# Picking flowers in the breast cancer field

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**R S du Toit**

*Department of Surgery, Faculty of Health Sciences, University of the Free State, Bloemfontein*
R S du Toit, MB ChB, MMed (Surg), FCS (SA)

*Corresponding author:* R S du Toit (dutoitrs@ufs.ac.za)

## A brief history of the Surgical Research Society of Southern Africa

Surgical research in our country was already well developed 40 years ago, and a forum was needed where researchers could present their work, in addition to the already established biennial Association of Surgeons of Southern Africa meeting. A further incentive to found a Surgical Research Society was the wish to stimulate surgical research even further. Motivated by these ideas, the late Professor Sonny du Plessis, Head of Surgery at the University of the Witwatersrand in Johannesburg, founded the Surgical Research Society of Southern Africa in 1972. Despite challenges over the years, the society has prevailed. Today it stands proud and occupies a pivotal position on our academic calendar each year. It is a southern African society, which invites all researchers in our region to become members and to present their work at its annual meetings.

I would like to pay homage to a great man with great vision, and at the same time remember the diligence, dedication and dignity of our predecessors who laid the foundation for us to build on.

## My breast cancer research

I will now report on a few studies I performed in my field of research – breast cancer.

### Study 1 – rehabilitation after mastectomy

I was asked to assist a student in a study towards her Master's degree, the subject of which was clothing-related problems patients may experience after treatment for primary breast cancer. I thought it sounded interesting, as I had not encountered anything on the subject in the breast cancer literature, and agreed to assist. We developed a questionnaire to obtain the information required, and mailed it to 331 patients who had finished their primary treatment for breast cancer at least a year before. The majority of patients in the cohort (68%) had had a mastectomy as part of their surgical treatment.

The first phase of the study was to identify the physical changes that occurred in these patients as a result of treatment for their breast cancer. The student found that, apart from losing a breast, the physical impact of treatment on these patients was threefold, namely lymphoedema of the arm in 50% and reduced shoulder movement in 34%, while 40% had gained weight after treatment. These findings are not surprising, as we are all familiar with them.

The next phase of the study was to see how these physical changes affected the clothing the patients wore, first looking at prosthesis-related problems. Only 8.8% of patients received reconstructive surgery, because for financial reasons it was not a priority in the state sector at the time. The majority of patients wore a prosthesis of some kind, but only 8.3% fitted their prosthesis into a special brassiere. Not surprisingly, a third of the respondents were dissatisfied with wearing their prosthesis in an ordinary bra, as there was a tendency for it to fall out or dislodge. The important finding in this context was that nearly half of the women (45%) said that they needed a special brassiere, with broader side-strips under the arms and broader shoulder straps to carry the weight of the prosthesis. Such a bra should also have a pocket on the inside to hold the prosthesis and prevent it from falling out or moving around. This is something that I think should receive attention at some stage, as it could substantially improve the quality of life of many women after mastectomy.

Of even greater importance was the contribution of the swollen arm and stiff shoulder to clothing-related problems. Nearly half of the respondents (47%) had stopped wearing many of their clothes, and 43% had had to alter their dresses. The most common clothing-related problems were sleeves being too narrow for a swollen arm and low necklines exposing their scars and their prostheses. The stiff shoulder also made it difficult to close a zip or buttons at the back of a dress. The bottom line of the study was that almost 50% of patients required not only a special bra but also guidance regarding clothing-related problems after treatment for breast cancer.

Rehabilitation programmes after treatment for breast cancer should therefore include information on the correct prosthesis and brassiere to be worn, and provide guidance on clothing-related problems and advice on how to cope with them if they occur.

This was the first study of which I was aware to address these issues in the breast cancer field.[1] I found it interesting because it highlighted something we as surgeons do not often think of, or realise the importance of in a patient's daily life.

### Study 2 – stage and age

It is well known that staging of malignancies assists in determining prognosis and guides optimal therapy for a specific patient with a specific disease stage. However, I had never come across any publication on how staging affects the disease status of a patient with breast cancer at the time of death.

One would imagine that a patient with early-stage cancer has a better chance of dying free of the disease, and therefore that the cause of death would be disease other than breast cancer. Furthermore, one would speculate that age at the time of diagnosis could also affect disease status at the time of death – the older a patient is at the time of diagnosis, the less likely she would be than a younger woman to develop end-stage metastatic disease.

The question therefore is, if this thought process is true, how do stage and age at the time of diagnosis relate to disease status at time of death in patients with breast cancer? To put it another way, can stage and age at diagnosis predict whether a patient will die of her cancer, or die with cancer but from another cause, or die from an unrelated cause and completely cured with respect to her cancer?

In order to answer the question we identified 491 breast cancer patients, all of whom had died. In all cases the stage at diagnosis and disease status at death were known. We then had to define what it meant to die in a so-called 'cancer-free' condition, as this can be interpreted in a number of ways. For the purpose of this study, we decided to define cancer free as having no evidence of recurrent or metastatic disease during follow-up after primary treatment, *and* no evidence of cancer at the time of death. For the sake of certainty, for cases to be included the last follow-up visit had to be less than 6 months before death.

The 491 cases that fulfilled the inclusion criteria were then divided into two groups, namely those with early (stage I and II) disease and those with locally advanced (stage III) disease at time of diagnosis. Each of these two groups was then subdivided into three age groups, namely younger than 50 years, between 50 and 69 years, and 70 years and older at the time of diagnosis.

In the first instance we showed that stage significantly affects the 'cancer cure' rate at the time of death. Patients with early-stage disease died significantly more often in a 'cancer-free' state compared with those who had locally advanced cancer at the time of diagnosis. Interestingly, this finding was not due to metastatic disease as one would expect, but to loco-regional recurrence. This was contrary to what we thought the impact of stage at diagnosis on disease status at the time of death would be.

We then looked at the effect of age on disease status at the time of death in the early-stage cohort. It was clear that the older the patient was at the time of diagnosis, the better chance she had of dying in a 'cancer-free' state, the reason being that the older she was at time of diagnosis, the less time she had to develop terminal metastatic disease. Age had no effect on the development of loco-regional recurrence, which was quite the opposite to what we noted when looking at stage.

This same tendency was observed in the cohort who presented with locally advanced disease at time of diagnosis, although the effect of age on 'cure rate' at time of death was now less robust, as one would expect.

This study therefore confirmed what we expected – stage and age do play a role in predicting disease status at the time of death. However, the way in which they affect this disease status differs between the two variables. In the case of stage the explanation was loco-regional recurrence, which is contrary to what we expected. In the case of age, the reason is metastatic disease, as one would expect.

From a clinical perspective, the interesting finding for me was that when a woman aged 70 years or older is diagnosed with early breast cancer, her chance of dying cancer free is nearly 60%. What

is more important from a tumour biology perspective is that if she is younger than 50 and diagnosed with either early or locally advanced cancer, her chance of dying without cancer is less than 10%. This implies that the majority of patients diagnosed with non-metastatic breast cancer already have micro-metastases at time of diagnosis. These cancer cells are kept in check for a long period by the body's defence mechanisms, but with advancing age these mechanisms start to deteriorate and the micro-metastatic cells escape from their checked state and develop into full-blown macro-metastatic disease, which eventually kills the host. This study therefore supports the existing concept that breast cancer is a systemic disease from very early on, and that is why aggressive and effective adjuvant systemic treatment is so important. It was published in *The Breast*.[2]

### Study 3 – nodes and prognosis
In 1988 I had the privilege of joining Professor Roger Blamey's breast unit at the City Hospital in Nottingham for a year as a visiting research fellow in breast cancer. Opportunities for research were ample and I completed three studies during that year.

Professor Blamey was not a believer in the TNM staging system for non-metastatic breast cancer. His reasoning was that this staging system for non-metastatic disease mainly takes tumour size and nodal status into consideration, and both are time-dependent factors. Such systems ignore tumour grade or differentiation, which reflects tumour biology. He showed that tumour grade plays a significant role in survival of patients with breast cancer and believed that a proper staging system should reflect both time-dependent and tumour biology factors.

With this as a basis, his unit developed their own prognostic index, which included tumour size, grade and nodal status. The index was as follows: T-size $\times$ 0.2 + grade (1 - 3) + N-stage (A, B, C). The weight of tumour size is reduced by multiplying it by a factor of 0.2, because of the three factors included in the index, tumour size has the least prognostic value. It is well known that the prognostic significance of N-stage overrides that of T-size, and the same applies to grade. For this reason the significance of T-size is reduced in the index. The index was developed retrospectively, but it was validated in a prospective analysis which showed that it has the ability to categorise patients with non-metastatic breast cancer into three prognostic groups. Twenty-five per cent have an index of less than 3.4 and an excellent prognosis of more than 90% survival at 10 years. A further 25% have an index of more than 5.4 and a very poor prognosis, namely 50% dead at 2 years. The remaining 50%, with a score between 3.4 and 5.4, fall between the two extremes and have an intermediate prognosis that varies according to the index score.

I found it peculiar when observing the way the unit managed the lymph nodes in these patients, in order to determine whether the nodal stage was A, B or C. No axillary dissections were done in Nottingham at that time, except when the patient had clinically obvious axillary lymph node involvement, because data had shown that axillary dissection had no impact on prognosis and, as we all know, adds significant morbidity. In all other cases lymph node status was determined by a triple-node biopsy, which meant sampling one node from the lower axilla, one from the internal mammary chain through the second intercostal space, and one from the apex of the axilla in the vicinity of the subclavian artery through an infraclavicular incision. If all three nodes were negative for

metastatic disease, the lymph node status was A and the score in the prognostic index would be 0. If only the axillary node was positive, the status was B and the score would be 1. For C-status and a score of 2 in the index, either the apical or the internal mammary node should be positive, alone or with either or both of the other two nodes. The survival curves for these three lymph node stages were clearly and significantly separated from each other.

Two questions came to mind regarding this triple-node issue. What contribution does each individual node really make to prognosis, and can a double-node biopsy provide the same prognostic information as a triple-node biopsy in their practice?

To address these questions we studied a cohort of 693 cases of early breast cancer, where all relevant information following triple-node biopsy was documented and available. All patients were under 70 years old and, as was policy in Nottingham at that time, none received any systemic adjuvant treatment. This made it a very clean cohort to study, uncontaminated by the variations one usually finds with adjuvant therapy regimens. The mean follow-up period was 48 months.

We compared the survival curves of each node positive for metastatic disease with those of the other two nodes, and each node with combinations of the other two nodes. What we found was that a positive apical node predicted the worst survival. That was more or less to be expected. The interesting thing, however, was that no difference could be found between the survival curves when a positive axillary node was compared with a positive internal mammary node. Simultaneously positive axillary and internal mammary nodes carried a poorer prognosis than either axillary or internal mammary node positivity alone. However, when the survival curve for simultaneously positive axillary and internal mammary nodes was compared with that for a positive apical node alone, no difference was noted. The same observation was made when this combination was compared with the overall stage C nodal group, in the index.

We were able to conclude that a positive axillary node has the same prognostic significance as a positive internal mammary node. That means that there is no difference in the prognostic weight carried by each lymph node chain when involved individually. When both nodes are positive simultaneously, the prognostic weight is the same as that of a positive apical node alone, or stage C nodal status overall. This implies that a positive apical node is a marker of extensive nodal disease *per se*. The apex can also be regarded as the area where the medial and lateral lymph channels of the breast converge. A positive apical node can therefore also serve as an indicator of involvement of both lymph channels, and this scenario, as we have shown, is as bad as a positive apical node alone. It would seem therefore that a double-node biopsy may provide the same prognostic information as a triple-node biopsy.

The problem now was to decide which two nodes should be removed, because tumour position in the breast has an influence on which nodes are potentially affected. Looking at this dilemma, we realised that for laterally located cancers of the breast the best likelihood of accurate assessment for a positive node was to biopsy the axillary and apical nodes. For central and medially located tumours, the axillary and internal mammary nodes should be biopsied. This means that for lateral tumours, if both axillary and apical nodes are negative the lymph node stage would be A, if only the axillary node is positive the stage would be B, and if both or

only the apical node is positive the stage would be C. For medial and centrally located tumours, if the axillary and internal mammary nodes are both negative it would be a stage A, if either of the two is positive it would be a B, and if both are positive it would be a C.

Finally, regarding the triple-node concept, I notice that the TNM staging systems for breast cancer currently incorporate this concept in their N3 lymph node category, where previously it was completely ignored. I think that our triple- or double-node biopsy principle from Nottingham can perhaps be seen as the predecessor of today's sentinel node biopsy concept. The work was published in the *British Journal of Surgery*.[3]

## Study 4 – lobular carcinoma

In the late 1980s there was a revival of interest in invasive lobular carcinoma of the breast. The main force behind this movement came from anatomical pathologists in the UK and the USA. At that time the histological classification of breast cancer was revised. I was taught at pre- and postgraduate level that invasive breast cancer can be divided into ductal and lobular cancers, and there it stopped.

However, over the years pathologists identified many histological subtypes of invasive ductal cancers based on the unique histological characteristics each one displayed. It was also noticed that the division of breast cancer into ductal and lobular was not entirely based on an anatomically different origin. For a long time it was thought that ductal carcinomas came from the ducts and lobular cancer from the lobules in the breast, but it became clear that both cancers develop from the same so-called 'terminal duct lobular unit' in the breast, the two differing with regard to cellular morphology and growth patterns. It was therefore decided that lobular cancer was just another unique subtype of breast cancer. In revising the histological classification for breast cancer the pathologists established a new category which they called 'special types', to accommodate all the special types identified at that stage. Lobular cancer was moved into this category.

All the activity in the laboratory eventually spilled over to the clinical arena. Clinicians began to wonder about the tumour behaviour of invasive lobular cancers and whether real differences in behaviour between lobular and ductal cancers exist. At that stage we knew that lobular cancer affects the opposite breast more often than ductal cancer. Anecdotal reports also stated that lobular cancer tends to be receptor positive more often than ductal cancer.

Against this background, we decided to perform a proper comparison between invasive lobular and invasive non-lobular carcinomas, to see whether real differences existed in prognosis, recurrence patterns and receptor status.

For both ductal and lobular cancers, we included in the study only tumours less than 5 cm in size. None of these patients received any systemic adjuvant treatment, as was the policy in Nottingham. The mean follow-up period was 64 months.

Five hundred and thirteen cases were identified, and we matched one case of lobular cancer to two cases of ductal cancer. Cases were controlled for age and stage. We made sure that the three cases in a matched group differed by no more than 5 years in age and by no more than 0.2 on the Nottingham prognostic index.

The main findings were that lobular cancers occurred significantly more often in the opposite breast, as had already been shown in other studies. They also tended to recur significantly more often in the operated breast following lumpectomy. This

finding was later substantiated in other studies. However, we found no difference between lobular and ductal cancers with regard to receptor status and distant metastatic disease patterns.

When we looked at survival, we noticed that lobular cancers had a slight but significant, overall survival advantage. Why are they associated with better survival? To answer the questions we divided the overall survival curve into the time up to the development of metastatic disease, the so-called 'metastatic disease-free interval', and the time after metastatic disease developed. We hoped that this would give us an idea of the response of the two types of cancer to treatment for metastatic disease. We found no difference between the two groups with regard to the metastatic disease-free interval. However, lobular cancer showed a significantly better survival than ductal cancer after metastatic disease developed. Exploring these findings further, we realised that metastatic lobular cancers respond better than metastatic ductal cancers to first-line endocrine treatment. The policy in Nottingham at the time was to treat metastases with endocrine treatment first, reserving chemotherapy for those who developed progressive disease on endocrine treatment.

We were able to conclude that in comparison with ductal cancers, lobular cancers attack the opposite breast four times more often and recur two and a half times more often in the operated breast after breast-conserving surgery. Lobular cancers are also associated with a slightly better survival rate because they respond better to first-line endocrine treatment for metastatic disease.

We could therefore show that there are differences in behaviour between lobular and ductal cancers. The take-home message of this study was that invasive lobular cancers are more aggressive locally and more prone to bilateral disease, be it synchronous or metachronous. The reason for this phenomenon is probably the propensity to be multicentric more often in both breasts, compared with ductal cancers. Clinically this underlines the importance of a disciplined follow-up programme for patients with lobular cancers, in the hope of diagnosing a loco-regional recurrence after lumpectomy or a second cancer in the other breast as early as possible. The work was published in the *European Journal of Surgical Oncology*.[4]

## Study 5 – subtypes of lobular carcinoma

As I have mentioned, a new interest in invasive lobular cancer developed during the 1980s. As more and more subtypes of invasive breast cancer were identified under the microscope, the pathologists started to recognise that lobular cancers as a group had the same tendency. It became clear that these cancers comprise a distinct family of subtypes. Eventually five subtypes of invasive lobular cancer were described by various pathologists in the UK and the USA. This led to reports being published in the literature at that time, mainly by pathologists, describing histological criteria for the classification of subtypes. However, information regarding clinical behaviour of these subtypes was scanty, anecdotal and incomplete. The reason for this is obvious. Invasive lobular cancers are relatively uncommon cancers, representing 10 - 15% of all breast cancers diagnosed. Subtypes are obviously even less common. It is therefore difficult for one centre to gather enough cases to do a proper clinical study on these subtypes.

In the study I discussed briefly above, I used the 171 cases of invasive lobular breast cancer discussed above to investigate the clinical behaviour of lobular cancer subtypes. The clinical information was already available, and we reviewed the histology of all the cases and classified the invasive lobular cancers into subtypes.

To recap briefly, these were all patients who presented with non-metastatic tumours of less than 5 cm. None received systemic adjuvant therapy after surgery, making them a very homogeneous group to study. The mean follow-up period for the whole group was 64 months. We investigated the different subtypes for differences in incidence, overall survival, disease-free survival, recurrence patterns and prognostic factors.

We found that invasive lobular cancers as a whole made up 13.6% of all breast cancers treated during the study period in Nottingham, which correlated well with prevalence figures in the literature. We also realised that the mixed variant (45.6%) and the classic variant (30.4%) are the two most common subtypes, accounting for about three-quarters of all subtypes. Third in line was the tubulo-lobular variant (13.5%), followed by the solid variant (6.4%) and lastly the rarest alveolar variant (4.1%).

The subtype with the best survival was the tubulo-lobular variant. The solid variant had the poorest overall survival, with the classic and mixed subtypes in between. The same trend was apparent when we looked at disease-free intervals. The alveolar variant was not included in these analyses, as the number was too small.

When looking at loco-regional recurrence rates and rates of distant metastatic disease, the same tendency prevailed. The tubulo-lobular variant fared the best and the solid and alveolar subtypes the poorest, with the other two in between. The loco-regional recurrence figures were a bit high, you might say, but remember that none of these cases received an axillary dissection in accordance with the practice in Nottingham. When they then developed metastatic lymph node disease during follow-up, the event was noted as a regional recurrence. I also showed you in the previous study that lobular cancers, as a family, have a higher local recurrence rate than non-lobular cancer after primary surgery. In addition, no patient received any systemic adjuvant treatment.

Finally, in order to find an explanation for these differences in behaviour, we looked for predictive factors. Looking at node positivity rates, the tubulo-lobular subtype again fared best and the solid subtype worst. The tubulo-lobular variant group also consists of relatively well-differentiated cancers, while the mixed and solid variants consist of relatively poorly differentiated cancers. Both these findings were statistically significant. This explains why tubulo-lobular cancers have such a good prognosis and the solid subtype such a poor prognosis. There was, however, no difference in receptor status between subtypes.

We could conclude that from a clinical perspective it is useful to subtype invasive lobular cancers, because there are differences in their behaviour. The tubulo-lobular subtype has the best prognosis and the solid subtype the worst, which can be explained by differences in various prognostic factors they display.

This was the first clinical study to address the clinical behaviour of invasive lobular cancer subtypes in a comprehensive way. The work was published in the *British Journal of Cancer*.[5]

## Study 6 – prognosis in stage III locally advanced breast cancers

It is common knowledge that stage III breast cancers are a heterogeneous group. Some are still operable, while others are advanced and inoperable. If one unravels all the variations in stage

III, one finds that 16 subgroups emerge. The TNM staging systems divide them into A and B subcategories, where 'A' means that the cancer is still confined to the breast. The B subcategory contains all the T4 tumours, which means the cancer has breached beyond the corpus mammae, infiltrating either the chest wall (T4a) or the overlying skin (T4b) or both (T4c). Inflammatory breast cancers (T4d) also fall into the B subcategory.

Of interest is that this division between A and B subcategories is based purely on the T-stage, namely T3 versus T4. Both A and B subcategories contain N1 and N2 cancers, and even N0 cancers in the B subcategory. Within the staging system we know that N-status overrides T-status in terms of prognostic significance. The question is, why did the authorities ignore this principle when they divided stage III breast cancers into A and B subcategories?

We decided to investigate by comparing survival curves of the different subgroups, and in doing so we actually analysed the prognostic significance of T- and N-status within this scenario.

To do this analysis, we compiled a cohort of 219 cases of stage III breast cancer treated over a 15-year period at our institution. Complete TNM data were available for each patient and all of them were followed up, until they died or for a minimum of 3 years if they survived that long.

Of the 219 cases, 51% fell into the stage III A subcategory where the tumour was still confined to the breast (T3), and 49% into the B subcategory where the tumour had breached the limits of the breast (T4).

Firstly we compared the survival curves of sub-stages A and B, and found that A had a better prognosis than B. This means that there is some prognostic sense in the current subgrouping of stage III breast cancers. We then compared within the A sub-category tumours with minimal (N1) nodal disease and those with more advanced (N2) disease (T3 N1 v. T1-3 N2). We showed that patients with minimal N1 disease fared significantly better.

In the B subcategory comprising T4 tumours, which had extended beyond the breast, we thought that those which invade only the skin (T4b) should carry a better prognosis than those which invaded the chest wall (T4a and c), or the so-called inflammatory cancers (T4d). The reason behind this thought process was that a mastectomy is still feasible in 70% of cases presenting with tumours invading the skin only (T4b), but is not indicated for tumours invading the chest wall, because it is not possible to obtain a clear margin. We therefore reasoned that tumours invading the chest wall were more advanced than those invading only the skin.

With this as background, we took all tumours with skin involvement only (T4b) and compared those with minimal (N0-1) nodal disease with those with more advanced (N2) disease (T4b N0-1 v. T4b N2). We could demonstrate again that patients with minimal nodal disease fared significantly better.

At that stage of the game we had two winners, namely the T3 N1 cases and the T4b N0-1 cases. We also had two losers, the T1-3 N2 cases and the T4b N2 cases. The obvious thing to do now was to play them off against each other. When we first compared the survival curves of the two winners with minimal nodal disease, we showed that patients with T3 tumours, still confined to the breast, did significantly better than those with T4b tumours, which invaded the skin. On the other hand, when we looked at the two losers with more advanced N2 disease there was no difference in survival, whether the tumours were confined to the breast (T1-3 N2) or

whether they invaded the skin (T4b N2). This means that N2 status predictably overrides the prognostic significance of T-status.

Because we could find no survival difference between the two so-called losers with the advanced N2 nodal disease, these cases could be combined into one group, labelled the T1-4b N2 subgroup. Finally, we had to compare this combined subgroup with the group of tumours invading the chest wall (T4a + c) plus those with inflammatory cancers (T4d), irrespective of their nodal status. These were the cases we thought would reflect the worst prognosis of all subgroups. When we did this comparison we found that the 'bad' group had a significantly poorer prognosis than the combined T1-4b N2 group. This illustrates what a poor prognostic sign chest wall invasion really is.

Although stage III breast cancers consist of 16 subgroups permutation-wise, this study illustrates that from a prognostic point of view, only four subgroups are really clinically relevant. These four subgroups are, ranked from the best to the worst prognosis, the T3 N1 group, followed by the T4b N0-1 group, followed by the combined T1-4b N2 group and finally the T4a, c, d N (any) group. This also demonstrates what prognostic roles T- and N-status play in stage III breast cancers.

The survival curves of these four prognostic subgroups are well spread out, and each one differs significantly from the others. The same principle prevails if we look at disease-free intervals.

We concluded that from a clinical perspective stage III breast cancer can be reduced from 16 to four subgroups with distinctly different prognoses. We consider this to be a more useful situation in clinical practice when it is necessary to predict prognosis and plan therapy in a patient presenting with locally advanced breast cancer. The study is still awaiting publication.

## Conclusion

I conclude by wishing this Society all success with its important role in promoting surgical research. This is the only forum in which young researchers can present their work in this region, and possibly on the continent. It is therefore vital that it continues, something which depends on our continued and dedicated support. Some may feel that the society does not yet compete fully in the international arena. If so, a great responsibility rests upon the shoulders of future presidents and executive committees, to guide and advance the society further so that it may eventually obtain international status. My advice would be to take from the past to explore the future. Be innovative in thought and action, and move boldly. This is ultimately my wish for the Society.

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