014. As the accrual is still ongoing, an Australian team published an advocacy to Australian and New Zealand investigators entitled: “surgeon knows best versus breast cancer surgical clinical trial equipoise: a plea for the sake of future trials” [19]. The authors argue the equipoise in this setting and the importance to not reproduce the errors made on the previous study. They highlight the importance to perform this trial in rigorous conditions (*e.g.* without selection bias, and correct accrual).

Alternative methodological design to randomized trials can be useful, when a procedure has been accepted as routine clinical practice without previous well conduct randomized phase III trials and when there is a loss of equipoise [20].

3. Example of MAPAM01 trial

3.1. Scientific rationale for MAPAM01 trial

Considering localized breast cancer, mastectomy is actually performed in approximately 20–30% of cases [21]. Immediate breast reconstruction (IBR) is generally offered to patients particularly when radiotherapy will not be indicated. In case of IBR, surgical mastectomy standard is "Skin Sparing Mastectomy" (SSM). The nipple areolar complex (NAC) is removed because of the observation that the NAC and its adjacent ducts may harbour tumor cells that have spread distally inside the ducts from the primary tumor. Then, reconstruction is performed by flap and/or implant according to the patient anatomy, her comorbidities, her wishes and surgeon's proposals. SSM has been validated by retrospective studies with a rate of local recurrence which varies between 0 and 10.4% depending on the duration of follow-up [22]. According to the literature data, the expected rate of local recurrence at 60 months is approximately 4% (1% per year). However, there is no randomized trial addressing this subject. Lanitis et al. [22] published in 2010 a meta-analysis of literature: 3436 patients from 7 retrospective studies were included. Aim of the study was to compare skin-sparing mastectomy *versus* non-skin sparing mastectomy. No statistically significant difference was found concerning local recurrence rates (OR = 1.25 [95%CI, 0.81–1.94]).

NAC can be reconstructed in a separate procedure, but this surgical step of the reconstruction has been reported as the most disappointing moment in the patient course [23]. Nipple sparing Mastectomy (NSM) preserves the skin and the NAC. This technique is accepted in prophylactic surgery for patients at high risk of breast carcinoma, due to *BRCA* germinal mutation for example. It is usually recognized that NSM has a major impact on patient body image, sexuality, psychological adjustment, and on short and long term quality of life concerns [24]. In cancer-proved setting, NSM is controversial regarding oncologic safety and complication rates. Available data on therapeutic NSM are based on retrospective, mostly small series with limited follow up. Reported local recurrence rate (skin, chest wall or nipple areolar complex) varies from 0 to 10% (Table 2). With 934 procedures and median follow-up of 50 months, Petit and al published the largest series [25]. They observed a local recurrence rate of 3.6% for invasive carcinoma and 4.9% for ductal carcinoma *in situ*. Methodology of these different retrospective studies can be questionable due to the heterogeneous patient