# Chapter 8
# Ethics and Evidence: Is Evidence from Randomized Controlled Trials Necessary to Firmly Establish a New Therapy?


**Abstract** In this chapter, I explore ethical issues that may arise in conducting randomized controlled trials to test therapeutic hypotheses, and address the question of whether randomized controlled trials are always necessary to firmly establish a new therapy. I illustrate the ethical issues by discussing several studies of extracorporeal membrane oxygenation therapy in newborn infants, and subsequently describe two cases in which a new cancer therapy was firmly established without randomized trial data: combination chemotherapy and radiation therapy in cancer of the anal canal, and multi-drug chemotherapy for disseminated carcinoma of the testis. I conclude that considerable opinion exists that the primary duty of physicians (*qua* physicians) is to the patients under their care and that conducting research is secondary, notwithstanding the immense benefit of medical research to society. I also conclude that randomized controlled trial data are sometimes unnecessary when other convincing data are available.

## 8.1 General

It seems to have become generally accepted among the medical community that evidence from RCTs is the most convincing type of evidence for establishing a new therapy. For many, it would appear that the *only* reliable evidence for this purpose comes from RCTs. Thus Tukey, for example, states, "Many of us are convinced, by what seems to me to be very strong evidence, that the only source of reliable evidence about the usefulness of almost any sort of therapy or surgical intervention is that obtained from well-planned and carefully conducted randomized, and, where possible, double-blind clinical trials" (1977, 679). And, Cowan writes, "With some exceptions, participation of any group of patients in a nonrandomized trial is wholly unjustified and unethical since nothing can be learned from it" (1981, 10).

Greenhalgh has maintained that RCTs are unnecessary when a clearly successful intervention for an otherwise fatal condition is discovered (2010, 39). But what of the more usual case, where it is claimed that based on evidence that at least by some may be regarded as preliminary, a new therapy is equivalent to, or superior to, an



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already established therapy for some condition? Must RCT evidence be acquired to establish the new therapy?

I will argue that the answer to the above question is, at least sometimes, "no," and illustrate this by discussing three examples: extracorporeal membrane oxygenation (ECMO) therapy for the treatment of respiratory failure in newborn infants, combination radiation therapy and chemotherapy for carcinoma of the anal canal, and multi-drug chemotherapy for disseminated testicular carcinoma. In the ECMO case, although RCTs were done, I will argue that they were unnecessary to establish ECMO as superior to currently available alternative therapies. This case raised serious ethical issues and has been previously discussed by others.[1] In the case of carcinoma of the anal canal, combined radiation therapy and chemotherapy became firmly established over surgery as initial treatment without an RCT being done. Similarly, three-drug chemotherapy became firmly established as standard therapy in disseminated testicular carcinoma without an RCT.

## 8.2 ECMO

### *8.2.1 Background and RCTs of ECMO*

Respiratory failure is one of the major medical problems in newborn infants, and is a common cause of death in this age group. Hyaline membrane disease accounts for most of the cases; other causes include meconium aspiration syndrome, neonatal sepsis, and persistent fetal circulation syndrome (Bartlett et al. 1982).

Prior to the 1980s, conventional therapy consisted mainly of the use of a tracheal tube and mechanical ventilation, with supplemental oxygen. Most infants did well on this regimen, but a minority, between 5% and 10%, failed to respond and died of respiratory failure. Another 10% developed bronchopulmonary dysplasia, a disabling lung condition thought to be due to the pressure and oxygen used for treatment. During the 1970s and early 1980s, Bartlett et al. (1982) developed ECMO as an alternative therapy for respiratory failure in the newborn. The procedure involves the use of a modified heart-lung machine that can support gas exchange for days or even weeks until the neonatal lung has recovered. Under local anesthesia, the right atrium is cannulated through the right internal jugular vein and blood is passed extracorporeally through tubing connected to a source of oxygen, a membranous lung for gaseous exchange, a heat exchanger, a heparin infusion pump, and other supporting elements. The oxygenated blood is then passed back into the infant's aortic arch via a cannula leading from the right common carotid artery. This apparatus functionally bypasses the heart and lungs and allows the lungs to "rest," thus preventing bronchopulmonary dysplasia and saving the lives of some of these patients (Bartlett 1984).

[1] See, e.g., Royall (1991), Truog (1993), and Worrall (2008).

Bartlett et al. (1982) reported a series of 45 cases of neonatal respiratory distress that they had treated during the preceding eight years using ECMO. The patients had been referred by neonatology colleagues who identified them as unresponsive to maximal therapy with less than a 10% chance of survival. They were selected from approximately 1500 seriously ill infants, and all were receiving 100% oxygen with mechanical ventilation. Twenty-five of the 45 infants survived (56%). The investigators considered this experience as part of a phase 1 trial, and believed that a prospective controlled randomized "phase 2" trial was needed to better establish ECMO as superior to conventional therapy.

In 1985 Bartlett and colleagues reported the results of their prospective randomized study. Criteria were established to select patients with severe respiratory failure with a mortality risk of at least 80%. The study design did not employ the more usual RCT method where subjects are assigned randomly to experimental and control arms in approximately equal proportions, but rather to a "randomized play-the-winner" statistical method (Zelen 1969; Wei and Durham 1978). The procedure is equivalent to the following: The treatments are coded A and B and two balls are placed in an urn, one labeled A, and the other B. For each patient, the assigned treatment is determined by which ball is drawn from the urn. After the first ball is drawn and the indicated treatment is administered, the ball is returned to the urn and a new ball is added. If the treatment was successful, the new ball carries the same letter; if not, it carries the other letter. When ten balls of one type have been added, that treatment is considered the winner. Thus a study of this type requires at least ten and at most 19 subjects (Royall 1991, 59).

The design provided that under the assumption that one treatment was substantially better than the other, the probability is very high that the randomized play-the-winner rule will select as the winner the treatment that is actually better. For the *a priori* probability that $P_A \geq 0.8$ and $P_A - P_B > .04$, where $P_A$ denotes the probability of survival when the infant receives the better treatment and $P_B$ the corresponding probability when the infant receives the poorer treatment, the probability of selection of the best treatment is at least 0.95. For the probabilities actually thought by the investigators to hold, namely $P_A = 0.9$ for ECMO and $P_B = 0.1$ for conventional therapy, the probability of selecting the better treatment is even greater (Bartlett et al. 1985, 484–485).

Twelve patients entered the study. The first patient was randomly assigned to ECMO and survived. The second patient was randomly assigned to conventional therapy and died. The next ten patients were assigned to ECMO and survived. At study termination, there was one control patient who had died, and 11 ECMO patients, all of which survived. They also included in their report that, since study termination, ten additional patients that met entry criteria for their study were seen at their institution. Eight were treated with ECMO and all survived. Two infants were not treated with ECMO, and both died. The authors concluded that based on 19 consecutive successes with ECMO, the lower 99% one-sided confidence interval on the survival with ECMO is 78.5. They state, for a 1% significance level, that ". . . the null hypothesis that the survival probability is the same for ECMO as for conventional therapy would be rejected in favor of a higher survival probability

for ECMO for any specification of a survival probability for conventional therapy less than 78.5" (Bartlett et al. 1985, 485). Since this survival probability is well above that observed in the past for this population when given conventional therapy, the investigators concluded that ECMO was statistically superior.

Nevertheless, the investigators were aware that their study design was unconventional, and they note that although the randomized play-the-winner statistical technique had been introduced in 1969, it had not previously been used in a clinical study (1985, 480). After all, only one patient had been randomized to the control arm. Perhaps anticipating criticism, they state, "In retrospect, it would have been better to begin with two or three pairs of balls, which would have resulted in more than one control patient" (1985, 484).

The study was criticized by Ware and Epstein, who argued that ". . . the results are not completely convincing. Why not? Because only one patient received the standard therapy, so that the interpretation of the study depends strongly on the belief that eligible patients would have experienced poor survival in the absence of [ECMO]" (Ware and Epstein 1985, 850). They conclude: "Further randomized clinical trials using concurrent controls and addressing the ethical aspects of consent, randomization, and optimal care will be difficult but remain necessary"(Ware and Epstein 1985, 851).

O'Rourke et al. (1989) reported a later RCT. Thirty-nine infants were enrolled, and the study was designed so that a maximum of four deaths were allowed in either the conventional therapy or ECMO group. The first 19 patients were randomly assigned to conventional therapy or ECMO. Nine patients received ECMO, and all survived. Ten patients received conventional therapy. Of these, six survived and four died. The RCT portion of the study was terminated at this point (phase I). The next 20 patients were assigned to ECMO (phase II). Of these, 19 survived and one died. The study was then terminated. Four deaths had occurred among ten infants given conventional therapy, and one death had occurred among the 29 patients given ECMO. Statistical analysis of the data by the authors showed that the results represented ECMO as the superior therapy ($p < .05$), which they argued was a conservative estimate of efficacy.

Pocock (1993) drew attention to the paucity of data when the RCT (phase I) was stopped, with only 19 patients having been randomized. Many believed that a larger RCT was needed, and subsequently a collaborative randomized trial was undertaken in the United Kingdom (UK Collaborative ECMO Trial Group 1996). Between 1993 and 1995, 185 neonates with severe respiratory failure were enrolled from 55 hospitals. Those randomized to ECMO were referred to one of five centers with ECMO facilities. Those randomized to conventional therapy continued to receive such therapy at their original hospitals. Ninety-three of the 185 patients were randomized to ECMO, and 92 were randomized to conventional therapy. Recruitment to the trial was stopped early on the advice of the independent data-monitoring committee, since the data showed a clear advantage with ECMO. Thirty of the 93 neonates that received ECMO died (32%) and 54 of the 92 infants randomized to conventional therapy died (59%). The relative risk was 0.55 (95% CI 0.39–0.77; $p = 0.0005$),

which is equivalent to one extra survivor for every three to four infants allocated to ECMO.

### 8.2.2 *Were the ECMO RCTs Necessary?*

The ECMO RCTs were, I will argue, unnecessary to establish ECMO as the preferred therapy for the class of neonates with respiratory failure that were considered eligible for randomization. The reasons involve both ethical and epistemic considerations.

Ethical considerations are an important element in the design and conduct of RCTs in clinical medical science because RCTs are experiments and the subjects are human beings. Any new therapy being advanced involves the belief that it is superior, or at least not inferior, to existing therapies before it can ethically be tested, regardless of study type. This is true whether the proposed new therapy is being studied, for example, in a small group of patients to establish toxicity profiles, or in a larger nonrandomized study of the efficacy of the new therapy in comparison with historical controls. Reasonable evidence of safety and efficacy must exist to advance a new therapy to the stage of an RCT. And as I have argued, and the EBM movement also maintains, RCTs provide the best evidence, i.e., the strongest epistemic underpinning, for confirming therapeutic hypotheses.

The emphasis on the acquisition of sound scientific evidence to undergird clinical decision-making, the main thrust of the EBM movement, is relatively recent. As noted previously, Worrall (2007, 986) has observed that most current medical therapies have not been established with RCT evidence. Goodman (2003, 6) notes that only about 10–25% of health care is based on high-quality or gold-standard evidence, and it is estimated that only about 50% of current medical practice is evidence-based (McGlynn et al. 2003, 2643). Thus, the basis for most medical therapy comes from the experience of clinicians, supported by research of various types short of an RCT.

Clinicians are ethically charged with administering, or at least recommending, what they believe to be the best available therapy for each individual patient. It must also be recognized that clinicians have many other ethical obligations, among them to family and society in general, in addition to those to the individual patient. But in the ordering of ethical obligations, the clinician, *qua* clinician, is widely regarded as being obligated to place primary consideration on the health of the individual patient under his or her care. This is promulgated in various codes: for example, in the 1948 Declaration of Geneva of the World Medical Association, it is affirmed that, "the health of my patient will be my first consideration" (Beauchamp and Childress 1994, 441). Schafer (1982, 720) notes that, "In his traditional role as healer, the physician's commitment is exclusively to his patient." Fried (1974, 50) states that, "The traditional concept of the physician's relation to his patient is one of unqualified fidelity to that patient's health." He calls this the *personal care concept*. And, Pelligrino (1979, 114) states, "Surely the first order of responsibility for clinicians must remain

with the patients they undertake to treat. Here, the moral imperatives are clear: competence of the highest order, integrity, compassion."

But, arguably, physicians also have an obligation to work to improve the quality of the care and treatment that patients on the whole receive. Physician-investigators thus generate and participate in various levels of research, and physicians in general are encouraged to seek to enroll eligible patients in ongoing studies. Does this mean, however, that physicians or physician-investigators should participate in studies, including RCTs, in which it is possible, by study design, that at least some patients will receive a therapy that they believe is inferior? Or, might they be ethically obligated *not* to participate?

Under the ethical principle that the *primary* duty of the physician (*qua* physician) is to the health and well-being of his or her individual patient, it would seem that the Bartlett et al. (1985) and O'Rourke et al. (1989) RCTs were in breach of that principle, since it seemed that the investigators clearly believed that ECMO was superior to conventional treatment. That they so believed is suggested by at least two observations: the consent process used, and the trial designs that were selected.

In order to proceed with the trials, the investigators were obligated to obtain informed consent from the parents of the neonates. A frank and honest discussion of the risks and benefits of ECMO and conventional therapy would have included the results to date observed with those alternatives, particularly what results they (the parents) could expect under each alternative. The consent process employed for both RCTs used a randomization method advanced by Zelen (1979), in which eligible patients are randomized before consent is sought. Neonates randomized to conventional therapy would receive the same treatment anyway, it is reasoned, and thus they are arguably not part of the experiment. Thus, consent from these parents need not be obtained. Consent is only sought for the "experimental" therapy, in this case, ECMO. Bartlett et al. (1985, 484) contended that ". . .if consent is sought before randomization, the distraught family is presented with confusing treatment options which they cannot fully understand. . ."[2] O'Rourke et al. (1989, 959) stated that, "This [Zelen (1979)] method was chosen in the belief that discussing the possibility of ECMO therapy with families whose child did not ultimately receive ECMO would not benefit those families and would create additional emotional distress."

Another indication of ethical conflict was the unconventional trial designs that were used in the two studies. This was clearly done to minimize the number of infants assigned to conventional therapy. Bartlett et al. (1985) justified their "play-the-winner" design because of their anticipation that ". . .most ECMO patients would survive and most control patients would die, so significance could be reached with a modest number of patients," and because "It was a reasonable approach to the scientific/ethical dilemma . . . we were compelled to conduct a prospective, randomized study, but reluctant to withhold a lifesaving treatment from alternate patients simply to meet conventional random assignment technique" (1985, 480). O'Rourke

[2]Recall that the investigators believed (or at least assumed) that the survival probabilities were 90% with ECMO and 10% for conventional therapy (Bartlett et al. 1985, 485).

et al. (1989, 962) rejected a fixed sample size design "...because of the potential for a large difference in mortality rates...".

Thus the investigators were seemingly not in a state of "personal equipoise." They apparently believed that ECMO was superior. But did clinical equipoise exist? Clinical equipoise, the existence of uncertainty and disagreement among the expert medical community about which treatment is better, is, as I argued earlier in relation to the mastectomy versus irradiation trials in early breast cancer, what ethically justifies the RCT. When the ECMO trials were initiated, was the relevant expert medical community in clinical equipoise? In other words, was there sufficient evidence already of ECMO's superiority?

When the trials were begun, it seems difficult to imagine that clinicians involved in the care and treatment of moribund infants in respiratory distress that were on conventional therapy and not responding, and thus with an expected high mortality rate, the very class of infants that were eligible for randomization, did not view ECMO as potentially lifesaving and clearly superior to continuing on conventional treatment. Indeed, they were referring such cases for ECMO when it was feasible to do so.

Most RCTs do not raise ethical concerns among the research subjects or clinicians involved. Most reservations are relatively minor and can be satisfactorily resolved at the institutional review board (IRB) level of oversight. As Truog (1993, 524) notes, "Few criticize the RCT that seeks to identify the best antibiotic for treating acute otitis media or the best antacid for peptic ulcer disease."

The ethical problems surrounding the ECMO RCTs derive from the fact that the therapies under consideration are potentially lifesaving. The neonates selected for the ECMO trials were judged to have a high mortality risk; for the Bartlett et al. (1985) study it was at least 80%, and was estimated to be about 75% for the O'Rourke et al. (1989) study. Data on infants treated with ECMO showed about a 75% survival rate (Bartlett 1984, 140) when the Bartlett et al. (1985) study was initiated, and an ECMO Registry report of 715 infants treated with ECMO showed an overall 81% survival rate when the O'Rourke et al. (1989) study was undertaken (Toomasian et al. 1988, 141).

How much evidence of efficacy of a potentially lifesaving therapy must exist for that therapy to become the preferred therapy? Is RCT evidence required? As Royall (1991, 60) notes, "Science desires randomized clinical trials, it does not demand them." And Fried states unequivocally that "...the claims for the RCT have been greatly, indeed preposterously overstated. The truth of the matter is that the RCT is one of many ways of generating information, of validating hypotheses. The proponents of the RCT, however, have elevated what is in theory a frequent (though by no means universal) advantage of degree into a gulf as sharp as that between the kosher and the non-kosher" (1974, 158). The investigators were themselves apparently convinced of the superiority of ECMO. And it appears that the parents of infants that were offered a choice between ECMO and conventional therapy were equally convinced. In the O'Rourke et al. (1989) study, after randomization, all

29 patients' parents who were approached for ECMO gave their consent for ECMO.[3]

The O'Rourke et al. (1989) study led to a debate over the unusual statistical design and the ethical questions it raised. This resulted in a rare reprimand of the Boston Children's Hospital's IRB by the National Institutes of Health (NIH) for failing to ensure that all subjects in a clinical trial were informed (Marwick 1990, 2420).

The RCT carried out in the UK was done because it was believed that ECMO was controversial in view of the varying interpretations of the available evidence. The UK trial organizers viewed the studies by Bartlett et al. (1985) and O'Rourke et al. (1989) as inconclusive. Most of the claims about ECMO were based on case series and other studies with historical controls, which, although suggesting large reductions in mortality, were carried out at a time when neonatal death rates were falling. Neonatal ECMO was introduced into the UK in 1989, but some clinicians were reluctant to refer potential neonates for ECMO because of concerns that any improved survival from the technique might be offset by an increase in long-term disability. Others were concerned about the costs of ECMO, which exceeded those of conventional therapy, while questions about its clinical effectiveness and cost-effectiveness persisted. Based on these factors, British clinicians agreed to limit neonatal ECMO to use within an RCT.

Consent was obtained from the parents of neonates in the usual manner in the UK trial, before randomization (Field 1995, 1370). Also, a conventional study design was used wherein patients were randomized in approximately equal numbers to conventional therapy or ECMO. The trial was carried out between 1993 and 1995, well after the results of the Bartlett et al. (1985) and O'Rourke et al. (1989) RCT results were available. Subsequently, the trial was criticized as unnecessary and unethical.

For example, Lantos (1997, 265) pointed out that by 1993, when the UK trial was initiated, more than 7500 neonates had been treated with ECMO in 75 programs in the United States and 17 programs in other countries. He states, "More certainty is always better than less certainty, but at some point we need to decide that we are certain enough" (1997, 266). Would another trial of ECMO to confirm the results of the UK trial be ethical? He says, "I think that the data that were available in the early 1990s on the benefits of ECMO were convincing... If I was on an ethics review panel, I would not have approved the trial" (1997, 267–268). In the same vein, he also suggests that since the "default" choice for parents with infants eligible for enrollment in the trial was conventional therapy, and the only chance to receive ECMO was to enroll in the trial, there was an implicit element of coercion in the trial design.

Other ethical issues arise when either the conventional or experimental therapy (or both) is rapidly evolving (Truog 1993, 525–526). In addition to being a

[3]This would seem to assume that these parents were fully informed of the risks and benefits of the alternative treatments.

potentially lifesaving therapy, during the period of the trials, ECMO was rapidly developing. For example, many institutions were switching from veno-arterial to a veno-venous technique utilizing the jugular vein for both withdrawing blood and returning it to the body. ECMO apparatus not requiring anticoagulants was under development. And, perhaps in response to avoiding the cost and complexity of ECMO, improvements in conventional therapy were further reducing the mortality rate associated with those therapies. Wung et al. (1985) reported treating 15 seriously ill neonates in respiratory failure with modifications in ventilatory therapy focused on reducing barotrauma. ECMO was not used, and all survived. Schapira and Solimano (1988) reported two deaths among 13 neonates (a mortality rate of 15%) with severe respiratory distress due to meconium aspiration syndrome treated between 1983 and 1987 that met criteria for ECMO, but were treated with conventional therapy. A retrospective review by Dworetz et al. (1989) of severely ill neonates that met ECMO trial entry criteria but were treated with conventional therapy showed an improvement in survival of those treated between 1980–1981 and those treated between 1986–1988. One of six patients survived in the earlier period (17%), whereas nine of ten patients (90%) survived in the later period, possibly due to changes in ventilatory therapy. Granted that the numbers from these case series were small and the results not generalizable, they do indicate that efforts at progress were being made. And, in the O'Rourke et al. (1989) study, six of the ten infants randomized to conventional therapy survived (60%), which was higher than expected.

RCTs of rapidly evolving therapies pose at least two ethical problems, one related to the requirements of RCTs, the other related to relevance (Truog 1993, 525–526). RCTs are usually designed to keep the treatments constant, and may take years to complete. Thus, innovations that occur while the study is underway may not be available to study subjects. Patients on either the control or experimental arm (or both) may wind up receiving inferior therapy compared to similar patients being treated outside the study. Also, the trial itself may retard the development of new approaches and technologies, particularly among the institutions involved in the study, as study results are awaited.

The other problem is relevance. Most consider it to be a fundamental ethical requirement that RCTs have the potential to generate useful knowledge. Cowan (1981, 10) for example, states that, "...good research design requires that any proposed clinical trial be scientifically sound and capable of yielding generalizable data; a study lacking these characteristics is inherently unethical." Over the time period of the studies, the mortality rate of conventional therapy changed markedly, from 80% to perhaps as little as 10%, as noted above. This severely questions the leading assumption of the trials: a high ($\geq$80%) mortality rate in neonates treated with conventional therapy. Thus, the information generated from such trials may be obsolete and not useful when the results become available.

If RCTs are not practical to generate evidence on which to base clinical decisions for these rapidly evolving therapies, what is the best method to accumulate and evaluate the evidence that is being acquired? One suggestion with seeming merit that has been advanced is establishment of a prospective observational database (Truog

1993, 526; Berry 1989, 309–310). For neonates with severe respiratory distress, for example, clinicians would treat patients with the methods that they believe to be the most efficacious. No restrictions on how patients are treated are imposed. All participating institutions would send pertinent patient and treatment information to a central registry. Data on the effectiveness of various interventions would be periodically analyzed. Algorithms would be devised to assess outcomes on patients matched for prognostic factors.

Truog (1993) believes that such a registry would have obviated the need for the O'Rourke et al. (1989) RCT. The ECMO registry of 715 neonates published in 1988 by Toomasian et al. demonstrated an 81% survival with ECMO and indicated that ECMO was statistically superior to any other therapy with a survival rate of less than 78%. Had the registry included similar conventionally treated neonates, it would have shown the superiority of ECMO. Possibly, the UK trial could also have been avoided.

In view of the foregoing, it is arguable that the ECMO RCTs were unnecessary, since ECMO was clearly a potentially life-saving therapy. The EBM movement also considers RCTs for such life-saving treatments to be unnecessary. As previously noted, Greenhalgh (2010, 39) has so stated, and Sackett et al. (1996, 72) maintain that ". . .some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted." Nowhere is the duty of the clinician to his or her individual patient stronger than when the patient's very life is at stake. Here, ethical considerations preclude the acquisition of evidence from the admittedly more epistemically desirable RCT. As the Physician's Oath of the World Medical Association states: "Concern for the interests of the subject [of research] must always prevail over the interests of science and society" (Beauchamp and Childress 1994, 441). And similarly, A.B. Hill (1963, 1047) says, ". . .the ethical obligation always and entirely outweighs the experimental."

## 8.3 Carcinoma of the Anal Canal

The anal canal is the terminal portion of the digestive tract and ends in association with sphincter musculature that control evacuation of the products of digestion. The columnar mucosa of the rectum transitions into a squamous histology, and squamous cell carcinomas include so-called basaloid, cloacogenic, and epidermoid carcinomas. These carcinomas are histologically distinct from the more frequently occurring rectal adenocarcinomas (Welton and Raju 2011, 344).

Until the 1970s the preferred treatment of squamous cell carcinoma of the anal canal was primarily surgical. Small tumors could usually be excised successfully without much morbidity, but larger tumors, which often invaded the sphincter musculature, required the more extensive and morbid abdominal perineal resection. This operation involved an intra-abdominal component and a perineal component, and resulted in removal of the distal rectum and anus, with closure of the perineal

defect and a permanent colostomy. Local recurrence rates ranged from 27% to 47%, and five-year survival rates ranged from 40% to 70% (Welton and Raju 2011, 345).

In 1974 Nigro et al. reported the use of combined radiation therapy and chemotherapy in the form of 5-fluorouracil (5-FU) and mitomycin-C in the treatment of anal canal cancer. Three patients were administered the combined therapy as part of a planned preoperative program to be followed by abdominal perineal resection. The purpose of the preoperative regimen was to improve the local control and cure rates. Two patients completed the planned radiation therapy and chemotherapy, and no evidence of cancer was found in the surgical specimen obtained after their abdominal perineal resections. The third patient completed the radiation therapy and chemotherapy, but refused surgery. There was no evidence of cancer in the patient 14 months after treatment. The authors included in their report a woman with metastases to the liver from cloacogenic carcinoma from the anal canal treated with the same chemotherapy regimen but with a lower radiation dose to the liver. Within a few weeks the enlarged liver had shrunk to less than normal size, and there was no evidence of residual disease either by biopsy or laparoscopy. The authors did not claim this to be curative, but noted that they had not seen such a dramatic response to any therapy for this condition before.

By 1976 reports of the use of the "Nigro regimen" (as it later came to be called) began to appear (e.g., Newman and Quan 1976), although, except for the less commonly appearing smaller tumors, abdominal perineal resection alone was still advocated as definitive therapy (Wilson et al. 1976; Golden and Horsley 1976). Newman and Quan (1976), for example, reported three patients with surgically incurable epidermoid carcinoma of the anus treated with the Nigro regimen; one died during the course of the therapy, but the two others achieved apparent complete resolution of their local tumor: one patient was alive and well nearly one and a half years after initiation of therapy, and the other underwent abdominal perineal resection after completing the radiation and chemotherapy, with no residual carcinoma seen on pathological examination of the surgical specimen. The authors included a fourth patient in their report who had biopsy-proven pulmonary metastases treated with 5-FU and mitomycin-C. Six weeks later, a chest radiograph showed essentially complete disappearance of the metastatic nodules. The authors concluded that their experience suggested that multimodality therapy might increase salvage in even locally far-advanced and metastatic epidermoid anal carcinoma.

During this period, improvements in radiation therapy equipment and technique were occurring, and some studies were reporting more favorable outcomes for some patients when radiation therapy was added to surgery (e.g., Green et al. 1980). And, by 1980, further reports of the use of combined modality chemotherapy and radiation therapy were appearing that seemed to indicate a potentially major advance in the treatment of anal carcinoma. Sischy et al. (1980) reported ten patients with anal carcinoma confined to the anorectal area. Four patients received preoperative radiation therapy and chemotherapy consisting of mitomycin-C and 5-FU and subsequently underwent abdominal perineal resection. None had residual tumor on pathological examination of the surgical specimen. The other six patients were treated definitively with the chemotherapy and irradiation alone, without surgery.

These patients were also found to be free of disease, proved by biopsy. They found it impossible to predict the outcome of the treatment by the size of the original lesion, which was remarkable since tumor size is usually an important predictive factor for tumor response to therapy. They state: ". . . in instances of squamous cell carcinoma of the anus, if the lesion has disappeared completely at the end of treatment, adequate biopsies may be taken, and only in those instances in which there is residual tumor should abdominoperineal resection be performed. In this way, it is possible that a large number of patients with squamous cell carcinomas could be spared abdominoperineal resection" (Sischy et al. 1980, 370).

Also, in 1980 Cummings et al. reported six patients referred to the Princess Margaret Hospital in Toronto with anal canal cancer treated between May 1978 and August 1979 with radical radiation therapy plus 5-FU and mitomycin-C chemotherapy. No patients had surgery, and all had complete disappearance of their tumor within two months of completion of therapy. None showed any evidence of late recurrence, and they all retained anal continence with good control of bowel function by the anal sphincter musculature.

The remainder of the 1980s saw further reports appear from several centers using the new approach of preoperative 5-FU and mitomycin-C combined with radiation therapy, in which surgery was increasingly being reserved for patients that failed the preoperative regimen. It became customary to closely monitor patients after the preoperative regimen for any sign of recurrence, with biopsies done as needed. Improvements in radiation targeting and delivery were also occurring, and by 1993 Cummings editorialized that,

> The need for a randomized trial in which radical surgery would be compared with radiation therapy or radiation combined with chemotherapy, desirable though it may have been a decade ago, has now passed, and there can be little doubt that radiation-based protocols are at least as effective as surgery in terms of overall survival rates, and enable anorectal function to be preserved. . . (1993, 173).

The principle of using a combination of chemotherapy and radiation therapy as planned definitive therapy, with surgery reserved for the salvage of the minority of patients that failed this strategy, had essentially by this time become firmly established as preferred therapy without an RCT to test this hypothesis. Further questions arose, however, such as whether 5-FU or mitomycin-C, or both, could be omitted without compromising outcomes, or whether some other chemotherapy drug, such as cisplatin, could be substituted for the more toxic mitomycin-C. These questions *were* addressed with RCTs.

For example, to study whether the addition of 5-FU and mitomycin-C chemotherapy to irradiation was necessary, the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups carried out an RCT to compare these approaches. One hundred ten patients from participating cancer centers in Israel and seven European countries were randomized to either radiation therapy alone or radiation therapy plus 5-FU and mitomycin-C chemotherapy. Results showed a significant increase in the complete remission rate from 54%

for radiation therapy alone to 80% for radiotherapy combined with 5-FU and mitomycin-C, leading to a significant improvement in locoregional control and colostomy-free survival ($p = .02$). The overall survival rate remained similar in both groups, due to the ability of surgery to salvage treatment failures (Bartelink et al. 1997).

Mitomycin-C is considered a relatively toxic chemotherapy drug. In addition to causing myelosuppression (lowering of blood counts), it is also known to have pulmonary, cardiac, hepatic, and renal toxicities, the latter of which can be life-threatening. To test the hypothesis that mitomycin-C could be omitted from the chemotherapy regimen, an RCT was performed in the U.S. Institutions in the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group participated. Between 1988 and 1991, 310 patients were randomized to receive radiotherapy and 5-FU, or radiotherapy, 5-FU, and mitomycin-C. At four years, colostomy rates were lower ($p = .002$), colostomy-free survival was higher ($p = .014$), and disease-free survival was higher ($p = .0003$) in the group that received mitomycin-C. Toxicity was greater in the mitomycin-C group. The authors concluded that notwithstanding the increased toxicity, the use of mitomycin-C is justified, particularly in patients with large tumors (Flam et al. 1996).

To test the hypothesis that cisplatin could replace mitomycin-C, a large randomized trial with 649 evaluable patients was carried out in the U.S. in which several trial groups participated. The randomization was between radiotherapy, 5-FU, and mitomycin-C versus radiotherapy, 5-FU, and cisplatin. Five-year disease-free survival and five-year overall survival favored the group receiving mitomycin-C ($p = .006$ and $p = .026$, respectively). There was a trend toward statistical significance for colostomy-free survival ($p = .05$), the rate of locoregional failure ($p = .087$), and colostomy failure ($p = .074$). The authors concluded that the combination of 5-FU and mitomycin-C yielded a statistically significant, clinically meaningful improvement in disease-free survival and overall survival, and has borderline significance for colostomy-free survival, colostomy failure, and locoregional failure when compared to 5-FU and cisplatin. They also concluded that radiotherapy with 5-FU and mitomycin-C remains the preferred treatment for anal canal cancer (Gunderson et al. 2012).

When the results of the early studies showing the promise of radiation therapy combined with 5-FU and mitomycin-C chemotherapy in the treatment of anal cancer were made available, such as those by Nigro et al. (1974), Newman and Quan (1976), and others, why were one or more RCTs not performed to directly test the new approach against the established conventional therapy of abdominal perineal resection? Any answer would necessarily be speculative, but one plausible explanation lies in the dramatic, unexpected response of this tumor to the new approach, which was completely different from responses seen in the anatomically nearby rectal cancers or in other cancers of epithelial origin, such as lung or breast cancer. And, surgery for the salvage of failures of the new approach was still available.

## 8.4 Disseminated Carcinoma of the Testis

Carcinomas of the testis are mostly of germ cell origin, which are cells that are destined to become sperm cells. Histologically, carcinomas of the testis are mostly embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, or some combination of these cell types. They are a disease of younger men, and are the most common solid tumors in men aged 20–34 years of age. The usual presentation is a nodule or painless swelling of the testicle. Initial treatment (and diagnosis) is accomplished by surgical removal of the affected testis. Unfortunately, in from 60% to 70% of cases, the disease is disseminated when the diagnosis is made. Before the advent of anticancer chemotherapy drugs, treatment of disseminated testicular carcinoma was largely unsuccessful and most patients died of their disease (Richie 1998).

Carcinoma of the testis was found early on to be moderately sensitive to some chemotherapy drugs. For example, in 1967 Wyatt and McAninch reported ten men with disseminated testicular carcinoma treated with methotrexate. Four achieved a complete remission, but none of the other six responded and all six died. In 1975, Samuels et al. reported 23 patients with disseminated testicular carcinoma treated with vinblastine and bleomycin. Nine of the 23 patients achieved a complete remission (39%) and eight achieved a partial remission (35%).

In 1977, Einhorn and Donohue reported 50 patients with disseminated testicular carcinoma treated with the three-drug combination of cisplatin, vinblastine, and bleomycin. Two patients died within one week of the initiation of chemotherapy, and a third patient died two weeks after the start of chemotherapy, all presumably due to massive tumor. All three of these patients had significant respiratory symptoms due to massive pulmonary metastases. This left 47 evaluable patients, and this regimen produced a complete remission in 35 patients (74%) and a partial remission in the other 12 (26%). Five of the patients with a partial remission became disease-free after surgical removal of residual disease, yielding an overall 85% disease-free status.

The three-drug regimen reported by Einhorn and Donohue (1977) became the "standard" or conventional treatment for disseminated testicular carcinoma. Further studies would be RCTs to test modifications of the regimen, for example to reduce toxicity or to improve remission and survival rates. In 1981, Einhorn et al. reported that five years after the Einhorn and Donohue (1977) study, 27 of their original 47 patients (57%) remained alive and disease-free, with a 19% relapse rate. Since the great majority of such patients relapse within three years of completing therapy, these 27 patients are presumed cured. In their report they presented the results of an RCT testing whether the addition of doxorubicin to the three-drug regimen improved results compared with the three-drug regimen alone, and whether "maintenance therapy," which is the continuation of some chemotherapy beyond the induction of remission, was of value.

A total of 184 consecutive patients were randomized to the three-drug regimen or the three-drug regimen plus doxorubicin. Those patients that achieved a complete remission or disease-free status following resection of residual disease that showed

no viable tumor were further randomized to no maintenance therapy or maintenance therapy of monthly vinblastine for two years. Results showed no statistically significant differences in the groups. Thus, the original three-drug regimen remained the standard treatment. The results with the three-drug regimen were replicated in numerous institutions in the U.S., Canada, and Europe, as well as cooperative groups (Einhorn et al. 1981, 729).

Vinblastine produces significant neuromuscular toxicity, and etoposide had shown activity against testicular carcinoma in patients that had failed the three-drug regimen. In 1987, Williams et al. reported the results of an RCT comparing cisplatin and bleomycin plus either vinblastine or etoposide in disseminated testicular tumors. Among 244 patients that were evaluable for a response, 74% of those receiving the regimen including vinblastine and 83% of those receiving the regimen including etoposide became disease-free with or without surgery; however, this difference was not statistically significant. Survival among the etoposide group was higher ($p = .048$). In addition, the etoposide regimen showed statistically significant less toxicity. The regimen of cisplatin, etoposide, and bleomycin became the new standard therapy.

## 8.5 Conclusions

Perhaps the most important common characteristic in the ECMO, anal canal carcinoma, and disseminated testicular carcinoma examples is the dramatic improvement in outcomes provided by the new therapy compared to what was available before. In these cases, an RCT to establish this was arguably unnecessary. Glasziou et al. (2007) provide some other examples where dramatic effects have established some approaches without an RCT. And, as Miller and Joffe (2011, 479) point out, evidence of large effect sizes on the basis of early clinical studies is one criterion for approval of new oncology drugs by the U.S. Food and Drug Administration. For example, cisplatin was approved in 1978 for the treatment of testicular cancer, following the 1977 report by Einhorn and Donohue that established cisplatin, vinblastine, and bleomycin as the new standard therapy in disseminated testicular carcinoma. Indeed, in a review of oncology drug approvals between 1973 and 2006, of a total of 68 drugs that were approved, 31 were done so on the basis of studies that were nonrandomized (Tsimberidou et al. 2009, 6243).

How should such evidence be treated in the weight of evidence account? I have argued that when evaluating a new therapy, the RCT (and by extension, systematic reviews and meta-analyses of RCTs) provides, in general, the most epistemically desirable testing method *among study types*. It must be remembered that the ethical justification for the RCT is clinical equipoise, disagreement among the expert medical community as to the best treatment, and that the objective is social, to change standards of practice (Freedman 1987). Useful, generalizable, abstract knowledge is expected to result. In the ECMO, carcinoma of the anus, and disseminated testicular carcinoma instances, *compelling and convincing* evidence emerged

almost serendipitously that the new approaches were superior to what was already available. It is worth emphasizing that what made the evidence so compelling was that the *majority* of patients fared better, and dramatically so, and thus clinical equipoise arguably did not exist.

In the weight of evidence account, the evidence from the ECMO and anal and testicular carcinoma examples must be considered strong. Thus, when responses occur that are clearly definitive, treatment approaches that have not been studied in an RCT can become the new standard approach and be incorporated into treatment guidelines by major organizations such as the NCCN and the American Society for Radiation Oncology.

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