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## Will Surgery Disappear From The Treatment Of Breast Cancer?

Remy J. Salmon

*Emeritus Professor, Department of Surgical Oncology, Curie Institute, Saint Jean de Dieu Foundation Paris, France*

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The buzzword today is "de-escalation" in the treatment of breast cancer. When analyzing recent publications, we realize that breast cancer will increase by 35% worldwide by 2040 to reach a figure of 2846000 new cases (Table 1)

On the one hand, the attraction of cancer specialties is becoming less and less in a way that the first choices of residents in France are mostly plastic and aesthetic surgery, dermatology and ophthalmology, so there would be no emergencies and a high income. This is the dream of our young colleagues! At the same time, four times as many surgeons and 5.5 times as many anesthetists would be needed to treat all these new cancers while the number of new cancer surgeons is decreasing in Western countries.

On the other hand, Multidisciplinary Team (MDT) management is a considerable progress in the management of new cancers, allowing the treatment of cancer in the most appropriate way for a given patient. But there remains a critical question; will surgery fade away or disappear in the management of breast cancer in the future?

According to NHS Breast Predict test on the internet, the percentage of cure at 5 and 10 years is always higher with surgery than with other hormonal and chemotherapy treatments, showing that surgeons remain indispensable.

Of 1000 breast cancers, 260 were candidates for neoadjuvant Chemotherapy (CT) (12% were Triple Negative and 14% were HER2+); 130-195 patients (50-75%) received neoadjuvant CT, and 49% of the patients were node positive. There was an increase in

false negatives in 12-18 patients with complete response in imaging or <1cm and 71% were with VPN pCR. Also, 37-70% had positive pCR which was in favor of surgery.<sup>2,3,4</sup>

As far as surgery is concerned, no one disputes the de-escalation that has occurred since William Halsted at the end of the 19th century. Total mastectomy with pectoral resection and extensive lymph node dissection gave way to the modified total mastectomy of Patey<sup>5</sup> and then Madden.<sup>6</sup> The development of radiotherapy allowed for conservative treatments from the 1970s and 1980s, the aesthetic results of which were improved by oncoplasty in the late 1990s. Aggressive lymph node dissections also disappeared and nowadays are replaced mostly by sentinel lymph nodes biopsy.<sup>7</sup> However, the major turning point came at the end of the 1980s with the first publications on neoadjuvant treatments. Giving chemotherapy before surgery allowed for in vivo testing of the efficacy of the drugs and a decrease in the size of the tumor, allowing for conservative treatment where amputation was initially essential. Dr. Jacquillat, in one of his publications called "Non-surgical Treatment of operable breast cancers"<sup>8</sup> proposed that patients who had responded well to the medical treatment could be excluded from the surgery and irradiation of the breast and a boost on the tumor bed would be sufficient.

Time has passed, and neoadjuvant treatments have become more and more targeted, and effective, and in recent years complete histological response is not uncommon, especially in HER2 overexpressing cancers receiving Trastuzumab, Pertuzumab and more recently in triple-negative cancers receiving immunotherapy.<sup>7</sup> Should we, therefore, continue to operate on these cancers that are in complete response after a well-adapted targeted treatment, and should we continue to remove axillary nodes that these same chemotherapies have sterilized?

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**\*Address for correspondence:**

Remy J. Salmon, MD,  
Emeritus Professor, Department of Surgical Oncology,  
Curie Institute, Saint Jean de Dieu Foundation Paris,  
France  
Email: dr.rjsalmon@gmail.com



**Table 1.** Estimation of increasing surgical treatment by tumoral site by 2040

Cancer site	% indication for surgery	impact 2018	indication for surgery 2018	impact 2040	indication for surgery 2040	increase	%
Breast	97%	2088000	2026000	2833000	2748000	722000	36
Melanoma	97%	287000	279000	387000	376000	97000	35
Uterus	85%	382000	324000	50000	425000	10000	31
Ovaries	83%	295000	245000	412000	342000	97000	40

Many clinical trials are underway to answer this question. The first thing to note is that inclusion in these trials is laborious, which would seem to prove that complete responses are not that numerous. Even if the dream comes true, only a small subgroup of patients reach a complete response but there are some arguments on this conclusion. The number of patients who have a complete response even in HER-2 enriched and TNBC after neoadjuvant treatment varies according to histological type, reaching 50-75%, although without surgery there are currently no clinical and biological parameters for the certainty of a complete response. It is worth noticing that the rate of complete response in luminal tumors is even less.

The first obstacle is imaging. Ultrasound, MRI, and PET scan, are used to evaluate this complete response and, depending on the team and the false negative rate varies between 10 and 30%.<sup>13</sup>

The importance of imaging and the possibility of identifying suspicious axillary nodes radiologically by clips is not universally available due to the cost of these examinations.<sup>2,4</sup> Patients must then undergo active, regular and prolonged surveillance, which can become very distressing for patients when changes in breast or axillary images appear. Here again, the cost of these repeated examinations is not negligible.

Finally, there is still insufficient experience with this type of strategy to make it widely available. Monica Morrow, from the Memorial Sloan Kettering Center in New York, humorously said, "What is the problem with doing a lumpectomy with a sentinel lymph node, which provides precise information on the histological response, makes it possible to evaluate the margins of the excision, lasts less than an hour, is inexpensive and therefore makes it possible to make a correct evaluation with a serene follow-up?"<sup>9</sup>

In addition, neo-adjuvant treatment remains disappointing in terms of complete histological response in the majority of luminal A and B cancers and lobular cancers. In that case, this non-operative attitude must still be accepted with caution and if it is adopted, patients must still be included in therapeutic

trials to validate this approach. Also, neoadjuvant strategy is not applicable in intra ductal cancers (In situ Carcinomas). The ultimate goal of a multidisciplinary approach should not be to not operate but to apply to each patient the treatment that will give her the best survival with the minimum of physical and psychological sequelae.<sup>10</sup>

However, oncology is constantly evolving, and in radiotherapy, the COVID pandemic helped to develop hypo-fractionation decreasing the six weeks treatment to 15 fractions and even 5 fractions in the fast and fast forward trials in post-operative treatment.<sup>11</sup> Obviously, in case of conservative treatment, irradiation becomes necessary and discussions may arise on the benefit of the boost on the site of the tumor that has disappeared.<sup>5</sup> More recently, localized partial irradiations, (APBI) associated with medical treatment have made it possible to obtain complete responses in some patients.

The recent explosion of new molecules on the market, such as immunotherapy, CDK4/6 inhibitors, and conjugated antibodies, have temporarily eliminated the notion of medical de-escalation.<sup>5</sup> Their exact interferences in these molecules and surgery remain to be discovered.

The molecular approach, where each patient and each tumor can benefit from NGS (New Generation Sequencing) associated with the study DNA and/or analysis of circulating cells, is close at hand. Still limited by costs, this approach, coupled with local and regional treatments and "real life" parameters, will impose the use of artificial intelligence in our diagnostic and therapeutic parameters.<sup>12</sup>

Surgery will not disappear any more than neo-adjuvant treatments have made it disappear. Surgeons will have to learn and find their place among the myriad of research projects that are underway, and while their historical role as the first line of treatment for solid tumors will diminish, their task will change, provided only that they keep abreast of developments.

To repeat the first part of this editorial, the increase in the number of cancer cases and the decrease in the number of surgeons and anesthetists



to treat them will be an urgent challenge for our supervisors. In France, these authorities are more concerned with legislating on the authorizations of centers than with training, in particular the breast surgeons of the future, while there are more than 60,000 new cases of breast cancer per year. Senology, after having belonged to "general" surgery, has passed into the field of gynecology where the means are shared between childbirth, peri-fetal medicine, fertility, etc. This is not the case in all countries, but there is an urgent need to train, especially to promote this complex surgery, to attract future young colleagues.

Failure to provide this training could result in a two-tier system between countries and institutions that are capable of modern management and those where, because of lack of screening, patients will arrive with advanced forms of the disease and will not have the means to access modern treatments. As Dr. Fabrice André, the president of ESMO presented in

the annual congress of ESMO 2022, "In the next five years, we will need more doctors, surgeons and nurses, with more healthcare and diagnostic infrastructure, to take care of the growing number of patients who will have benefited from "multiple" detection tests."

#### CONFLICT OF INTEREST

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