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A Rapid Genetic Counselling and Testing in Newly Diagnosed Breast Cancer is Associated With High Rate of Risk-reducing Mastectomy in BRCA1/2-positive Italian Women †

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Abstract and Introduction

Abstract

Background: Risk-reducing mastectomy (RRM) decreases breast cancer (BC) risk in *BRCA1/2* mutation carriers by up to 95%, but the Italian attitude towards this procedure is reluctant.

Patients and Methods: This is an observational study with retrospective design, using quantitative and qualitative research methods, aimed at evaluating the attitude towards RRM by rapid genetic counselling and testing (RGCT), at the time of BC diagnosis, compared with traditional genetic counselling and testing (TGCT), after previous BC surgery. Secondary aims were to investigate patient satisfaction after RRM and the rate of occult tumour in healthy breasts. A total of 1168 patients were evaluated: 1058 received TGCT, whereas 110 underwent RGCT.

Results: In TGCT, among 1058 patients, 209 (19.7%) mutation carriers were identified, with the rate of RRM being 4.7% (10 of 209). Conversely in RGCT, among 110 patients, 36 resulted positive, of which, 15 (41.7%) underwent bilateral mastectomy at the BC surgery time, showing an overall good satisfaction, measured by interpretative phenomenological analysis 12 months after the intervention.

Conclusions: Our study shows that RGCT in patients with a hereditary profile is associated with a high rate of RRM at the BC surgery time, this being the pathway offered within a multidisciplinary organization.

Introduction

BRCA1 or *BRCA2* germline mutations have been found in 15%–30% of patients from high-risk families, [1,2] and are responsible for up to 88% lifetime risk of developing breast cancer (BC). [3] *BRCA1/2* mutation carriers previously affected by BC have a 47% cumulative risk of developing contralateral BC (CBC) after 25 years. [4] Thus, newly diagnosed *BRCA1/2* BC patients could undergo bilateral mastectomy (BLM) to reduce the risk of CBC and avoid radiotherapy. Today, the new technologies available create opportunities for providing rapid genetic counselling and testing (RGCT) in about 3–4 weeks, delivering information potentially relevant for deciding the type of surgery and adjuvant therapy in real time [5,6] compared with traditional genetic counselling and testing (TGCT) that usually requires 6 months to be completed. Consequently, up to one half of the BC patients carrying a *BRCA1* or *BRCA2* mutation opt for a BLM. [7]

Data from the literature highlighted that psychological distress in BC patients approaching genetic counselling after surgery was not worsened by any extra psychological burden. [8] Wevers et al. showed that RGCT in high-risk BC patients may influence surgical treatment, causing no long-term psychosocial distress in the majority of cases. [9] Women who underwent contralateral prophylactic mastectomy (CPM), experienced no change in self-esteem (83%), level of stress (83%), and emotional stability (88%), but dissatisfaction with body appearance, feelings of lost femininity, and sexual problems have been reported. [10]

Our RGCT model was focussed on a multidisciplinary approach by involving into the counselling process oncologists, psychologists and general and plastic surgeons.

In this observational study we evaluated the attitude towards risk-reducing mastectomy (RRM) by RGCT, at the time of BC diagnosis, compared with TGCT, after previous BC surgery. Furthermore, we investigated patient satisfaction after RRM and the rate of occult tumour in healthy breasts.

Methods

Genetic Counselling

From January 1995 to January 2008, at the Modena Family Cancer Clinic, TGCT was exclusively offered to patients already treated for BC, according to an oncologist-based model for hereditary BC (HBC). [11] Patients belonging to families with the following characteristics were selected for *BRCA1/2* gene testing: (i) at least three relatives affected by BC in two different generations, with a first-degree relationship between each other and at least one BC diagnosed before the age of 40 or bilateral; (ii) at least one BC diagnosed at age ≤35, regardless of family history; (iii) at least one BC and one OC diagnosed in the same patient or in the same family; (iv) at least one BC diagnosed in a male, regardless of family history. [12] The complete analysis was carried out within 6 months. The post-test genetic session was scheduled for a month later.

Starting on January 2008 until December 2012, in parallel with TGCT, RGCT was offered to all newly diagnosed BC cases suspected of inheritance according to the same criteria used for TGCT. The different steps of RGCT, provided within 3–4 weeks from the BC diagnosis, are subsequently described.

At the time of BC diagnosis, information on family history is collected and in cases of suspected HBC, RGCT is proposed within a few days. The patient is invited for a pre-test counselling session in the presence of the oncologist and a psychologist; blood collection is carried out on the same day and *BRCA1/2* analysis is completed within 3 weeks. During this period, the patient meets, at least twice, with the psychologist and plastic surgeon to be supported and informed about the technique of RRM. As soon as the results become available, post-test genetic counselling is immediately scheduled with the oncologist and psychologist; general and plastic surgeons are involved only in cases of mutation detection. Finally, the patient undergoes breast surgery within 1 week after the post-test session.

The multidisciplinary pathways for RGCT and TGCT are shown in Figure 1.

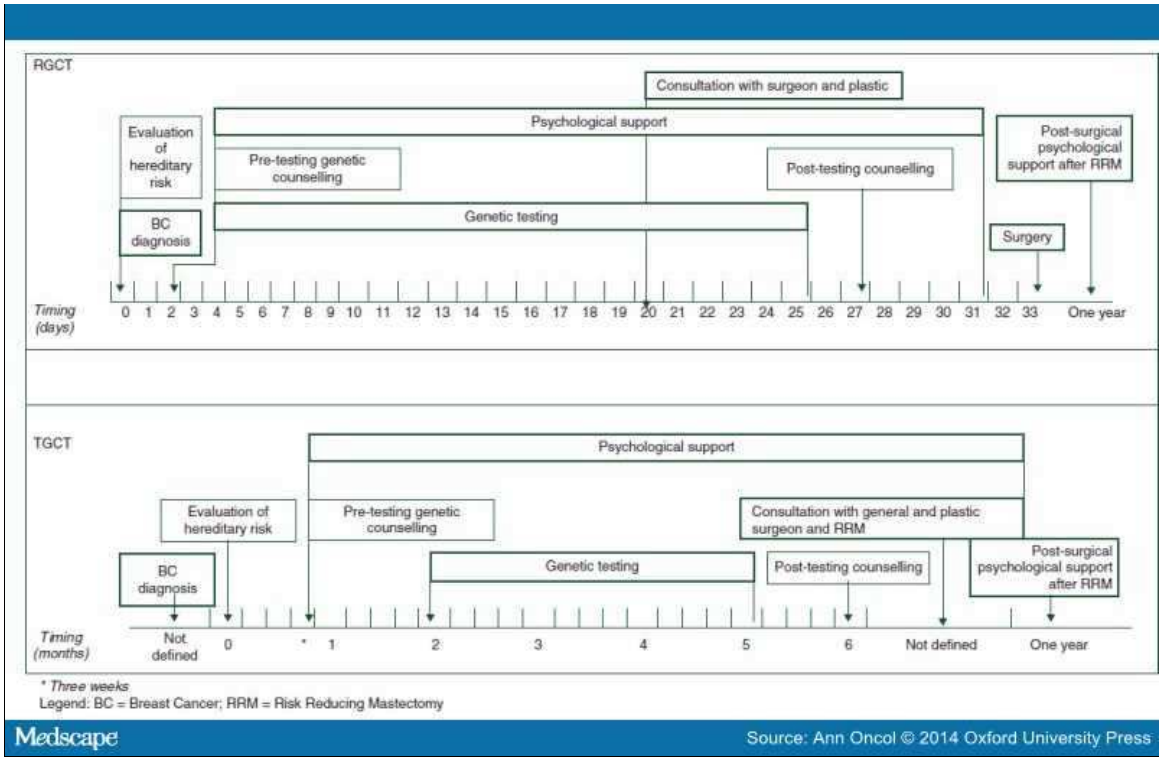

Figure 1.

Multidisciplinary RGCT and TGCT pathways.

***BRCA1* and *BRCA2* Gene Analysis**

The human investigations were carried out following approval by the local Human Investigations Committee.

Mutational screening was carried out by direct automated sequencing.

Screening for large genomic rearrangements in the *BRCA1* gene was done by multiplex ligation-dependent probe amplification and confirmed by long-range PCR.

Risk-reducing Mastectomy

The mode of RRM was different for affected and healthy breasts and between TGCT and RGCT.

In cases of TGCT, patients already affected by BC and treated with quadrantectomy plus radiotherapy, received autologous reconstruction with abdominal tissue. The breast mound was obtained from a pedicled transverse rectus abdominis muscle flap or as a free tissue transfer. A microvascular technique was required for a free flap, usually achieved by anastomosis of the deep inferior epigastric vessels (flap) and thoraco-dorsal or internal mammary vessels. The latissimus dorsi muscle flap with or without a skin paddle flap was also used for breast reconstruction. Otherwise, in cases of previous mastectomy, a delayed reconstruction with tissue expander and subsequent permanent implant was employed. For healthy breasts, a subcutaneous mastectomy with total preservation of the nipple-areola complex (NAC), positioning of tissue expander and subsequent permanent implant was used.

In cases of RGCT, affected breasts were treated with mastectomy, sparing or not the NAC depending on tumour localization, whereas the same technique used for TGCT was employed for healthy breasts.

Psychological Intervention

Two kinds of psychological intervention were routinely offered both in TGCT and in RGCT: (i) pre- and post-testing support for all patients; (ii) post-surgical support for 1-year composed of fortnightly appointments for patients subjected to RRM.

Statistical Analysis

The study employed a retrospective design, with quantitative and qualitative research methods.

Pre-test uptake rate, *BRCA* gene testing results and prophylactic surgery rate were compared by different approaches for TGCT and RGCT groups with the χ^2 test or Fisher's exact test.

To analyse attitude towards and satisfaction with RRM, a semi-structured interviews was conducted at 12 months after the surgery. Broad open questions were used. The interviews lasted about 45 min and allowed patients the time to raise issues as they wished. All interviews were tape-recorded with participant permission, transcribed verbatim and qualitatively analysed using 'interpretative phenomenological analysis'. [13] Two researchers independently conducted the initial analysis on the transcripts. They categorized the transcripts into fairly broad themes. A summary of the main themes that emerged from each transcript was compiled by the researches. Then, they compared their documents and came together to discuss them. This led to the identification of definitive broad themes. These broad themes were then broken down into more specific, fine-grained themes. This was achieved using a number of readings of each transcript. Fine-grained themes across transcripts were then compared again to reach a final complete agreement. When discrepancies occurred between the researchers, the themes were discussed until a consensus was reached. Broad themes and fine-grained themes were

coded and are presented in the Results.

Results

Sample Characteristics

Beginning in 1992, 3375 family histories were collected by the Modena Family Cancer Clinic.

In this database, we identified 1630 patients eligible for pre-test genetic counselling: 452 with multiple cases of BC, 648 belonging to pedigrees of either ovarian and BC, 443 cases of early-onset BC (<35 years of age) without a family history of BC and 87 male BC.

In total, 1168 patients (71.6%), mostly Caucasian, with a median age of 44 years and ranging between 18 and 90 years, underwent pre-test genetic counselling to date. One thousand and fifty-eight (69.6%) received the TGCT (1012 index cases and 46 affected familial cases), whereas 110 (100%) underwent RGCT (103 index cases and 7 affected familial cases), with a statistically significant difference (*P* = 0.02).

Of 1058 patients, 209 (19.7%) in the TGCT pathway tested positive, whereas 36 (33%) in the RGCT were revealed as *BRCA1/2* mutation carriers.

Rate of Uptake of RRM

Only 10 patients in the TGCT (4.7%) among 209 *BRCA* patients underwent RRM, compared with 15 (41.7%) in the RGCT. The consort diagram is displayed in Figure 2.

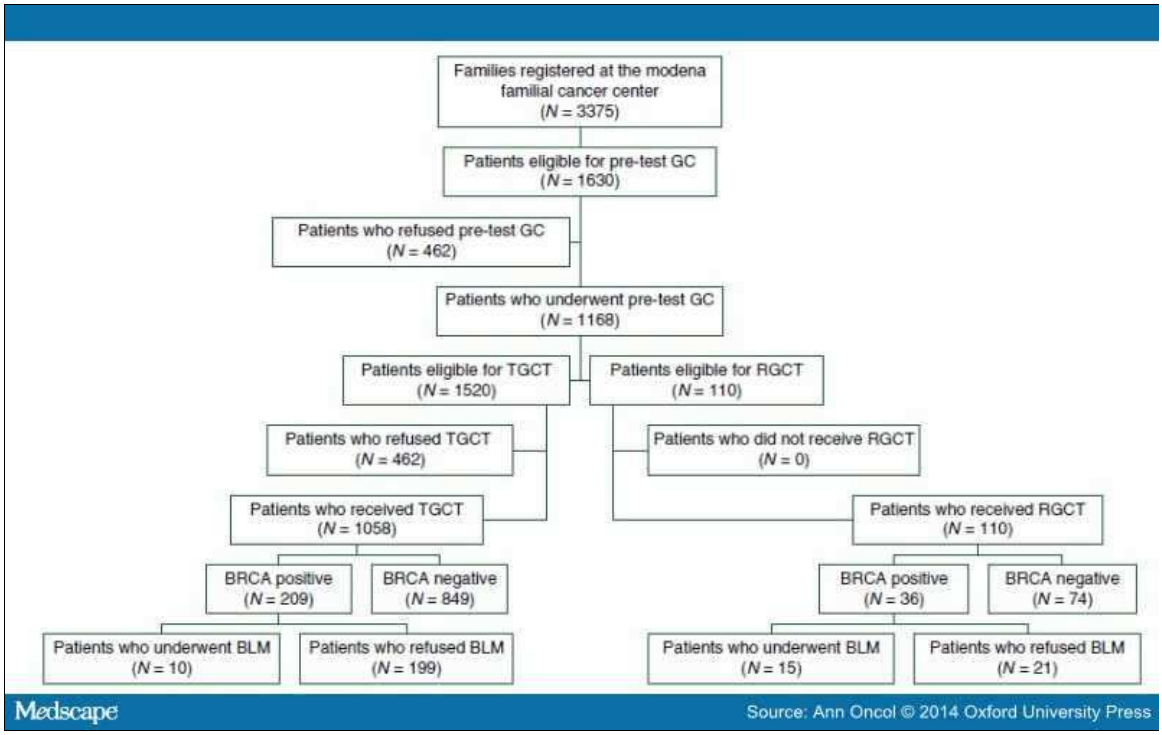

Figure 2.

CONSORT flow-diagram. GC, genetic counselling; TGCT, traditional genetic counselling and testing; RGCT, rapid genetic counselling and testing; BLM, bilateral mastectomy.

Details on results are shown in .

Table 1. Distribution of TGCT and RGCT steps among different risk categories

	Patients eligible for pre-test GC			Pre-test GC						Positive BRCA1/2						BLM					
	Tot	TGCT	RGCT	Tot (%)	TGCT		RGCT		*P*	Tot (%)	TGCT		RGCT		*P*	Tot (%)	TGCT		RGCT		*P*
					IC	AFP	IC	AFP			IC (%)	AFP (%)	IC (%)	AFP (%)			IC (%)	AFP (%)	IC (%)	AFP (%)	
Multiple BC	452	411	41	418 (92.5)	Tot 377 (91.7)		Tot 41 (100)		NS	84 (20)	Tot 70 (18.6)		Tot 14 (34)		<0.001	14 (16)	Tot 6 (8.5)		Tot 8 (62)		NS
					360		40				62 (17)		13 (32)				4 (6)		7 (58)		
						17		1				8 (47)		1 (100)				2 (25)		1 (100)	
BOC	648	624	24	359 (55.4)	Tot 335 (53.7)		Tot 24 (100)		<0.001	107 (29.8)	Tot 98 (29.2)		Tot 9 (38)		0.001	7 (5.1)	Tot 4 (4)		Tot 3 (33)		NS

					310		20				81 (26)		8 (40)				3 (4)		3 (38)		
						25		4				17 (68)		1 (25)				1 (5.8)		0 (0)	
EOBC	443	401	42	318 (71.7)	Tot 276 (68.8)		Tot 42 (100)		0.001	44 (13.8)	Tot 32 (11.6)		Tot 12 (29)		0.04	4 (9)	Tot 0 (0)		Tot 4 (33)		NS
					272		40				29 (11)		11 (27)				0 (0)		3 (27)		
						4		2				3 (75)		1 (50)				0 (0)		1 (100)	
MBC	87	84	3	73 (84)	Tot 70 (83.3)		Tot 3 (100)		NS	10 (13.7)	Tot 9 (12.8)		Tot 1 (33)		NS	0 (0)	Tot 0 (0)		Tot 0 (0)		NS
					70		3				9 (13)		1 (33)				0 (0)		0 (0)		
						0		0				0 (0)		0 (0)				0 (0)		0 (0)	
Tot	1630	1520	110	1168 (71.6)	Tot 1058 (69.6)		Tot 110 (100)		0.02	245 (21)	Tot 209 (19.7)		Tot 36 (33)		NS	25 (6)	Tot 10 (4.7)		Tot 15 (41.7)		NS
					1012		103				181 (18)		33 (32)				7 (4)		12 (37)		
						46		7				28 (60.8)		3 (43)				3 (10.7)		3 (100)	

GC, genetic counselling; BLM, bilateral mastectomy; IC, Index case; AFP, affected familial people; TGCT, traditional genetic counselling and testing; RGCT, rapid genetic counselling and testing; BOC, breast-ovarian cancer; EOBC, early-onset breast cancer; MBC, male breast cancer.

Tumour characteristics of BC in both breasts of patients subjected to RRM are shown in .

Table 2. Characteristics of BC in affected and contralateral breast of patients undergone RRM

	Affected breast (*N* = 25)		**Contralateral BC (*N* = 6) (24%)**	
	TGCT (10)	**RGCT (15)**	**TGCT (2)**	**RGCT (4)**
Histology				
DIC	7 (70)	13 (87)	0 (0)	1 (25)
LIC	1 (10)	0 (0)	0 (0)	0 (0)
DCIS	1 (10)	2 (13)	1 (50)	1 (25)
DIN1a	0 (0)	0 (0)	0 (0)	2 (50)
DIN1b	1 (10)	0 (0)	1 (50)	0 (0)
Grading [a]				
1	0 (0)	0 (0)	0 (0)	0 (0)
2	3 (37)	4 (40)	0 (0)	0 (0)
3	5 (63)	9 (60)	0 (0)	1 (100)
ER [a]				
Positive	3 (37)	8 (53)	0 (0)	0 (0)
Negative	5 (63)	5 (47)	0 (100)	1 (100)
PgR [a]				
Positive	2 (25)	9 (69)	0 (100)	0 (100)
Negative	6 (75)	4 (31)	0 (0)	1 (100)
Ki67 [a]				
≤14%	3 (37)	3 (23)	0 (0)	0 (100)
>14%	5 (63)	10 (77	0 (100)	1 (100)
c-Erb [a]				
Positive	0 (0)	2 (15)	0 (0)	0 (0)
Negative	11 (15)	11 (85)	0 (0)	1 (0)
BRCA1	6 (60)	5 (33)	0 (0)	1 (25)
BRCA2	4 (40)	10 (67)	2 (100)	3 (75)
T size [a]				

T1	5 (63)	9 (69)	0 (0)	1 (100)
T2	3 (37)	4 (31)	0 (0)	0 (0)
Nodes [a]				
N0	3 (37)	9 (69)	0 (0)	0 (0)
N1	4 (50)	3 (23)	0 (0)	1 (100)
N2	1 (13)	1 (8)	0 (0)	0 (0)

Values are *n* (%).
[a]Only for invasive carcinoma.
DIC, ductal infiltrating carcinoma; LIC, lobular infiltrating carcinoma; DCIS, ductal carcinoma *in situ*; DIN, ductal intraepithelial neoplasia; ER, oestrogen receptor; PgR, progesterone receptor.

In total six pathological findings, 4 among 15 individuals subjected to RRM in the RGCT pathway (26.7%) and 2 among 10 patients subjected to RRM in the TGCT pathway (20%) were found in healthy breasts. In the RGCT, two patients showed a pre-neoplastic disease (DIN1a), one a DCIS and one a pT1a, triple-negative ductal infiltrating carcinoma with a positive lymph node in axilla, whereas in the TGCT pathway, one patient showed a DCIS and one a DIN1b.

Statistically, more *BRCA1* patients carried out RRM in the TGCT pathway than in the RGCT one (60% versus 33%, $P = 0.041$), whereas *BRCA2* carriers had more RRM in the RGCT than in the TGCT pathway (67% versus 40%, P = NS).

BRCA2 mutation carriers experienced more *in situ* (2 cases) and pre-neoplastic lesions (3 cases) in the healthy breasts than *BRCA1* carriers.

Considering the surgical results after RRM, only one 31-year-old *BRCA1* patient experienced an expander rejection in the TGCT pathway.

Psychological Issues of RRM

Sociodemographic features of women who accepted psychological support were superimposable between the two groups: for five patients (50%) belonging to the TGCT group the mean age was 38 years with a standard deviation (SD) of 7 years; two patients were not married, one was nulliparus; the mean years in education were 13 (SD = 5 years). For eight patients (53%) in the RGCT group, the mean age was 37 (SD = 6 years); two patients were not married, two were nulliparus; the mean years in education was 14 (SD = 5 years).

The remainder refused because they were already being followed in other oncological centres, or they lived far from our centre. No differences in socio-demographic features between patients who did or did not receive psychological support were highlighted.

Qualitative analyses of all verbatim transcriptions led to the identification of four broad themes that are resumed.

1. *Decision for RRM*
   In both groups, women were influenced by: the attempt to preserve their lives; worry about cancer; the presence of young children for whom patients felt responsible. Among the TGCT group, the decision was influenced also by stress experienced during surveillance programmes.

2. *Impact of surgery on body image*
   Almost all, women experienced low satisfaction because they had not yet completed breast reconstruction with permanent implant at the time of interview.

3. *Satisfaction with the decision of RRM*
   All women were satisfied with their decision to undertake RRM. A further fine-grained themes emerged concerning satisfaction: both groups were satisfied with the genetic counselling received.

4. *Worry about cancer and Psychological Adjustment*
   After RRM, all patients were relieved about the BC risk reduction and were psychologically well adjusted to the situation. Only one patient belonging to the TGCT developed depression after RRM probably due to reconstruction failure. Significant negative changes in sexual functioning were reported by three women in the RGCT group and two women from the TGCT group even if their partners were supportive.

Discussion

Usually, patients suspected of HBC are investigated by genetic counselling for *BRCA1/2* testing after surgery. [14] Then, women found to be *BRCA1* or *BRCA2* carriers may opt for delayed BLM, although this could prove quite challenging, particularly in cases of previous quadrantectomy plus radiotherapy. [15]

By offering RGCT at the time of BC diagnosis, it is possible to incorporate genetic results into treatment decision-making, informing women about the risk of developing second tumours and making informed choices regarding primary surgical treatment. The results of the RGCT are not only expected to influence the choice of surgical treatment, but may also, in the near future, have an impact on new targeted therapies such as PARP inhibitors. [16]

Uptake rates in BC patients for contralateral mastectomy ranged between 0% and 49% in *BRCA1/2* carriers. [2,17] The low rate of uptake and the long interval period of delayed CPM in TGCT threaten *BRCA1/2* carriers with a new primary BC. Our study is the first to compare two different modalities of genetic counselling showing that moving from TGCT to RGCT increases the uptake rate of RRM. Another important result of our study relates to the identification of contralateral disease in 24% of healthy breasts. Among six pathologic reports, three were considered as pre-neoplastic lesions (two DIN1a and one DIN1b) and three were ductal carcinomas (two DCIS and one DIC). Unfortunately, the only DIC, although it was a pT1a tumour, had a micro-metastatic nodal involvement, underlying the aggressiveness of triple negative BRCA-related tumour. The rate of second tumour, also considering the potential evolution of pre-neoplastic lesions, was in favour of *BRCA2* carriers rather than *BRCA1* ones. This was in contrast with previous published experiences [18] where *BRCA1* carriers showed the highest rate of CBC. Furthermore, we found that the RGCT identified more gene mutation carriers (33%) than the TGCT (19.7%), even if no statistically significant differences were observed between the two groups. These data could be explained by the improvement in genetic analysis over time.

As suggested by Kurian et al. [19] if RRM is capable of decreasing the risk of BC onset we could expect that the RGCT will improve the survival of *BRCA1/2* carriers. Furthermore, as previously reported, [11] patients subjected to RRM showed good psychological adjustment although they did experience sexual problems and body image dissatisfaction related to the incomplete reconstructive procedure. The RGCT was viewed as highly acceptable by all participants as reported before. [6]

An important study limitation is the fact that causal inferences cannot be drawn due to the observational study design. Concerning psychological evaluation this study employed qualitative methods, but further research with standardized measures should be considered.

Regarding clinical implications, the current findings suggest the importance of actively involving surgeons in the counselling process to assist patients to have realistic expectations about surgery outcomes, and to promote autonomous and informed decision-making. In conclusion, the findings of this research may be used to inform a prospective study examining the impact of TGCT compared with RGCT on psychological and surgical outcomes.

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