Diploma Thesis

Differences in the interpretation of the R classification
-with a special focus on breast cancer

Submitted by

Philipp Fischer

for the Academic Degree of

Doktor der gesamten Heilkunde

(Dr. med. univ.)

at the

Medical University of Graz

Diagnostic and Research Institute of Pathology

under the supervision of

Dr.[in] Sandra Sunitsch

and

Ao. Univ.-Prof. Dr. Peter Regitnig

Graz, Date 26.06.2023

Declaration of Academic Integrity

I hereby declare that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, Date 26.062023 Philipp Fischer m.p.

Acknowledgements

I would like to express my genuine appreciation to my first supervisor, Dr.in Sandra Sunitsch, for her time, patient guidance, and constructive as well as valuable input throughout the entire writing process.

I am also grateful for the advice and support provided by my second supervisor, Ao. Univ.-Prof. Dr. Peter Regitnig.

I would also like to thank Research Prof. Priv.-Doz. Mag.rer.nat. Dr.rer.nat. Alexander Avian for his support and input regarding the construction and analysis of the survey.

I am grateful to the following organizations for distributing the survey web link to their members: IAP Austria, Österreichische Gesellschaft für Senologie, Deutsche Gesellschaft für Senologie, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe, Österreichische Gesellschaft für Radioonkologie, Radiobiologie und Medizinische Radiophysik, Österreichische Gesellschaft für Chirurgie, and Austrian Society of Surgical Oncology.

A special thanks belongs to the participants of this survey. Thank you for taking the time to contribute your opinions.

Lastly, I would like to express my gratitude to my friends and family, who have supported me throughout my studies.

I. Table of Contents

II. List of Abbreviations

- AJCC American Joint Committee on Cancer
- BCS Breast Conserving Surgery
- BCT Breast Conserving Therapy
- CAP College of American Pathologists
- CRM Circumferential Resection Margin
- DCIS Ductal Carcinoma In Situ
- EIC Extensive Intraductal Component
- MRI Magnetic Resonance Imaging
- NCCN National Comprehensive Cancer Network
- NST Neoadjuvant Systemic Therapy
- P Pathologists
- S/G Surgeons / Gynaecologists
- SLN Sentinel Lymph Node
- SLNB Sentinel Lymph Node Biopsy
- UICC Union Internationale Contre le Cancer
- WBRT Whole Breast Radiation Therapy

III. Table of Figures

IV. List of Tables

V. Zusammenfassung

Hintergrund: Die “Residualtumor- (R) Klassifikation“ der TNM-Klassifikation der UICC gibt Auskunft über das Vorhandensein oder Fehlen von Tumorgewebe nach einer Behandlung. In der vorliegenden Arbeit wurden zahlreiche Leitlinien sowie die “TNM Klassifikation maligner Tumoren“, das “TNM Supplement“ der UICC und das “AJCC Cancer Staging Manual“ hinsichtlich ihrer Interpretation der “R Klassifikation“ überprüft. Zudem wurde ein anonymisierter Fragebogen erstellt, um die Meinungen verschiedener medizinischer Fachrichtungen, die sich mit Brustkrebs befassen, zu sammeln. Ziel dieser Arbeit war es, dieses Thema zu bearbeiten und verschiedene Perspektiven vorzustellen. Dabei sollte herausgefunden werden, welche unterschiedlichen Auffassungen zwischen den verschiedenen medizinischen Fachrichtungen bestehen.

Methoden: Der Fragebogen bestand aus 22 Fragen und wurde in drei Abschnitte unterteilt: “Allgemeines“, “Allgemeine TNM-Klassifikation“ und “Spezifische Fragen zur Diagnose von Brustkrebs“. Insgesamt nahmen 303 Ärzt*innen an der Umfrage teil und beantworteten sie entweder vollständig (172), teilweise (131) und manche öffneten den Fragebogen ohne eine Frage zu beantworten (101). Jedoch konnten nur Antworten von Gynäkolog*innen/Chirurg*innen (88) und Patholog*innen (80) berücksichtigt werden, da nur in diesen Berufsgruppen die Stichprobengröße groß genug war, um analysiert zu werden. Nach Beendigung der Umfrage wurden die gesammelten Antworten der Teilnehmer*innen mithilfe von “SPSS Version 26“ analysiert. Dabei wurden absolute Häufigkeiten und Prozentsätze verwendet, um die Antworten einzelner Fragen zu zeigen. Zudem wurde der Person-Chi-Quadrat-Test durchgeführt, um festzustellen, ob es signifikante Unterschiede zwischen den Meinungen der verschiedenen medizinischen Fachrichtungen gibt.

Ergebnisse: Die Studie konnte zeigen, dass erhebliche Unterschiede hinsichtlich der Interpretation der “R Klassifikation“ sowohl zwischen den untersuchten medizinischen Fachrichtungen als auch innerhalb derselben Fachrichtung bestehen.

Conclusio: Die Arbeit schließt mit Implikationen für weitere Forschungen, schlägt eine separate Klassifikation für den Resektionsrand vor und nennt zwei unterschiedliche Ansätze zur Bewertung der “R Klassifikation“. Dies sollte entweder gemeinsam interdisziplinär im Tumorboard durchgeführt werden oder vom*von der behandelnden Arzt*Ärztin, welche*r mit der medizinischen Vorgeschichte des*der Patient*in am besten vertraut ist.

VI. Abstract

Background: The “Residual Tumour (R) Classification” of the TNM classification of the UICC reports about the presence or absence of residual tumour after treatment. In this study, we reviewed numerous guidelines as well as the “TNM Classification of Malignant Tumours”, the “TNM Supplement” of the UICC and the “AJCC Cancer Staging Manual” regarding their interpretation of the “R classification” and created an anonymised questionnaire to gather the opinions of the “R classification” in various medical professions dealing with breast cancer. The aim of this thesis was to work on this topic and present different perspectives. The objective was to find out what different understandings exist between the various medical professions.

Methods: The questionnaire consisted of 22 questions and was divided into three sections: “General”, “General TNM Classification” and “Specific Questions Regarding Breast Cancer Diagnosis”. A total of 303 practitioners participated in the questionnaire, answering it either fully (172), partially (30), and some participants solely opened it without starting (101). However, only the answers of gynaecologists/surgeons (88) and pathologists (80) could be considered because the sample sizes of these two professions were large enough to be analysed. When the survey closed, the collected answers and the participants’ opinions were analysed using “SPSS version 26”. Frequencies and percentages were used to display responses to individual questions as well as Person’s Chi-Square Test to analyse if there is a significant difference between the opinions of the various medical professions.

Results: The study could show that there exist considerable differences regarding the interpretation of the “R classification” among the examined medical professions as well as within the same medical profession.

Conclusion: The thesis concludes with implications for further research, proposes a separate classification for the resection margin, and lists two different approaches to the assessment of the “R classification”. It should either be done together on an interdisciplinary basis in the tumour board or by the treating physician who is most familiar with the patient’s medical history.

1 Introduction

The "Residual Tumour (R) Classification"[1(p. 10)] of the TNM classification of the UICC reports about the presence or absence of residual tumour after treatment. This applies to the primary tumour site with its local extent as well as potential remaining distant metastases.[1, 2]

Some clinicians use the "R classification" as a sole resection margin definition and use "R0" synonymously for tumour-free resection margins.[3] This applies not only to individual clinicians, but also to pathologists. The "residual tumour" under the "R classification" means the residual tumour load in the patient after surgery and not just a "pure" resection margin assessment with its locoregional extent.[2, 3]

The aim is to work on this topic, with a special focus on breast cancer, as part of a diploma thesis by carrying out a survey in the medical profession using an anonymised questionnaire with the research hypothesis that there are significant differences in the interpretation of the "R classification" between different medical professions. The objective is to find out what different understandings exist between the various medical professions.

To achieve this, there is first a theoretical part with a literature review of the "R classification" of the "TNM Classification of Malignant Tumours"[1] as well as the "TNM Supplement"[2] of the UICC, the "AJCC Cancer Staging Manual"[4] and of selected guidelines[3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15] regarding the treatment of breast cancer. The second part tries to analyse the views of the "R classification" in different medical professions dealing with breast cancer. To do so, an anonymised questionnaire was created, using the knowledge of the theoretical part, and it was distributed to specialists. Finally, the findings are analysed by statistical analysis, presented, and discussed.

1.1 TNM Classification

1.1.1 Historical Overview of the "R classification" in the UICC TNM System

The beginnings of the TNM system were established by Dr. P. Denoix in Paris from 1943 to 1952. In 1950, the "Union Internationale Contre le Cancer" (UICC) convened the "Committee on Tumour Nomenclature and Statistics". For the classification of the clinical stages, this committee has used the common definitions of the local extent of malignant

tumours, as proposed by the "Subcommittee on the Registration of Cases of Cancer as well as Their Statistical Presentation" of the "World Health Organisation" (WHO).[16(p.IX)]

In 1953, a meeting of the "Committee on Tumour Nomenclature and Statistics" and the "International Commission on Stage Grouping in Cancer and Presentation of the Results of Treatment of Cancer" (ICPR), organised by the "International Congress of Radiologists", was held. In this meeting, they agreed on a common classification for malignant tumours on the basis of the TNM system.[16(p.IX)]

In 1954, the UICC established the "Committee on Clinical Stage Classification and Applied Statistics", to classify malignant tumours on different anatomical sites.[16(p.IX)] From 1954 to 1967, this committee published nine brochures in which 23 different sites were described. In 1966, the committee was reorganised into the "Committee on TNM Classification".[17(pp.VII-VIII)] In 1968, all nine brochures were published together in the "Livre de Poche".[16(p.X), 17(p.VIII)]

In the 1980s, several meetings between the UICC and the "American Joint Committee on Cancer" (AJCC) were held to standardise various interpretations of classifications and develop a unified TNM system. As a result, the fourth edition of the "TNM Classification of Malignant Tumours" was published in 1987. The third edition of the "Manual for Staging of Cancer", which was published in 1988, contains the exact same rules of classification and stage groupings.[18, 19] The "Residual Tumour (R) Classification" was mentioned for the first time in the fourth edition of the "TNM Classification of Malignant Tumours".[16, 17, 18, 20]

In the above-mentioned fourth edition, the "R classification" of the UICC has been stated as the absence or presence of „residual tumour after treatment" and should be described as "R". The application of "R" is optional in this edition. The categories are:

"RX Presence of residual tumour cannot be assessed
R0 No residual tumour
R1 Microscopic residual tumour
R2 Macroscopic residual tumour"[18(p.10)]

In 1993, the first "TNM Supplement" was published, with the goal to clarifying specific definitions and rules that had not been clearly described in the fourth edition of the "TNM Classification of Malignant Tumours".[21(Preface VI)]

In the chapter “Residual Tumor (R) Classification“, it is depicted that TNM and pTNM only characterise the anatomic extent of the tumour without consideration of the treatment. The “R classification“ deals with the tumour situation after treatment; therefore, it reflects the efficiency of a therapy, influences subsequent treatment, and is a “strong predictor of prognosis“. [21(p.9)]

Furthermore, it is explained that in the “R classification“, not only the local-regional tumour is taken into consideration, but also the remaining distant metastases[21].

Following this, the definition of the “R0“ classification is explained. “R0“ means complete remission or a surgical resection for cure. This is applied if no residual tumour can be detected by any diagnostic means. It does not preclude undetectable residual tumour, from which a tumour recurrence or metastasis can occur. “R0” “corresponds to no detectable residual tumour and is not identical to cure”[21(p.12)].

The “R classification“ can be used after surgical resection, after radiotherapy, chemotherapy or multimodal therapy. For nonsurgical treatments, the existence of residual tumour can be identified through clinical methods. After surgery, the application of the “R classification“ is possible through a close exchange between the surgeon and the pathologist. The procedure for this process is illustrated in Figure 1:

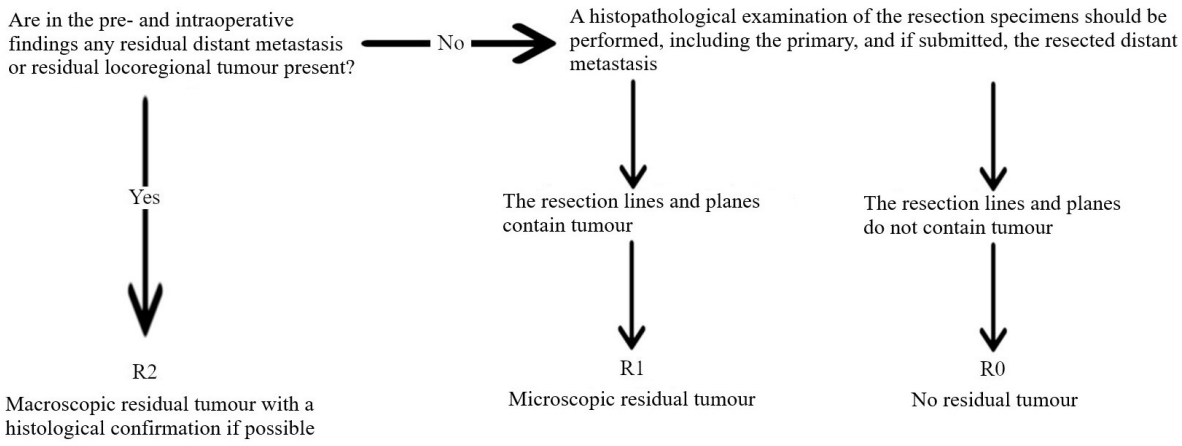

Figure 1: Illustration of the procedure of Residual Tumour (R) Classification

(Recreation of “Hermanek P, Henson DE, Hutter RVP, Sobin LH editors. TNM Supplement. Berlin: Springer-Verlag Berlin Heidelberg; 1993 “)

It is possible that in the “R0“ group, there are cases that are designated with “M0“ or “M1“. In the latter, beside the primary tumour, the lymphatic drainage as well as the distant metastases also have to be removed entirely.[21(p.12)]

The “R classification“ is not affected if, in a tumour resection specimen with formal lymphadenectomy, the “marginal“ or “apical“ lymph node is involved. Such a node is

characterised by being the most distant from the primary tumour and the closest to the resection line.[21(p. 13)]

The tumour should be removed with a clear topographical orientation of the resected tissue. If it is not removed “en bloc“, but rather in multiple pieces, a “RX“ classification should be used.[21(p. 14)]

If a peritoneal lavage cytology is positive, it is classified as “M1“ and “R1“ even if there is no evidence of residual tumour. If a conservative resection of breast cancer is performed, cell suspensions scraped off the surface of the resection margin can be examined cytologically. If this examination is positive, it corresponds to a “R1”, even if the following histological examination is negative.[21(p. 14)]

In the chapter “Optional Proposals for Testing New Telescopic Ramifications of TNM“, optional subdivisions of the existing T, N, and M categories are proposed. This is to accommodate the collection of additional data without altering the definitions of the existing TNM classification. This concept permits an orderly expansion of TNM and allows the testing of subcategories for prognosis and treatment planning considerations. In the subchapter “Markers of Residual Tumour“, it is suggested that “R0“ is subdivided into two categories. “R0a“ in case of negative tumour markers “after tumour resection for cure“. “R0b“ when there are still elevated or even rising tumour marker levels within four months “after tumour resection for cure”. [21(p.102)]

In 1997, the fifth edition of the “TNM Classification of Malignant Tumours“ was published. Although there are some changes regarding the “R classification” from the previous edition, they have already been described in the first edition of the “TNM Supplement“.[22]

The second edition of the “TNM Supplement“ was published in 2001. There are no relevant changes concerning the statements and definitions of “R”. Also, the definitions for “R0” and “R1” stay the same. The first noticeable change is that cases with a macroscopic residual tumour “R2“ can be differentiated, either into “R2a“, if there is no histological confirmation of a residual tumour or into “R2b“, if a histological confirmation is given.[23(p.11)]

Additionally, it is mentioned that if a non-invasive carcinoma, an in situ component, exists at the resection margin, it should be recorded with the suffix “R1(is)“.[23(p.12)]

Examination of resection margins is done by conventional methods in processing of suspicious areas by gross examination. Besides these conventional methods, there are newer techniques to refine the "R classification". Below are three examples of such refined techniques:

1. As introduced by Veronesi et al.[24] for breast cancer, imprint cytology for evaluation of the resection margin can be used. This has been applied to other tumour types as well, like stomach cancer.[23]
2. For the detection of metastasis on the peritoneum which are grossly not recognisable, a cytological examination of ascites or abdominal lavage fluid can be applied. This method can be used for gastric carcinomas. In the "R classification", "R1 (cy+)" may be used.[23]
3. An examination of bone marrow biopsies of patients, who do not show evidence of bone metastasis with monoclonal antibodies against cytokeratin, has been applied for gastric carcinomas by Schlimok et al.[23, 25]

It is clarified that "R1" should be applied only if the tumour is transected; in any other case, "R0" should be used. However, different opinions exist regarding this topic: on the one hand, Erlangen and Australia have diagnosed "R1" only if the tumour has been present at the resection margin; on the other hand, Quirke[26] and Compton et al.[27] have used "R1" in cases where the tumour has been present 1mm in distance from the resection margin. The German Documentation system suggests applying the rules but recording the cases, where tumour cells are found 1mm or less away from the resection margin. [23]
In the "R classification", the serum levels of tumour markers are not considered.[23]

The sixth edition of the "TNM Classification of Malignant Tumours" was published in 2002. The statements and definitions regarding the "R classification" stayed the same. In the German edition, there is a translator note which states that the "R classification" is not an integral part of the TNM classification for historical reasons, but for its prognostic value, especially after surgical treatment, it is an essential component. In the "Working Group of German Tumour Centres" (ADT) and the German Cancer Society, its use is mandatory for the tumour classification beside the TNM system.[28(p.15)]

The third edition of the ”TNM Supplement“ was published in 2003. The only difference to the second edition, in regard to the “R classification“, is a reference to a journal article from Wittekind et al. “TNM residual tumour classification revisited“[29], in which further details of the “R classification“ are discussed.[30(p.14)]

It is mentioned in this paper that the assignment of the “R classification” must be performed by a designated individual who has access to the complete patient data. This person could be a surgeon, medical oncologist, radiation oncologist, tumour registrar, or pathologist.[29(p.2513)]

In 2009, the seventh edition of the “TNM Classification of Malignant Tumours“ was published. The statements and definitions regarding the “R classification” stayed the same. Regarding the “R classification”, there is an additional note: sometimes this classification is used for the primary tumour site and the locoregional extent, while sometimes also the distant metastases are included in the classification. It is suggested that you clarify the specific application.[31]

In 2012, the fourth edition of the “TNM Supplement“ was published. One difference from previous editions is that if the “R classification“ is used, it should also be indicated at which site the residual tumour is located. For example, if a colonic polypectomy margin is positive for cancer, the classification is “R1 (colon)”. If in the subsequent colectomy the resection margin is free of tumour, it would change to “R0 (colon)“. If at the colectomy a microscopical liver metastasis is found, which is confirmed histologically, it is reported as “R2 (liver)“. But this described process needs close cooperation between the surgeon and the pathologist.[32]

Moreover, the positive “marginal“ or “apical“ lymph node does not affect the “R classification“, as already mentioned before, unless it is transected at the resection margin.[32]

Additionally, the term “R0-ablation“ has occasionally been used in cases, where no residual tumour after radiofrequency ablation of a liver metastases can be detected. However, a “R0“ classification needs a histopathological examination of the resection specimen; therefore, the correct term would be “complete clinical response“.[32]

Furthermore, in the previous editions of the “TNM Supplement“, it has been pointed out that there are disagreements concerning the application of “R1“, in cases where tumour

cells can be found 1mm in distance from the resection margin. It is once again mentioned that, according to the UICC, "R1" can only be applied when the tumour is transected. In recent years, an alternative definition of the involvement of the resection margin has been used, the "circumferential resection margin (CRM)". The first specification of the "CRM" has been made for rectal cancers, but also for other tumour sites.[32]

The "CRM" is positive when a tumour can be detected directly at the resection margin or at a distance of 1mm or less from the "CRM". The term "CRM negative" can be used when the distance between the tumour and the "CRM" is more than 1mm.[32]

Furthermore, it is pointed out that, especially in the United States (US) and Canada, the "R classification" has only been used to describe the extent of the primary tumour and its locoregional site, while elsewhere the distant metastases have also been included in the "R classification". [32]

Because of its strong prognostic value, distant metastasis should be included in the "R classification", which is in accordance with the initial definition of 1977[33] [32].

Further ambiguities exist because of different definitions regarding the resection margin. To prevent further uncertainties regarding the resection margin, an enhanced "R classification" has been proposed with the following categories:

"RX	Presence of residual tumour cannot be assessed
R0 > 1mm	No residual tumour, minimal distance between tumour and resection margin >1mm
R0 ≤ 1mm	No residual tumour, minimal distance between tumour and resection margin ≤ 1mm
R1-dir	Microscopic residual tumour, tumour directly at the resection margin (tumour transected)
R2a	Local macroscopic residual tumour
R2b	Distant macroscopic residual tumour
R2c	Macroscopic residual tumour in both sites"[32(p.17)]

After neoadjuvant treatment, the "R classification" can only be applied if viable tumour at the resection margin is considered. Scars, fibrotic nodules, granulation tissue, or mucin lakes occurring at the margin do not qualify as "R1".[32(p.17)]

The next chapter discusses the "Definitions of Completeness of Resection", with the prefix "R0(un)". This category has been proposed for testing to classify the cases in which "R0"

is too imprecise. Because of "General Rule No. 4"[32(p.3)], which states that if there are any concerns regarding the correct selection from any category of the TNM system, the less advanced should be applied due to the otherwise negative prognostic influence. Thus, this category has been suggested to list characteristics which fall into the category "uncertain resection", meaning no visible or histological verification of residual tumour, but fall into any of these two reservations:

1. The examination of the lymphadenectomy specimen contains a smaller number of nodes or nodal stations than is ordinarily included in a lymphadenectomy specimen.
2. For lung cancer, if the highest mediastinal lymphatic node examined is positive.[32(p.17)]

1.1.2 Historical Overview of the "R classification" in the AJCC System

In January 1959, the "American Joint Committee for Cancer Staging and End-Results Reporting" (AJC) was established to develop a tumour classification which is compatible with the classifications published by the UICC. Therefore, the principles of the TNM system have been implemented, as far as they are in accordance with other staging recommendations that have already been used before. The sponsoring organisations for the AJC have been the American Colleges of Surgeons, -Radiology, -Pathologists, -Physicians, the American Cancer Society, and the National Cancer Institute. [33] In 1980, the organisation was renamed the "American Joint Committee on Cancer" (AJCC). [34]

The first edition of the "Manual for Staging of Cancer" was published in 1977. Under the chapter "General Rules and the Relationship between Time and the Staging of Cancer", the ninth rule of the category "Postsurgical Treatment- Pathologic Staging" states that after surgical resection, the cancer may have been completely resected, but it is possible that some residual tumour has been left behind. In this case, any residual tumour must be identified under "R", to assist in the further treatment of the patient. It is also important that "R" does not enter into the staging of the tumour.[33]

Under the chapter "Definition of Symbols", the definition of "Residual Tumour (R)" is clarified. It is again emphasised that the "R classification" does not enter into staging, and if the cancer is treated with "Definitive Surgical Procedures", any residual cancer has to be recorded. The categories are:

- "R0 No residual tumor

- R1 Microscopic residual tumor
- R2 Macroscopic residual tumor" [33(p. 5)]

The second edition, which was published in 1983, declares that the AJCC and the UICC try to work together to agree on similar rules of classification. Both committees try to collaborate in order to eliminate the differences in their staging methods. The "R classification" does not change in the second edition. [34].

The joint work of the two committees, the AJCC and the UICC, concluded in the 1980s that the third edition of the "Manual for Staging of Cancer", which was published in 1988, and the fourth edition of the "TNM Classification of Malignant Tumours" of the UICC (1987) are identical in their recommendations regarding all definitions of TNM and on-stage groupings. In the third edition of the "Manual for Staging of Cancer", some changes have been made. The "R" is now defined as "residual tumour after treatment" instead of "residual tumour following surgical treatment". Additionally, it is stated that the use of "R" is optional. The term "RX" has been added in cases when the presence of residual tumour at the primary site cannot be assessed[19, 33, 34].

The fourth edition was published in 1992, and here further explanations regarding the "R classification" are given. It is described that TNM and pTNM only depict the anatomic extent of the tumour, without considering treatment. Furthermore, TNM and pTNM can be complemented with the "R classification", which describes the tumour status after treatment. It reflects the efficiency of a treatment, influences subsequent therapy procedures, and is a potent predictor of prognosis. [35]

Regarding the "R classification", there are no changes until the seventh edition in 2010. [36, 37, 38]

In the seventh edition of the "AJCC Cancer Staging Manual" in the chapter "Histopathologic Type, Grade, and Other Descriptors", it is stated that cTNM and pTNM can be complemented by the "R classification", which describes the tumour status after treatment. Causes of residual tumour at the primary tumour site following surgery and/or neoadjuvant treatment can either be incomplete resection or locoregional tumour that expands beyond the limit or ability of resection.[36]

Additionally, the existence of a tumour on the resection margin can be a predictor of risk for recurrent cancer and is more likely with more advanced "T" or "N" category tumours.[36] In addition to the "R categories", the recording of a "margin status" is suggested as follows:

- "Negative margins (tumor not present at the surgical margin)
- Microscopic positive margin (tumor not identified grossly at the margin, but present microscopically at the margin)
- Macroscopic positive margin (tumor identified grossly at the margin)
- Margin not assessed"[36(p.14)]

1.1.3 The "R classification" in the current edition of the UICC System

The 8th edition of the "TNM Classification of Malignant Tumours" of the UICC was published in 2017. In this edition, the "R classification" is defined as the absence or presence of residual tumour after treatment and should be described as "R". Furthermore, it explains that TNM and pTNM only define the anatomical extent of the tumour, without the consideration of treatment. They can be complemented with the "R classification". This classification reflects the efficiency of a therapy, influences subsequent treatment, and is a potent predictor of prognosis. [1]

The different categories of the "R classification" are:

"RX Presence of residual tumour cannot be assessed
R0 No residual tumour
R1 Microscopic residual tumour
R2 Macroscopic residual tumour"[1(p. 11)]

A note at the end of the chapter mentions that some apply the "R classification" only for the primary tumour and its locoregional extent, while others also include distant metastasis. It is recommended to indicate the specific usage when "R" is applied.[1]

The 5th edition of the "TNM Supplement" was published in 2019. The statements and definitions of the TNM, pTNM, and "R classification" stayed the same as in the 8th edition of the "TNM Classification of Malignant Tumours".[1, 2] The "R classification" characterises the locoregional residual tumour as well as distant metastasis, as it has been mentioned originally. [2]

“R0“ is similar to clinical remission or resection for cure; therefore, it should be applied in cases when no residual tumour can be detected by any diagnostic means. It does not exclude any form of non-detectable residual tumour, which could lead to tumour recurrence or metastasis. It is stated that “R0” “corresponds to no detectable residual tumour and may not be identical to cure.“[2(p. 16)]

If a tumour is classified as “R1“ or “R2“, it should be documented which local tumour site is positive. For example, if a microscopical residual tumour has been found at the resection margin of a polyp in the colon, it should be classified as “R1 (colon)”. If in the subsequent colectomy the resection margin is free of tumour, it would change to “R0 (colon)”. Though, if at the colectomy a histologically confirmed liver metastasis is found, it would be considered “R2 (liver)”. This process requires close cooperation between the surgeon and the pathologist.[2]

The “R classification“ can be applied after surgical treatment, radiotherapy, chemotherapy or multimodal therapy. Following nonsurgical treatment methods, the existence of residual tumour is classified through clinical methods. Following surgical treatment, the “R classification” needs close cooperation between the surgeons and the pathologists; see also Figure 1 on page 3.[2]

In the “R0” group, there are cases with a “M0” and a “M1”, in the latter, the primary tumour as well as the distant metastasis have to be removed entirely.[2]

When a tumour is removed with a formal lymphadenectomy, the “R classification“ is not affected if the “marginal“ or “apical“ lymph node or a “sentinel lymph node” (SLN) is involved unless the infested lymph node has been transected at the margin.[2]

A precise assessment of the resection line cannot be made if the tumour is removed in two or more parts. “RX” should be applied in these cases.[2]

If a non-invasive carcinoma exists at the resection margin, this should be documented with the suffix “(is)“, for example, “R1(is)“.[2]

The term “R0-ablation“ has been used in some cases after a radiofrequency ablation of liver metastasis when no residual tumour could be detected by clinical (including imaging) techniques. The correct classification would be “complete clinical response“, because for a “R0“, a histopathological examination is mandatory.[2(p. 17)]

Patients with residual tumour categorised with conventional methods and those categorised with new specialised methods cannot be compared. Therefore, the methods which have been used to categorise the residual tumour should be documented.[2]

Furthermore, in the "R classification", the serum level of tumour markers is not considered[2].

Besides the conventional methods (the histopathological processing of suspicious areas by gross examination), there are newer techniques to refine the "R classification", of which three examples are given below:[2(p. 17)]

1. Imprint cytology of the resection margin has been used for breast cancer, this method was introduced by Veronesi et al.[24] This has also been applied to other tumour types, i.e., stomach cancer.[2]
2. For the detection of metastases on the peritoneum which are grossly not recognisable, a cytological examination of ascites or abdominal lavage fluid can be applied. This method can be used for gastric carcinomas. In the "R classification", a "R1(cy+)" may be used.[2]
3. For patients who do not show evidence of bone metastasis, an examination of bone marrow biopsies with monoclonal antibodies against cytokeratin has been performed. Schlimok et al.[25] describe such an examination for gastric carcinomas.[2]

"R1" can only be applied if the tumour is present at the resection margin, meaning the tumour is transected. Some have also applied a "R1" if the tumour is 1mm or less from the margin. Only if the tumour is transected should "R1" be used. To settle this inconsistency, alternative definitions have gained increasing acceptance. The CRM was first accepted for rectal cancers and later for other tumour sites as well. The following definitions have been proposed:

- "CRM positive" when the tumour is present directly at the CRM or the minimal distance between the tumour and the resection margin is less than or equal to 1mm
- "CRM negative" when the minimal distance between the tumour and the CRM is more than 1mm[2(p. 18)]

After a total mesorectal excision as treatment for rectal cancer, the CRM is a potent prognostic factor. Therefore, if a tumour can be found within 1mm of the CRM, instead of characterising it as "R1", "CRM positive" can be applied. [2]

It is pointed out that, especially in the US, Canada, and the United Kingdom (UK), the "R classification" has been applied only to the primary tumour site, while others have also included distant metastasis. In view of the prognostic value of the "R classification",

distant metastasis should also be included, which would also be consistent with the initial definition in 1977. [2]

To eliminate any ambiguities that could result from various definitions of resection margin involvement, an enhanced uniform "R classification" has been proposed, and it contains the following definitions:

"RX	Presence of residual tumour cannot be assessed
R0 > 1mm	No residual tumour, minimal distance between tumour and resection margin is > 1mm
R0 ≤ 1mm	No residual tumour, minimal distance between tumour and resection margin is ≤ 1mm
R1-dir	Microscopic residual tumour, tumour directly at the resection margin (tumour transected)
R2a	Local macroscopic residual tumour
R2b	Distant macroscopic residual tumour
R2c	Macroscopic residual tumour in both sites"[2(p. 19)]

After neoadjuvant treatment, the "R classification" can only be applied if a viable tumour at the resection margin is considered. Scars, fibrotic areas, fibrotic nodules, granulation tissue, or mucin lakes occuring at the margin, do not qualify as "R1".[2]

The next chapter discusses the "Definitions of Completeness of Resection", with the prefix "R0(un)". This category has been proposed for testing, to classify the cases in which "R0" is too imprecise. Because of "General Rule No. 4"[2(p.5)], which states that if there are any concerns regarding the correct selection of any category from the TNM system, the less advanced should be applied due to the otherwise negative prognostic influence. Thus, this category has been suggested to list characteristics which fall into the category "uncertain resection", meaning no visible or histological verification of residual tumour, but fall into any of these two reservations:

1. The examination of the lymphadenectomy specimen contains a smaller number of nodes or nodal stations than is ordinarily included in a lymphadenectomy specimen.
2. For lung cancer, if the highest mediastinal lymphatic node examined is positive.[2(p. 19)]

1.1.4 The "R classification" in the current edition of the AJCC System

The eighth edition of the "AJCC Cancer Staging Manual" was published in 2017. The current "Residual Tumour and Surgical Margins" definition of the AJCC is described in the chapter "Principles of Cancer Staging" under the subchapter "Additional Staging Descriptors and Guidelines".[4]

It explains that the symbol "R" characterises the presence or absence of residual tumour after treatment, while cTNM and pTNM only characterise the extent of tumour without consideration of subsequent therapy. Additionally, they can be supplemented with the "R classification".[4]

The "R classification" is not integrated into TNM staging, but it influences the prognosis and eventual subsequent treatment of the patient and should therefore be recorded. In the current edition, the categories of the "R classification" at the primary tumour site are:

- "RX Presence of residual tumor cannot be assessed
- R0 No residual tumor
- R1 Microscopic residual tumor
- R2 Macroscopic residual tumor at the primary cancer site or regional nodal sites"[4(p.29)]

Additionally, it is noted that "R2" should not be used to express an identified metastatic disease that has not been resected by the surgeon. [4]

Subsequently, a table with "Component of residual tumour and margins" was added, with a description for each of the following factors:

The first one is about the "causes of residual tumour". It is illustrated that residual tumour can remain after surgical and/or neoadjuvant treatment at the primary site and/or regional sites. This derives from incomplete removal, when the disease expands beyond the capability of resection.

The second one deals with "indications of residual tumour". The existence of a residual tumour shows the effect of a therapy, impacts the subsequent treatment, and is a strong predictor of prognosis.

The third one describes the "indicator of risk". The existence of a tumour on the resection margin is a risk factor for recurrent cancer and is linked with more advanced T- or N-categories.

The fourth one discusses “margin status”. This status follows a surgical resection and is based on the pathology report. If it is necessary, the pathology report should be correlated with the operative report, and the “margin status” should be noted with one of the following options:

- “negative margins (tumor not present at the surgical margin)
- microscopic positive margin (tumor not identified grossly at the margin, but present microscopically at the margin). For rare sites, definitions of margin positivity may vary, and relevant interpretation is specified in the respective chapter.
- macroscopic positive margin (tumor identified grossly at the margin)
- margin not assessed”[4(p.30)]

1.2 Special Considerations of the “R classification” in Breast Cancer

1.2.1 Interdisciplinary S3 Guideline for Early Detection, Diagnosis, Therapy and Aftercare of Breast Cancer

The 4.3 version of the “Interdisciplinary S3 Guideline for Early Detection, Diagnosis, Therapy, and Aftercare of Breast Cancer” guideline was published in February 2020[3] by the “German Guideline Program in Oncology” (GGPO). This programme was launched in 2008 by a collaboration between the “Association of the Scientific Medical Societies in Germany“ (AWMF), the “German Cancer Society” (DKG), and the “German Cancer Aid” (DKH). The leading expert associations have been the “German Society for Gynaecology and Obstetrics” (DGGG) and the DKG.[3, 39] The necessity for updating this guideline is due to the consistently high epidemiological significance of breast cancer and the associated burden of disease. For this reason, the current knowledge of evidence-based medicine and accepted treatment concepts are taken into consideration. A further goal is to achieve comprehensive care for breast cancer that is multidisciplinary, cross sectoral, and quality assured.[3(p. 28)]

In the chapter “Pathomorphological Examination”, there is a subchapter called “Documentation of Microscopic Processing and Assessment”. Here, the different factors of the microscopical examination that should be documented are listed. Besides information about the type of tissue, the histological type, and the grading, it should also be noted

whether an associated “ductal carcinoma in situ” (DCIS) is present or not. Furthermore, information about the size of the invasive carcinoma and, if present, the size of the associated DCIS should be documented. It should also be noted if further tumour lesions are present, as well as if they are multifocal or multicentral. Additionally, the resection margin has to be reported, and it has to be specified if the tumour is directly on the resection margin. If the tumour is not directly on the resection margin, the minimal distance between the tumour and the resection margin has to be stated in millimetres. Additionally, it has to be mentioned which resection margin is meant. Also, the minimal distance of the DCIS to the resection margin has to be mentioned.[3(pp.105-106)]
For evaluating the prognosis and the prediction, it is strongly suggested to record the resection margin status using the “R classification” according to the current eight edition of the “TNM classification”[1], as well as the distance to the resection margin.[3(p.118)]

In the chapter “Surgical Treatment for Invasive Carcinoma”, it is stated that in an invasive carcinoma, a complete resection of a tumour with clear resection margins is a condition for a low risk of local recurrence. The risk of local recurrence is significantly determined by the tumour biology, but it is stated that an enlargement of the resection margins in biologically aggressive tumours (like triple-negative or HER2-positive) has no impact on the reduction in local recurrences. For this reason, for all tumour subtypes with or without accompanying DCIS, a resection is deemed sufficient if no tumour tissue is detectable on the resection margin, also indicated as “no ink on tumour”. A metrically defined minimum distance between tumour tissue and the resection margin is not required. This only applies if the indicated adjuvant therapy measures, like systemic therapy or radiation therapy, including boost, are carried out. A re-resection is not indicated for a “R0”, even with narrow incision margins. However, in the case of an “extensive intraductal component” (EIC), a larger distance to the resection margin may be useful.[3(p.93)]

In the chapter “Surgical Treatment for DCIS”, it is stated that a complete excision is the therapeutic basis for the treatment of DCIS. A “breast conserving therapy” (BCT) can nowadays be regarded as the standard choice of treatment for DCIS, especially when the ratio between the extent of the lesion and the size of the breast is favourable. Histopathological studies on the growth pattern of the DCIS show that it is 90% unicentric lesion, but it could be potentially a multifocal lesion. Assuming a segmental oriented operation with sufficient resection margins, DCIS can theoretically be treated with surgery

alone. The suggested width of the resection margin at BCT depends on whether postoperative radiotherapy will be performed or not. The benefit of radiation therapy is minor if the resection margin is 10mm or more. In cases where a mastectomy is performed, a re-resection can reduce the risk of local recurrence if a resection margin is affected or the resection margin is less than 3mm. Postoperative radiotherapy is not recommended in this situation. [3(p.84)]

In consideration of a careful pathological analysis and radiological-pathological correlation, regarding the topography and the size of the DCIS, a minimum resection margin of at least 2mm appears to be sufficient if adjuvant radiation therapy is performed. If radiation therapy is not performed, the resection margin should be enlarged, although no optimal width can be given. Furthermore, other risk factors should be considered: wheter the DCIS reaches the resection margin over a large area or only in small areas; the size of the DCIS; and the grading of the DCIS. If, during a re-resection, a complete excision cannot be achieved, a secondary mastectomy should be considered. If the resection margin is less than 2mm, the necessity of a re-resection should be discussed as an individual decision in the tumour board, taking into consideration the resection margin, the DCIS' size and grading, as well as the patient's age.[3(pp.84-85)]

In the chapter "Pathomorphological Examination", in the subchapter "Lymph Nodes", the "sentinel lymph node biopsy" (SLNB) is further specified. It is a procedure to remove the SLN, which is marked with ink or radionuclides. It is the primary method for determining the node status, under the condition of compliance with the recommended quality criteria. The basic aim of the histological examination is the detection of all macrometastases (>2mm). The identification of micrometastases (>0.2mm and or >200 tumour cells, but not larger than 2mm) is desirable, but not obligatory. If micrometastases are present, the infestation of further lymph nodes can be expected in about 20% and in 30% with micrometastases >1mm. The histological examination of SLN is not targeted to detect isolated tumour cells.[3(p.140)]

The "axillary lymphadenectomy" is nowadays only in exceptional cases the primary surgical procedure for the determination of the lymph node status. In most cases, it is used for complementation of infested SLN. The aim of the histological examination is the detection of all macrometastases (>2mm).[3(p.140)]

In the chapter “Surgical Therapy for the Axilla”, it is stated that the axillary staging should be part of the surgical treatment for the invasive carcinoma. This should be carried out with SLNB if the lymph node status is normal on palpation and ultrasound.[3(p.99)] The SLNB is used to identify patients with increased systemic and local risk and to plan adjuvant therapy. Under the condition of a standardised and quality-assured performance, the SLNB has a high degree of staging accuracy, significantly reduced shoulder-arm morbidity, and an excellent axillary recurrence rate (<1%). This procedure is indicated for all patients with a clinically negative lymph node status, which therefore requires axillary staging. It is not indicated for patients with a clinical suspicion of lymph node involvement (which should be proven preoperatively with a biopsy or fine needle aspiration) or for proven tumour-infiltrated lymph nodes. In patients with histologically proven tumour involvement of the axilla, the surgical removal of the axillary lymph nodes may be indicated. The number of affected lymph nodes or the ratio of affected to examined lymph nodes may be used for the selection of the following adjuvant systemic and radiation therapy.[3(p.101)]

The role of an axilla dissection is disputed. Patients with a T1- or T2 tumour and 1 to 2 positive SLN can be offered to waive the axillary dissection at a BCT, given that they are informed about the currently available data. Instead of an axillary dissection, radiotherapy of the axilla could be considered as an alternative. An axillary dissection is not recommended for patients with micrometastases in the SLN, as there is no evidence of an increased locoregional risk of recurrence. An axillary dissection is recommended for patients treated with mastectomy or patients who are not treated with postoperative radiotherapy of the affected breast. An axillary staging is not indicated for patients in the stage of distant metastases (M1). [3(p.102)]

For patients who are treated with primary systemic therapy, the optimal procedure for the lymphatic drainage path has not yet been clarified. A distinction has to be made between patients who primarily have a suspicious lymph node status and those whose status is normal. For patients with unsuspicious clinical and or imaging lymph node status, who are planned for primary systemic treatment, the SLNB can be performed either before or after the systemic treatment. For patients with a primarily suspicious lymph node, an evaluation of this node should be performed by biopsy or fine needle aspiration. If primary lymph node involvement is confirmed, the success rates of SLNB are clearly limited, and therefore an axillary dissection is recommended. Newer methods which could lead to improved detection as well as accuracy of SLNB in primarily node-positive patients, like

clip or seed marking, have not been adequately evaluated and can therefore not be recommended for the clinical routine. The data on the locoregional risk of recurrence for SLNB after a primary systemic treatment is insufficient. It has not been clarified whether the less favourable false-negative rate of SLNB after a primary systemic treatment in patients with primarily positive lymph node status correlates with an increased rate of locoregional recurrence or poorer overall survival.[3(p.102-103)]

1.2.2 The St. Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer

The "St. Gallen International Breast Cancer Conference" (SONK) was founded by Prof. Hansjörg Senn in 1978 and is held bi-annually. A consensus session is the traditional end of each conference, which forms the basis for the updated "St. Gallen Consensus Guidelines/ Recommendations". An international group of scientists writes the consensus of around 50 international breast cancer specialists from most continents. This consensus is rapidly published as the "St. Gallen Guidelines / Recommendations" for the optimal treatment of patients with early breast cancer in the journal "*Annals of Oncology"* and reaches out to breast cancer specialists all over the world. In 1996, the "St. Gallen Oncology Conferences" became a private charitable and tax-exempt non-profit organisation according to Swiss law, registered and supervised by the Department of Interiors of the Swiss Canton of St. Gallen. Since 2015, the conferences are held in Vienna and are now called the "St. Gallen International Breast Cancer Conference in Vienna".[40] The 16th conference was held in 2019 and the updated "Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019" was published in the "*Annals of Oncology"*.[15]

In the chapter "Surgical Margins", it is stated that the Panel has again expressed its approval for the "no ink on tumour" standard as an optimal surgical margin following "breast conserving surgery" (BCS) for patients with invasive breast cancer if the patients receive postsurgical radiation therapy. This recommendation has been endorsed regardless of the tumour histology, namely lobular or ductal carcinoma, of the presence of an "extensive intraductal component" (EIC), and regardless of the histological grading. For patients with "neoadjuvant systemic therapy" (NST), it is recommended to remove all known residual tumour with the aim of "no ink on tumour" for the margin, regardless of

the presence of unifocal or multifocal cancer. As long as the residual tumour bed and areas of persistent abnormal imaging have been resected with careful pathological review of the specimen, wider resection margins are no longer recommended. These more limited surgical approaches have not been supported for patients with inflammatory breast cancer. Furthermore, “no ink on tumour” margins are recommended for women who undergo skin-sparing and/or nipple-sparing mastectomy, especially if radiation therapy is planned. When imaging shows a close proximity between tumour and skin, the Panel recommends caution for skin-sparing surgery. In cases with centrally located tumours, members of the panel have different opinions about whether preservation of the nipple-areolar complex is suggested.[15]

If a surgical margin at a breast conserving surgery is focally positive, the vast majority of the panel has suggested a re-excision, particularly if the margin’s involvement is not minimal. In some cases, when the involved margin is smaller (1mm in width), opinions differ as to whether a re-excision is essential and outweighs the negative aspects of further surgical excision. Recent studies suggest that a focally positive margin, when receiving a BCT and radiation therapy with a boost to the primary tumour bed, has an acceptable low risk of local recurrence, but the risk is only slightly higher than following a re-excision with “no ink on tumour” (2,9% versus 1,1% at 5 years). These findings are important for clinical practise, especially in cases where a re-excision would negatively affect the cosmetic impact or a mastectomy would be needed. Anecdotally, the vast majority of the Panel has also accepted instances of microscopic involvement of margins (<1mm width) under the condition that patients also receive radiation therapy.[15]

In the chapter “Ductal carcinoma *in situ*”, it is stated that a DCIS is a precancerous lesion frequently detected mammographically. The standard treatment includes surgical procedures, either lumpectomy in combination with radiation therapy or mastectomy. This is to prevent the subsequent development of invasive cancer or recurrent DCIS. Even in a low-risk population of patients with a recurrence risk of ~10% after BCS, randomised trials have shown that these populations might benefit from post-lumpectomy radiation therapy by reducing the risk of in-breast recurrence or invasive cancer. However, due to the modest absolute benefit of radiation therapy in such cases and a lack of survival impact for treatment of DCIS, the panel has recommended for patients with favourable prognostic features (including low- or intermediate-grade, the absence of comedonecrosis, and age >50) and generous surgical margins (usually >0,5cm) the waiver of radiation and

endocrine therapy if they are willing to accept a slightly higher risk of in-breast recurrence.[15(p. 1551)]

In the chapter "Managing Positive Sentinel Lymph Nodes", it is stated that the SLNB is the standard method for patients presenting with a clinically negative axilla and undergoing a lumpectomy. For patients with cT1-2, cN0 tumours and tumour involvement of 1-2 SLN, the completion of axillary dissection is not indicated if the patients receive post-lumpectomy radiation and appropriate systemic adjuvant therapy. The panel has endorsed for patients presenting with tumours >5cm and with 1-2 positive SLN to omit the axillary dissection following a SLNB, under the condition that a regional nodal irradiation including the axilla has been planned as a part of the locoregional treatment. Further, the panel has recommended that patients who undergo a mastectomy and who have positive SLN receive additional treatment to the axilla, either in the form of a completion of the axillary dissection or a regional radiation therapy. As for BCS, the panel believes that the axillary dissection can be omitted in patients with 1-2 positive SLN under the condition of planned regional irradiation therapy. If no radiation has been planned or only chest wall radiation has been planned, it is recommended to complete the axillary dissection after mastectomy in patients with positive SLN. A SLNB is not indicated in elderly patients presenting with clinical stage 1 disease and tumours with favourable biology, given that it is unlikely to change treatment.[15(p. 1546)]

In the chapter "Sentinel Lymph Node Biopsy after NST", it is recommended that patients with clinically positive nodes after neoadjuvant treatment have a completion of the axillary dissection. The panel has considered that for patients who present with a clinically positive (cN1) axillary node and then receive a neoadjuvant treatment which downstages the axilla to clinically negative, a SLNB instead of an axillary dissection should be performed, under the condition that ≥3 SLN are identified and all of them are negative. The panel has been divided on whether 1-2 negative SLN represent adequate axillary surgery due to a higher rate of false-negative findings with these more limited sentinel node assessments. Targeted axillary approaches, including clipping of positive nodes at diagnosis, may prevent axillary dissection if the marked node and one or two additional SLN are removed and under the condition that all removed nodes are negative. It is recommended for patients with residual nodal disease after a NST in a SLNB to complete the axillary dissection. Even in the setting of micrometastatic residual disease in a SLNB following a NST, it is strongly

recommended to complete the axillary dissection unless a regional nodal irradiation has been planned. Patients with cN2 axillary disease should undergo axillary dissection and receive regional nodal irradiation.[15(p. 1547)]

1.2.3 NCCN Clinical Practice Guidelines in Oncology for Breast Cancer

The "National Comprehensive Cancer Network" (NCCN) is a non-profit organisation consisting of an alliance of 30 cancer centres in the United States of America dedicated to patient care, research, and education. Through the expertise of clinical professionals at NCCN Member Institutions, clinical practise guidelines appropriate for patients' use, clinicians, and other health care decision makers are developed and improved. The NCCN programmes offer access to expertise, superior treatment, and safety initiatives and therefore continuously improve the effectiveness and efficiency of cancer care globally.[41]

In the chapter "Margin Status Recommendations after Breast-Conserving Surgery for Invasive Cancers and DCIS", suggestions for the margin status after surgical treatments are given. It is stated that the margins of surgical specimens from BCT should be evaluated. An optimal margin evaluation includes the orientation of the surgical specimen, a description of the gross and microscopic margin status, and information about the distance, orientation, and type of tumour (DCIS or invasive tumour) in relation to the closest margin.[5(p. BINV-F 1)]

The complete resection of a mammographically detected DCIS with microcalcifications should be documented by an analysis of margins and a specimen radiograph. Furthermore, a mammogram after excision can be considered if there are uncertainties.[5(p. BINV-F 1)]

The NCCN acknowledges the definition regarding negative margins after BCT from the "2014 SSO/ASTRO Margins Guideline"[10] for Stage I and II invasive breast cancer. For DCIS, the "2016 SSO/ASTRO/ASCO Guideline"[11] is recommended.[5(p. BINV-F 1)]

For patients with Stage I or II invasive carcinoma after BCS, the definition of a positive margin is further defined as "ink on tumour", including any invasive cancer or DCIS cells "on ink". In general, these patients require further surgery to achieve a negative margin, meaning either a re-excision or a mastectomy. If a re-excision is technically possible and "no ink on tumour" can be achieved within a BCS, a resection of the involved margin, guided by the orientation of the initial resection specimen, or re-excision of the entire excision cavity, is needed. If a patient with a Stage III invasive cancer is eligible for BCS, the evaluation of the margin status should be done with similar definitions.[5(p. BINV-F 1)]

If a patient with DCIS alone is treated with BCS and "whole breast radiation therapy" (WBRT), any tumour that is in distance to the resection margin width of at least 2mm is associated with a reduced risk of ipsilateral breast tumour recurrence compared to a margin width under 2mm. However, the routine practise of aiming for margins greater than 2mm from the tumour to improve the outcome is not supported by the evidence. If there is only minor or focal DCIS involvement close to the margin, the risk of re-excision has to outweigh the risk of recurrence for an individual patient by clinical judgement. If a patient with DCIS is treated with surgical excision alone without WBRT, the risk of an ipsilateral tumour recurrence is considerably higher regardless of the margin width, even in low-risk cases. Nevertheless, the margin width in such cases should at least be 2mm, with some evidence suggesting a more favourable recurrence rate with higher margin widths. A DCIS with microinvasion, which is defined as an invasive focus ≤1mm in size, should be surgically treated with a margin width of more than 2mm. Such DCIS should refer to the DCIS margin definition because the majority of them are comprised of DCIS, and the application of systemic treatment for this lesion more closely reflects the treatment pattern for DCIS than invasive carcinoma.[5(p. BINV-F 1)]

In cases with lesions consisting of an invasive breast cancer and a component of DCIS, regardless of its extent, based on the invasive margin guideline[10] the negative margin definition is "no ink on tumour" for both the DCIS and the invasive tumour component. This is due to the natural history, treatment, and outcome of these lesions, which are more similar to invasive cancer than to DCIS. In cases that are specifically challenging, clinical judgement and a discussion with the patient should be done before a routine re-excision.[5(p. BINV-F 2)]

Due to limited data regarding local recurrence in patients undergoing accelerated partial breast irradiation, these margin recommendations cannot be applied directly to them. Individualised clinical judgement should be utilised on a case-by-case basis, using postoperative mammography for the detection of residual calcifications and clinical pathological factors such as quantitative extent of tumour close to the margin, the presence of EIC, young age, or multiple close margins to identify patients who may have an increased risk of an ipsilateral tumour recurrence and who would benefit from a re-excision. [5(p. BINV-F 2)]

Patients with invasive breast cancer after a BCS and with microscopically focally positive margins without an EIC, should be considered for a higher radiation boost dose to the

tumour bed. The reason for this is the general recommendation of a boost to the tumour bed for patients with a higher risk of recurrence,[5(p. BINV-F 2)] as stated in the chapter of "Principles of Radiation Therapy".[5(p. BINV-I 1)]

For DCIS that is primarily treated with lumpectomy without lymph node surgery, the goal is to obtain a negative margin. If, in patients who desire a BCT, adequate surgical margins cannot be achieved with a lumpectomy, a mastectomy has to be performed. The use of breast "magnetic resonance imaging" (MRI) has neither been shown to increase the likelihood of negative margins nor to decrease the conversion to mastectomy. Statements on improved long-term outcomes cannot be made due to insufficient data. The use of WBRT following a lumpectomy lowers the recurrence rates in DCIS by about 50%, of which approximately one-half are invasive tumours and the other half are DCIS. [5(p. DCIS-1)]

If the margins of the mastectomy from an invasive cancer specimen are positive, re-excision is advised to achieve negative margins. If this is not possible, it is strongly suggested to apply radiation therapy to the chest wall, including the supraclavicular and infraclavicular regions, internal mammary nodes, and any part of the axillary bed at risk.[5(p. BINV-3)]

Prior to lumpectomy for an invasive cancer, an evaluation of the possible cosmetic output should be performed with oncoplastic techniques, which could extend the breast-conserving surgical options in situations where the resection itself would lead to an unacceptable cosmetic outcome. These techniques may also reduce the need for a mastectomy and decrease the need for secondary surgery. However, patients should be informed that the need for secondary surgery can arise if the margins are positive, which would lead to segmental re-excision or mastectomy with or without the loss of the nipple. If the preoperative margin status is unclear, a staged partial mastectomy reconstruction should be considered.[5(p. BINV-H 1)]

In the chapter "Surgical Axillary Staging", it is mentioned that if no palpable lymph node is found at diagnosis, or if ≤2 suspicious nodes on imaging or if ≤2 positive nodes are confirmed by needle biopsy with or without a clip placement, the further procedure would include a sentinel node mapping and the excision of these with an evaluation of the SLN. If it is negative, no further axillary surgery is needed. If the SLN cannot be identified, an axillary dissection is recommended. If the SLN in a post-mastectomy specimen is positive

and only micrometastases can be seen, no further axillary surgery is necessary. If the positive SLN is a T1-T2 tumour with 1-2 positive SLN, the patient receives a BCS with a planned WBRT, and no neoadjuvant chemotherapy has been administered, then no further axillary surgery is needed.[5(p. BINV-D)]

For patients in this setting but with a mastectomy instead of a BCS who have been initially cN0 but have positive nodes on the SLNB and no axillary dissection, the radiotherapy should include the chest wall, supraclavicular with or without the internal mammary nodes, and the full axilla. If a positive SLN is diagnosed and one of the mentioned criteria is not fulfilled, an axillary dissection should be performed. An alternative for patients with a clinically negative axilla who undergo mastectomy and for whom radiation therapy is planned, is axillary radiation, which can be chosen instead of an axillary dissection for regional control of disease. If a patient has clinically suspicious, meaning palpable lymph nodes or ≥3 suspicious nodes on imaging, or if preoperative systemic therapy is being considered and there are suspicious lymph nodes at diagnosis on exam or imaging, an ultrasound guided fine-needle aspiration or a core biopsy with or without clip placement should be performed. If the findings of these are negative, SLN mapping and excision should be carried out. If they are positive and no neoadjuvant chemotherapy has been given, an axillary dissection should be performed. If neoadjuvant treatment has been given, either an axillary dissection for residual disease or a SLNB in cases where the nodes are clinically negative after neoadjuvant treatment can be administered. For patients who have been N+ before the NST, the SLNB has a >10% false-negative rate. This can be improved by marking the biopsied lymph nodes to document their removal, by the use of dual tracers, and by removing ≥3 SLN.[5(p. BINV-D)]

In the Discussion section, whose update is still in progress, the “Pathology Assessment” is further elaborated. It is declared that a central component of the treatment is full knowledge of the extent of the disease and its biological features. From these features, the disease stage is determined, an estimation of the risk of recurrent cancer can be made, and with these pieces of information, the response to therapy can be predicted, for example, with the oestrogen, progesterone, and HER2 receptor status. This information is dependent on the examination of the resected tissue and is documented in a written pathology report. To achieve an accurate pathology report, communication between the clinician and the pathologist is required. The report is affected by relevant patient history, prior breast

biopsies, prior irradiation to the chest, pregnancy status, if an abnormality is biopsied (palpable lesion or mammographically detected microcalcifications), the clinical state of the lymph nodes, if there is presence of an inflammatory change or other skin abnormalities, and any prior treatments like chemo- or radiation therapy that have been administered. It is also important to inform the pathologist about the orientation of the specimen and if specific requests for the determination of biomarkers are needed. It is recommended to use consistent, unambiguous standards for the pathological reporting because surveys[42, 43] have shown that about 50% of pathology reports for breast cancer are missing some crucial elements for the management of the patients, including failure to orient, of reporting surgical margins, and reporting the tumour grade consistently.[5(p. MS-3)]

In the discussion chapter "Ductal Carcinoma in Situ", it is stated that the primary treatment of DCIS focuses on the prevention of its progression into an invasive breast carcinoma. To achieve this, surgical methods like mastectomy or lumpectomy, radiation therapy, and adjuvant endocrine treatment can be applied to reduce the risk of recurrence. The primary surgical treatment options are either a lumpectomy with or without WBRT or a mastectomy. It has been pointed out that the choice of local treatment has no impact on the overall disease-related survival; thus, the individual patient's acceptance of the possibility of an increased risk of recurrent tumour must be considered. For the confirmation of an adequate excision, a post-excisional mammography is a valuable examination, especially for DCIS patients who initially present with microcalcifications. [5(p. MS-6-7)]
In the discussion chapter of "Margin Status after Breast Conserving Therapy" of "Ductal Carcinoma in Situ", it is stated that in a retrospective study[44] of 445 patients with pure DCIS with resection as sole treatment, the margin width has been the most important independent predictor of local recurrence. The trend for reducing the local recurrence risk with an increased margin width has been most evident with margins <1mm compared to ≥10mm. In a meta-analysis[45] of 4660 patients with DCIS treated with BCS and radiation therapy, a resection margin of <2mm has been associated with an increase in ipsilateral tumour recurrence in comparison to resection margins of 2mm. No significant difference has been observed if the margin has been greater than 2 to 5mm or greater than 5mm. A newer study[46] of retrospectively reviewed 2996 patients with DCIS with BCS has come to the conclusion that wider margins are only significantly associated with a lower rate of recurrence if the patients have not received radiation therapy. The "2016

SSO/ASTRO/ASCO Guideline"[11] says that a margin of at least 2mm treated with WBRT is associated with low rates of ipsilateral tumour recurrence. Afterwards, further factors are listed which have to be considered for an adequate resection (residual calcifications, life expectancy of the patient, and which margin is close, e.g., anterior against the skin or posterior against the muscle, medial, superior, inferior, or lateral). If a DCIS is admixed with an invasive carcinoma, "no ink on tumour" is supported as an adequate margin for both the invasive and non-invasive tumour components. A complete resection has to be documented by an analysis of the margins and specimen radiography. When there is uncertainty about the sufficiency of the resection, post-excision mammography should be performed. Furthermore, clips have to be used to demarcate the biopsy area because of the possibility of clinically occult DCIS, which would require further surgery depending on the margin status review by pathology. [5(p. MS-9)]

In the discussion chapter of "Invasive Breast Cancer", more precisely in the subchapter "Locoregional Treatment", it is stated that after an excision, it is essential to assess the resection margins histologically. For the benefit of a lumpectomy, it is important to attain pathologically negative margins after an excision. It is again emphasised that "no ink on tumour" is the standard for negative surgical margins regarding invasive breast cancer, with or without a component of DCIS. The change from lumpectomy to mastectomy may be required for local disease control if the surgical margin remains positive after further re-excisions. To adequately assess the surgical margins, it is suggested that the specimens be directionally oriented and that the pathologist describe the gross and microscopic margin status as well as the distance, orientation, and type of tumour, meaning if it is an invasive cancer or a pure DCIS, in relation to the closest margin. When appropriate, the tumour bed should be marked with clips to facilitate accurate planning of the radiation boost field. It may be reasonable to treat selected patients with invasive cancer without an EIC with a BCT, despite a microscopically focally positive margin. [5(p.MS-14-15)]

1.2.4 The Official Statements of the American Society of Breast Surgeons

The "American Society of Breast Surgeons" (ASBrS) was founded in 1995, and by now there are over 3000 members in the United States and in more than 50 countries throughout the world. The membership is open to general surgeons, non-surgeon physicians, health care professionals, residents, and people with a special interest in breast disease.[47]

As stated in the "Performance and Practise Guidelines for Breast-Conserving Surgery/Partial Mastectomy" [6] a BCS, which is also called a "lumpectomy", "wide local excision", "partial mastectomy", "segmental resection", "tylectomy" or "quadrantectomy", means the removal of breast cancer with clear surgical margins. The indication for a lumpectomy is "a biopsy-proven diagnosis of DCIS or invasive breast cancer clinically assessed as resectable with clear margins and with an acceptable cosmetic result"[6(p. 1)].
The stated contraindications are early pregnancy, a multicentric tumour which involves two or more quadrants of the breast, diffuse malignant or indeterminate microcalcifications, inflammatory breast cancer, and persistently positive resection margins. Furthermore, relative contraindications are given, like general contraindications for radiation therapy (like prior breast radiation, collagen or vascular disease, morbid obesity, or unavailability), a very large breast size, or a very large tumour size in comparison to the breast volume. It is noted that neoadjuvant chemotherapy may allow a lumpectomy for some patients for whom it would otherwise not be possible, including second and third trimester pregnancies.[6(p. 1)]
Concerning excisional breast biopsy procedures, specimens should be removed intact, not piecemeal. Excisions carried from the subdermal plane to the pectoral fascia do not require re-excision for a positive anterior or posterior margin. All specimens should be oriented by the surgeon using structures, clips, or ink. Additionally, they need to be labelled appropriately and submitted fresh for identification of the margins, or the margins should be assessed intraoperatively, following each institution's protocol. A specimen x-ray or intraoperative ultrasound should confirm the removal of the lesion, and clips (at the preference of the radiation oncologist) should be placed to mark the excision cavity.[6(p. 2-3)]

BCS has replaced mastectomy for a majority of breast cancer patients in the developed world, with level I data confirming comparable survival and local control of disease, but many patients still require mastectomy, and some prefer it. Current indications for mastectomy are as follows: any cancer unsuitable for BCS (based on large tumour-to-breast-size ratio, multicentric tumour, insufficient response to neoadjuvant chemotherapy or endocrine therapy, persistently positive margins of excision, inflammatory breast cancer, extensive malignant or indeterminate microcalcifications, early pregnancy, proven or suspected genetic susceptibility, local recurrence following a BCS or radiotherapy, and contraindications to radiotherapy), for prophylaxis in high-risk but unaffected patients with

a proven or suspected genetic susceptibility, a history of prior mantle radiotherapy, or patient preference.[7(p. 1)]

In a nipple-sparing mastectomy, it is particularly important to remove the entire breast tissue directly behind the nipple and to send this margin to the pathology separately. The breast is dissected off the underlying pectoralis major, the entire breast tissue is removed, and, by surgeon preference, the pectoral fascia. If the tumour is adherent to the muscle, the portion of adherent muscle has to be removed with the breast specimen, taking additional deep margin specimens and placing clips as needed. The breast specimen is oriented with sutures and submitted fresh to pathology for processing.[7(p. 3)]

In the "Consensus Guideline on Breast Cancer Lumpectomy Margins", whose purpose is to provide an algorithm for re-excision surgery after lumpectomy or BCS for both in-situ and invasive breast cancer, it is stated that the "surgical margin status" is the presence or absence of malignant tumour cells on the edge or close to the edge of a partial mastectomy specimen. It also serves as a surrogate marker of residual disease in breast cancer and has an impact on the patient's risk of ipsilateral tumour recurrence. It is pointed out that there is proof of significant variation in margin definition, positive margin rates, and re-excision lumpectomy rates in patients who undergo BCS. The surgeon's opinion of a negative margin ranges from ink negative to >1cm.[8(p. 1)]

The margins of indeterminate, high-risk, or confirmed breast cancer tissue specimens should be oriented intraoperatively by the surgeon, including clear communication with radiology and pathology. Following the orientation of the specimen by the surgeon, the surgeon or the pathologist should ink the margins so that the surfaces of the excised specimen can be identified. It should be documented in the operative report whether the specimen and fascia have been removed from the muscle or if any skin has been removed. If a nonpalpable lesion which has been detected by imaging methods is resected, a radiographic conformation of the resection by mammography or ultrasound is required. The resultant specimen imaging findings should be passed on intraoperatively to the surgeon and should also be accessible to the pathologist. For each specific margin, the pathologist should document grossly and histologically the orientation, distance, and extent of involvement between the invasive and the in situ cancer according to the "College of American Pathologists" (CAP) [12, 13] breast cancer reporting protocol.[8(p. 1-2)]

In 2015, the ASBrS held a multidisciplinary consensus conference named "Collaborative Attempt to Lower Lumpectomy Rates" to discuss multiple methods and techniques which have been described to reduce the chances of microscopically positive lumpectomy margins. On the basis of this, they created a "Toolbox to Reduce Lumpectomy Reoperations and Improve Cosmetic Outcome in Breast Cancer Patients"[48] to point out different techniques with varying levels of evidence to reduce lumpectomy reoperations.[8, 48] Ideally, these new techniques of intraoperative margin assessment should not add too much time to the surgery, lessen the costs, as well as have improved efficacy compared to presently available technologies[8(p. 2)]

If there is a histologic positive, also defined as an ink positive margin after a lumpectomy, regardless of whether it is an in situ or invasive breast carcinoma, the ipsilateral tumour recurrence rate is higher in comparison to patients with negative margins. Ipsilateral and local regional recurrence following a lumpectomy for invasive cancer can influence the patient's survival. A re-excision to achieve negative margins is desirable and should be performed in most patients with ink positive margins. Before proceeding with re-excision, many factors such as the patient's age, comorbidities, life expectancy, the extent of the planned excision, the extent of the margin involvement, tumour characteristics, and whether the patient will receive adjuvant therapies should be taken into account. The "margin index"[8(p. 2)], which is based on the margin status and the tumour extent at the margin, may assist in predicting residual malignancy in the breast. If the underlying muscle fascia or the overlying skin have been removed, a re-excision may not be necessary for the involved anterior and posterior margins. If a re-excision is not performed for a positive margin, the reason should be documented in the medical record.[8(p. 2)]

When the margin is ink-negative, a variety of opinions of adequacy of the margin width that do not require re-excision exist. This results in differences in definitions and practises among surgeons, pathologists, and radiation oncologists. In the "B-06" study of the "National Surgical Adjuvant Breast and Bowel Project"[49], a negative margin has been defined as no tumour cells on the inked edge of a surgical specimen. A meta-analysis[50] that evaluated the effects of margin status and margin distance on ipsilateral tumour recurrence in patients with early-stage invasive breast cancer has concluded that the odds ratio for recurrence has been 2.42 (P<0,001) for positive versus negative margins. A greater radial width of negative margins than 1mm has only borderline significance for an improved local recurrence rate compared to wider margins. The difference has been insignificant

when the patients have received a radiation boost or an endocrine therapy. The consensus guidelines of the ASCO/SSO/ASTRO[51] and the 2.2017 NCCN guidelines[52] recommend that “no ink on tumour” should be used as a definition of negative margins for invasive breast cancer, with or without DCIS receiving BCS with WBRT. A meta-analysis[45] which has evaluated lumpectomy and radiation therapy for DCIS has concluded that a margin of >2mm has no increase in the tumour recurrence rate compared to a 2mm margin. This has resulted in the recommendation in the 2.2017 NCCN guideline[52] and the ASCO/SSO/ASTRO consensus guideline[11] that margins for pure DCIS, with or without microinvasion, which are treated with lumpectomy and radiation therapy, should at least be 2mm. A close surgical margin (<1mm) at the fibroglandular boundary of the breast, equal to the chest or skin, does not order re-excision but could be an indication for a higher radiation boost dose to the involved lumpectomy site. If the margins after a lumpectomy for patients with invasive breast cancer are negative but <1-2mm, which would be defined as close, the value of re-excision is unclear in cases when these patients also receive appropriate adjuvant radiation and systemic therapies. There is also insufficient evidence to support re-excision of DCIS for margins wider than 2mm. Either way, the reason for any re-excision should be documented. Afterwards, three justifiable reasons for re-excision are stated. The first one is residual adjacent malignant appearing calcifications which have been identified on post-lumpectomy mammography. The second one is an ink-negative margin with the proximate involvement of a large volume cancer within 1-2mm of the margin. The last one is for fragmented lumpectomy specimens, which cause uncertainty about the margin status. [8(p. 2-3)]

It is mentioned that the decreased risk of ipsilateral tumour recurrence probably depends more on the improved adjuvant treatments than on changes in patient management regarding the margin status because the re-excision of ink-positive margins has been practised for decades. Due to a better understanding of the influence of molecular and genomic profiling on tumour behaviour and the introduction of targeted therapies, the margin status has become only one of many factors regarding local recurrence because it is widely recognised that not all breast cancer is removed in patients who undergo a lumpectomy, even with negative margins. Histopathological research has demonstrated that about two-thirds of breast cancers are multifocal or diffuse, while only one-third are unifocal. While breast MRI can find some of these multifocal or diffuse cancers,

comprehensive histology can even find more of them. Usually these extra cancer sites are controlled with adjuvant treatment methods.[8(p. 3)]

The use of the "re-excision lumpectomy rate" [8(p. 3)] as a quality measurement is controversial. On the one hand, because of the lack of data regarding the minimal or optimal quality threshold. On the other hand, there are concerns that unintended adverse consequences may occur if the importance of this rate is elevated too high. Surgeons might change their criteria for eligibility for lumpectomy in patients with inherently high risk for positive margins, which would result in an increase in mastectomy rates or increased excisional volume that would worsen cosmesis. If the re-excision lumpectomy rate is used as a quality measurement tool, it should be incorporated into a programme that simultaneously measures other quality aspects of lumpectomy like the cosmetic outcome, patient satisfaction, ipsilateral tumour recurrence, and the BCT rate. [8(p. 3-4)]

The recommendations regarding the follow-up to a BCS are described below:

- In cases of an invasive cancer with a negative margin, meaning no tumour on ink, with or without DCIS, a re-excision is not recommended under the condition that standard radiation therapy is performed as indicated. If a re-excision is carried out, the reason should be documented.
- In cases of in-situ cancer with a negative margin, meaning no tumour on ink and all margins are ≥2mm wide, with or without a microinvasive component, no further surgery is necessary if the patient is undergoing standard radiation therapy as well as other recommended adjuvant treatments as indicated. If a re-excision is performed, the reason should be documented.
- In cases of an invasive cancer with a close margin, meaning widths <2mm, with or without DCIS, a re-excision is not recommended but should be considered on a case-by-case basis. The decision should be made depending on the number of margins with close disease, the location of the margin, as well as the receipt of radiation therapy. If a re-excision is performed, the reason should be documented.
- In cases of in-situ cancer with a close margin, meaning widths <2mm, with or without a microinvasive component, a re-excision is recommended. If a re-excision is not performed, the reason should be documented.
- In cases of an invasive cancer as well as an in-situ cancer with a positive margin, meaning a tumour on ink, a re-excision should be performed. If a re-excision is not performed, the reason should be documented.

The recommendations regarding DCIS apply to pure DCIS or DCIS with microinvasion. Any invasive cancer with an intra-ductal component should be treated based on the invasive cancer recommendations. The margins of a DCIS component in a specimen also containing invasive cancer, which are <2mm, are acceptable.[8(p. 4)]

In the recommendations of the "Consensus Guideline on the Management of the Axilla in Patients with Invasive/ In-Situ Breast Cancer", the following points are listed.

- The indication for SLN surgery in patients with a clinically negative axilla, for whom axillary staging would provide actionable or relevant information, is that they should be offered a SLNB.
- Patients with 1-2 positive SLNs without gross extracapsular extension (histological extracapsular extension is allowed) who undergo BCS may omit an axillary lymph node dissection. This applies under the condition that they meet the inclusion criteria of T1-2 tumours, patient acceptance and completion of standard whole-breast radiation therapy, and the recommended adjuvant systemic therapies like endocrine, cytotoxic, or both therapies.
- There are no clear indications for directed axillary radiation in patients with 1-2 positive SLNs who undergo a BCS. Patients with 1-2 positive SLNs with either micro- or macrometastatic disease who undergo a mastectomy an axillary radiation alone without a complete axillary lymph node dissection may be considered.
- Immunohistochemical cytokeratin staining should be used at the discretion of the pathologist based on an inability to resolve an area of concern for metastatic disease in the node. It is not recommended for routine use in patients with surgical excision as a first line treatment. However, it should be considered in patients who are treated with neoadjuvant chemotherapy and have node-positive disease at presentation.
- Regarding the indications for SLN surgery in patients who undergo neoadjuvant systemic treatment, a SLNB prior to neoadjuvant therapy is not recommended as this prevents the assessment of nodal response to the systemic treatment. If a patient presents with a clinically negative axilla, a SLNB is recommended after neoadjuvant treatment. The choice of SLN surgery in patients with biopsy-proven nodal metastases prior to neoadjuvant treatment should be made by the surgeon after a shared decision-making discussion with the patient. The false negative rates

of the ACOSOG 1071[53] and the SENTINA[54] trial should be taken into account in this decision. If a SLNB following neoadjuvant treatment is attempted, a dual tracer should be used. At least two, ideally three, SLN should be identified and removed due to an improved false-negative rate with more SLN. The false-negative rate can also be lowered if a clip has been placed in the lymph node at the time of the initial biopsy and the clipped node is removed at the time of SLNB. In cases where the SLN or clipped node cannot be identified, axillary lymph node dissection is recommended.

- Observational data suggests that SLNB may be considered for patients with multifocal or multicentric cancer, with prior breast or axillary surgery, and during pregnancy. For patients with inflammatory breast cancer, SLNB is not considered an acceptable staging method. A SLNB should be performed for patients who undergo surgery for DCIS only, for those having an initial mastectomy, or for those for whom the breast conservation surgery may prevent further SLN mapping. [14(p. 8-9)]

The "Performance and Practice Guidelines for Axillary Lymph Node Dissection in Breast Cancer Patients" describes the technique by which an axillary lymph node dissection is achieved. The extent of the dissection should be based on the tumour characteristics, the patient's anatomy, and intraoperative findings. It should be sufficient to remove all gross evidence of disease and contain at least 10 lymphatic nodes. If a gross tumour extends behind the musculus pectoralis minor, it should be divided or excised to facilitate the removal. The identification of the long thoracic, thoracodorsal, and medial pectoral nerves should be done to achieve the preservation of these structures, unless they are grossly infested with tumour. Furthermore, the preservation of the T2 and T3 sensory nerves should be accomplished if anatomically suitable. Any unresectable residual disease should be clipped to ease radiation treatment planning. The presence of residual disease after the surgery should be documented.[9(p. 2)]

1.2.5 American Society for Radiation Oncology Consensus Guidelines

The "American Society for Radiation Oncology" (ASTRO) was founded in November 1958. The "American Club of Therapeutic Radiologists" has been looking to represent their speciality outside of the "American College of Radiology", the "Radiological Society

of North American", and the "American Roentgen Ray Society". The membership, starting with 58 radiation therapists, has rapidly grown, and in 1962, the "American Club of Therapeutic Radiologists" was officially incorporated in Colorado with a membership of 250. In 1966, the name was changed to "American Society for Therapeutic Radiologists" (ASTR). In 1968 and 1970, their bylaws changed to create an executive committee. The first independent scientific meeting was held in Phoenix in November 1970, followed by the sponsorship of its official journal, the "*International Journal of Radiation Oncology ▪ Biology ▪ Physics*" in 1976. The name was changed in 1983 to "American Society for Therapeutic Radiology and Oncology" (ASTRO), and they became their own independent society in 1998. The change of name to its current form happened at their 50th Annual Meeting in 2008, while keeping the acronym ASTRO.[55]

In the "SSO-ASTRO Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer"[10], a breast-conserving therapy is defined as "surgical excision of the primary tumor and a margin of surrounding normal tissue followed by a whole-breast radiation therapy" [10(p. 554)]. This is equivalent to a mastectomy for the treatment of Stages I and II invasive breast cancer. [10(p. 554)]
This guideline defines a positive margin for Stages I and II of invasive breast cancer as "the presence of ink at the surface of the surgical specimen on either invasive tumour cells or DCIS"[10(p.556)], which would imply a potentially incomplete resection. A positive margin is associated with at least a twofold increase in ipsilateral breast tumour recurrence. This increased risk is nullified neither by the delivery of a boost dose of radiation nor by a systemic treatment consisting of endocrine, chemo- or biologic therapy, nor by favourable tumour biology.[10(p.556)] Moreover, in the introduction of this guideline, it is stated that the definition of "no ink on tumour", or microscopically clear margin, has been defined in the results of the "National Surgical Adjuvant Breast and Bowel Project" by Fisher et al. (NS ABP 06)[49]. In this study, it is concluded that a lumpectomy, if followed by breast irradiation, is an appropriate treatment for women with breast cancer, under the condition that the margins of the resected specimens are free of tumour[49(p. 1233)]. Furthermore, it is described how the procedures were performed and that the specimen margins had been inked[49(p. 1239)]. This paper also refers to a study by Fisher et al. (1985)[56], where the procedure of how the margins should be inked by the pathologists is further described and that tumour-free margins provide a significant advantage for patients[10(p.554)].

A negative margin is defined as “no ink on invasive carcinoma or DCIS, which substantially reduces the risk of local recurrence compared with positive margins”.[10(p.557)] The routine practise to obtain wider negative margin widths is not indicated and is controversial. Holland et al.[57] have shown that clinically unicentric T1-T2 breast cancers are frequently associated with subclinical foci of invasive cancer with or without DCIS in the surrounding breast tissue, which could also be present at larger distances from the index lesion. These foci of invasive carcinoma and DCIS at considerable distances from the primary tumour site could contribute to the fact that an increase in the lumpectomy margin width (1mm) has no significant impact on the risk of local recurrence. Another confounder in the interpretation of margin width related data with regard to the risk of local recurrence could be the technical limitations of lumpectomy margin evaluation. Artificially narrower margin widths than in vivo could result from a flattening of the specimen due to the lack of support from surrounding tissue and compression when submitted to specimen radiography. The ink which is applied to the surface of the specimen often tracks into deeper portions of the specimen, which can result in a significant challenge for the pathologist to histologically determine the location of the true margin.[10(p.557)]

The process of margin evaluation is highly prone to sampling error, given that no standard method for margin evaluation exists. The two major options for margin evaluation in BCS consist of either sectioning the specimen perpendicular to the inked margin, where a precise distance to the margin can be determined, or shaving the specimen margins and examining them en face. In the latter, any residual tumour cells found in the specimen are considered a positive margin. Both methods can be used if the surgeon submits separate margins obtained from the walls of the biopsy cavity after the removal of the lumpectomy. It is pointed out that the “shaved margin method” [10(p.557)] enables the examination of a greater surface area of the specimen margin compared to the “inked method” [10(p.557)]. However, the use of this “shaved margin method” results in the categorisation of many margins as positive, which would be negative with the “inked method”, leading to unnecessary re-excision or even a mastectomy. A further point is that the sampling of lumpectomy specimens ranges from the submission of a limited number of sections to the total sequential embedding of the entire specimen. Nevertheless, it is pointed out that even the total sequential embedding results in the examination of only <1% of the lumpectomy margins. Furthermore, the presence of a tumour at a certain distance from the inked margin

on a single slide may not represent the true state of that margin three-dimensionally. [10(pp. 557-558)]

There is a great degree of variability in margin assessment, and for that reason, regardless of the technique used, a negative margin does not guarantee the absence of a residual tumour in the breast. As shown by a meta-analysis[58], which evaluated the relationship between specific margin widths (1mm, 2mm, and 5mm) and the ipsilateral tumour recurrence, there is no statistically significant evidence that the risk of recurrence is associated with margin distance. There is also no statistical evidence for a trend that the odds of tumour recurrence decrease as the distance to declaring negative margins increases.[10(p.558)]

Systemic therapy, used for most patients with breast cancer, reduces the overall risk of ipsilateral tumour recurrence. There is no evidence that, for patients who do not receive systemic treatment, margins wider than "no ink on tumour" would result in any further reduction of tumour recurrence. There is also no indication to obtain wider margins than "no ink on tumour" for any biological breast cancer subtype.[10(pp. 559-560)]

The margin width should not be used to determine the delivery technique or fractionation for whole-breast irradiation therapy. In patients with "no ink on tumour" the use and dosage of a tumour bed boost should be based on an a priori estimation of local failure risk. For that reason, the margin width has no impact on this decision either. [10(pp. 560-561)]

Young patient age, defined as patients under 40 years, has been associated with an increased risk of tumour recurrence. However, there is no evidence that once a negative margin has been achieved, these patients would benefit from a greater margin width than "no ink on tumour". [10(pp. 561)]

The "SSO-ASTRO-ASCO Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma in Situ"[11] states that breast-conserving therapy, a surgical excision of the primary tumour with a margin of surrounding normal breast tissue followed by a whole-breast irradiation, results in a long-term cause-specific survival rate of over 95% for patients with DCIS. Although the addition of WBRT has no impact on the patient's survival, it considerably reduces the risk of ipsilateral breast tumour recurrence.[11(p. 288)]

The definition of a positive margin for DCIS is the presence of ink on ducts containing DCIS on the specimen surface. A positive margin implies a potentially incomplete

resection and is associated with a higher rate of ipsilateral tumour recurrence. In a meta-analysis of randomised DCIS trials,[59] the ipsilateral tumour recurrence risk of patients with a positive margin has been twofold higher compared to patients with negative margins, and approximately half of them have been invasive recurrences.[11(p. 289)]

The negative margin width of a DCIS should be ≥2mm to be associated with a reduced risk of ipsilateral tumour recurrence in patients who undergo whole-breast irradiation, although it is not supported by the evidence to aim for wider negative margin widths. Most cases of DCIS are unicentric, but the involvement of the segment may be multifocal, including so-called gaps of uninvolved tissue between foci of DCIS. Due to this reason, a negative margin does not guarantee the absence of residual DCIS. The technical limitations in the margin assessment, like artifactually narrower margins ex vivo, tracking of the surface ink into deeper portions of the specimen, the problem of non-representative tumour-to-ink distances on a single slide, and the advantages and disadvantages of the two common methods for margin evaluation, the perpendicular sectioning to ink and the shaved margin examination, are also mentioned. In a meta-analysis by Marinovich et al.,[60] specific margin width thresholds of 2, 3, 5, and 10mm have been compared to margins defined as >0 or 1mm in relation to tumour recurrence. The recurrence risk between the 2-10mm margin widths has not been significantly different. However, there has been a significantly decrease in the recurrence rates between the 2mm margin width groups compared to >0-1mm margin widths. Although the 2mm margin optimises local control, clinical judgement has to be used to determine whether patients with a margin width of 0-1mm require a re-excision. The assessment of the ipsilateral tumour recurrence risk, the cosmetic impact of re-excision, and the overall life expectancy have to be taken into account. Factors which should be considered in the recurrence risk assessment are residual calcifications on postexcision mammography, the extent of DCIS in proximity to the margin, and which margin is close. For example, whether the anterior margin is excised to the skin, the posterior margin is excised to the pectoral fascia, or if there are margins associated with residual breast tissue.[11(pp. 289, 291)]

If a patient is treated with an excision alone, the rates of ipsilateral tumour recurrences are considerably higher than treatments including a WBRT, even in predefined low-risk patients. The optimal margin width for such a treatment is unknown but should at least be 2mm, with some evidence suggesting that lower recurrence rates can be achieved with margins wider than 2mm.[11(p. 292)]

While endocrine therapy is associated with reduced rates of ipsilateral tumour recurrences, there is no evidence that an association between endocrine therapy and negative margin widths exists. Multiple patient and tumour features like young patient age, histologic pattern, comedo necrosis, nuclear grade size of the DCIS, and unfavourable gene profile scores have been associated with a modified risk of tumour recurrence. Nonetheless, there has been no data addressing whether margin widths should be influenced by these factors.[11(p. 293)]

There is also no evidence that the negative margin width as a single factor should determine the radiation delivery technique, the fractionation of the WBRT, or the use and dose of a boost. The optimal margin width in accelerated partial breast irradiation cannot be given considering the insufficient evidence. [11(p. 294)]

For "DCIS with microinvasion" (DCIS-M), which is defined as "the extension of cancer cells beyond the basement membrane with no focus more than 0,1cm in greatest dimension" [11(p. 294)], studies have suggested that the risk of ipsilateral tumour recurrence is similar to those with pure DCIS. Due to the lack of specific data but based on expert opinion, a DCIS-M should be considered DCIS regarding the optimal margin width given that the majority of the lesion is composed of DCIS and that systemic therapy utilisation for these lesions more closely reflects the treatment pattern for DCIS than for invasive carcinoma. An invasive cancer with a DCIS component, regardless of its extent, should be treated according to the invasive cancer guideline.[10, 11(p. 294)]

1.2.6 The Protocol for the Examination of Resection Specimens of the Breast of the College of American Pathologists

The "College of American Pathologists" (CAP) was established in the 1940s by a group of pathologists to create a United States-wide organisation that could win recognition and respect for their speciality and improve laboratory medicine in the US. On December 12th and 13th 1946, the CAP was formed at an organisational meeting in Chicago, where its first president, Frank W. Hartman, was elected. In 1986, the first cancer specimen reporting guidelines were published in "*Pathologist*".[61] On their website, the "CAP Pathology and Laboratory Quality Center for Evidencebased Guidelines" and the "CAP Cancer Reporting and Biomarker Reporting Protocols" can be downloaded for free. It is also stated that their "Cancer Reporting Protocols" are used by pathologists and other medical professionals to provide complete and uniform reporting of malignant tumours.[62]

The “Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of the Breast”[12] can be used in excisions less than total mastectomy, which includes specimen-designated excision, segmental resection, lumpectomy, quadrantectomy, and segmental or partial mastectomy with or without axillary contents. They can also be applied to total mastectomy specimens, including skin- and nipple-sparing mastectomy, again with or without axillary contents. It can be applied to any type of invasive breast carcinoma, with or without DCIS.[12(p. 1)]

In the “Explanatory Notes”, the individual protocol points are further described. The sampling of invasive cancer specimens aims to achieve the following objectives:

- It is stated that the clinical or radiologic lesion for which surgery has been performed has to be examined histologically. If it is a nonpalpable imaging finding, a specimen radiograph with or without additional radiologic studies may be necessary to identify the lesion. The complete lesion or area with the imaging finding should be submitted in a sequential fashion for histologic examination if feasible.
- If the specimen consists predominantly of a DCIS with microinvasion, the entire specimen, or at least the entire grossly involved area, should be submitted to identify additional areas of invasion with or without lymphovascular invasion.
- Every gross lesion in the specimen has to be sampled.
- Each designated margin has to be evaluated for involvement by DCIS and invasive carcinoma. It should be noted if the specimen has been sectioned or fragmented, which will limit the ability to evaluate the margin status.[12(p. 14)]

It should be aimed to remove the area of carcinoma in a single intact specimen; if it has been incised or if it is fragmented, then it may not be possible to accurately assess the margins; this should be noted under “Additional Pathologic Findings”.[12(p. 14)]

If a patient has an invasive carcinoma associated with DCIS, the risk of local recurrence in breast conserving surgeries increases. In cases where the in situ component is predominant, for example, DCIS with microinvasion or extensive DCIS associated with a T1a carcinoma, it is crucial to document the features of the DCIS. However, if the DCIS is a minimal component of the invasive carcinoma, these features have less clinical relevance, and therefore most of the reporting elements for DCIS are optional and should be used at the discretion of the pathologist. EIC positive carcinomas are associated with an increased

risk of local recurrence in cases where the margins are not evaluated or focally involved. Although in cases where the DCIS does not extend close to the margins, findings of EIC positivity have less significance.[12(p. 22-23)]

In the chapter "Margins", whenever it is practicable, the surgical specimen should be oriented so that the pathologist can identify the specific margins. This is particularly important for surgical procedures less than total mastectomy, where the need for the excision of residual tumour from a specific margin may arise. Furthermore, the identification of surgical margins allows for measurements of specific margin distances. Every identifiable margin should be evaluated both grossly and histologically for tumour involvement. The method of orientation may be chosen by placing sutures or clips on the specimen surface or by other means of communication between the surgeon and the pathologist. The method should be documented in the pathology report. The methods of margin identification range from using different coloured inks to submitting of the margins in specific cassettes or submitting each margin as a separately excised specimen. The application of ink should be done carefully to avoid deep penetration into the specimen.[12(p. 26)]

Any macroscopic or histologically identified involvement of the margins by invasive carcinoma or DCIS should be noted in the report. If an orientation of the specimen is given, the specific involved margin or margins should be noted by the pathologist, as well as the distance from the tumour to the closest margin if the margins have been sampled with perpendicular sections. Due to the growth pattern of DCIS in the ductal system, a negative but close margin does not ensure that no DCIS is present in the adjacent tissue. A positive margin is defined as "ink on carcinoma", and if the specimen is oriented, the specific margin or margins which are involved should be reported.[12(p. 26)]

A deep muscle fascial margin positive for DCIS is unlikely to have clinical significance due to the unlikelihood of additional breast tissue beyond this margin. However, if an invasive carcinoma is present at this margin, especially if it is associated with muscle invasion, postmastectomy radiation is often indicated. A superficial, or generally anterior, margin may be immediately below the skin, and therefore it is unlikely that additional breast tissue is beyond this margin. It may be possible that breast tissue remains in skin flaps, with an increased likelihood depending on the thickness of the flap.[12(p. 26)]

Specimen radiography is important for the assessment of the adequacy of the excision. It should be avoided, or at least minimised, to compress the specimen, as it can severely compromise the ability to assess the distance of the DCIS from the margin. For this reason, mechanical compression devices should be used with caution and preferably only for nonpalpable lesions which require this technique for imaging, for example, microcalcifications. [12(p. 26)]

Furthermore, the approximate extent of margin involvement can be specified as unifocal (for one focal area of carcinoma at the margin with <4mm in size), multifocal (for ≥2 foci of carcinoma at the margin), or extensive (for carcinoma present at the margin over a broad front with >5mm).[12(p. 26)]

In the chapter "Lymph Node Sampling and Reporting", it is stated that most patients with invasive carcinoma are going to have lymph nodes sampled. The size of each grossly positive node should be recorded. For grossly negative nodes, the sampling has to be adequate to detect all macrometastases, meaning all metastatic deposits >2mm, as they are known to have prognostic importance. For this reason, every node should be thinly sliced along the axis of the node at 2mm, and all slices should be submitted for histological examination. At least one representative hematoxylin-&-eosin (H&E) level has to be examined, and additional sampling methods such as further H&E levels or immunohistochemical studies may detect isolated tumour cells or micrometastases, although the clinical impact of such metastases is minimal. It is important that the nodes be submitted in such way that every node can be evaluated and counted separately. In the majority of cases, if metastases are present, the SLN will be involved. In rare cases, it can happen that only non-sentinel lymph nodes contain metastases. This can occur if the SLN is completely replaced by tumour tissue, which results in the inability to detect it with dye or radioactive tracer, if the patient has unusual lymphatic drainage, or if the identification technique has a failure. Such findings should be included in the pathology report.[12(p. 26-28)]

The "Protocol for the Examination of Resection Specimens From Patients With Ductal Carcinoma In Situ (DCIS) of the Breast"[13] can be used for the same procedures as mentioned before in the "Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of the Breast"[12]. The tumour types for which this can be used are DCIS without invasive carcinoma or microinvasion, Paget disease of the nipple

not associated with invasive breast carcinoma, and encapsulated and solid papillary carcinoma without invasive carcinoma.[13(p. 1)]

In the "Explanatory Notes", the specimen sampling for specimens with DCIS is further described. The clinical or radiological lesion for which surgery has been performed has to be examined histologically. If the targeted lesion is a nonpalpable imaging finding, a specimen radiograph with or without additional radiologic studies may be necessary to identify the lesion. The entire specimen should be submitted in a sequential fashion for histological examination if feasible. If not, at least the entire region of the lesion should be examined histologically. Every other gross lesion which has been noted in the specimen has to be sampled. The resection margins have to be evaluated for involvement by DCIS. It should be noted if the specimen is sectioned or fragmented, which will limit the ability to evaluate the size of the lesion and the margin status. If the specimen is from an incisional biopsy, the margins do not need to be evaluated.[13(p. 8)]

It is recommended for specimens from patients with a known diagnosis of DCIS that the entire specimen be examined. When feasible, serial sequential sampling should be applied to exclude the possibility of invasion, for a complete evaluation of the margins, and aid in the determination of the extent of DCIS. If not the entire specimen or grossly evident lesion is examined histologically, the approximate percentage of the specimen or lesion which has been examined should be noted. [13(p. 8)]

The extent of DCIS is an important factor in patient management. The extent correlates with the risk of residual tumour after re-excision, with close or positive margins, local recurrence, and the possibility of missed areas of invasion. If wide margins are obtained during surgery, their extent is not as important for the prediction of local recurrence. Mammographic assessment of DCIS, which is usually done based on the distribution of calcifications, frequently underestimates and sometimes overestimates the extent of DCIS. In general, a precise measurement of the extent of DCIS is difficult or even impossible due to the following reasons: If gross findings are present in a specimen, like areas of thickened tissue and/or punctate necrosis, they often do not correspond to the entire involved area since the branching pattern of the DCIS, which involves the ductal system, is only apparent by histological examination. Due to the high compressibility of the ductal system and the surrounding tissue, the specimens may be distorted during surgery, specimen processing, or specimen radiography. There may be diagnostic gaps in ductal involvement, especially

in low-grade DCIS. Because DCIS is often not removed in a single excision but instead presented in multiple specimens, an exact measurement is also complicated.[13(p. 9)]

For DCIS with sizes ≤20mm, a negative margin at a BCS can be achieved in most women. It is recommended to examine the entire area which is involved in DCIS histologically. To include all areas which are likely to contain DCIS (for example, tissue with radiologic calcifications or grossly abnormal tissue), a complete histological examination of smaller biopsies or a sampling of large surgical specimens is required. For DCIS with sizes of >20 to ≤40mm, it may be difficult to achieve wide negative margins in some women with BCS. In such cases, it is recommended to examine the entire involved area histologically, but it may be difficult. For DCIS specimens with sizes >40mm, it may be impossible to achieve negative margins with breast conserving surgeries. The histological examination of the entire involved area is recommended but may be impractical. It may be possible that areas of invasion remain undetected if the whole area involved in DCIS is not entirely examined. Lymph node sampling may be recommended in these cases. [13(p. 10)]

Regarding the margins of DCIS, it is stated that the specimen should be oriented to make the identification of specific margins possible. The methods for specimen orientation as well as margin identification are the same as for invasive cancer. If the margins of a DCIS specimen have been sampled with perpendicular sections, the pathologist should report the distance from the DCIS to the closest margin. However, due to the growth pattern of DCIS in the ductal system, DCIS could still be present in the adjacent tissue if the margin is negative but close. A margin is positive if ink is present on DCIS, and if the specimen has been oriented, the specific margin or margins should be reported. The recommendations for DCIS regarding the deep muscle fascia and the superficial margin, as well as the specimen radiography, are similar to the recommendations for invasive cancer. The extent of margin involvement for DCIS, which is associated with the likelihood of residual disease, can be reported as focal (for DCIS at the surgical margin in an area <1mm in one block), extensive (for DCIS at the margin in an area ≥15mm or in ≥5 low-power fields or in ≥8 blocks) or minimal or moderate for cases between focal and extensive.[13(p. 13-14)]

The sampling of lymph nodes in patients with DCIS may be required in the following situations:

- Patients with extensive DCIS are more likely to have areas of invasion, and it may be difficult or not feasible to examine every involved area of the breast histologically.

- If, at a prior needle biopsy or excision, pathologic findings have been found, this may indicate an invasion or microinvasion, which is defined as an invasion measuring ≤1mm in size. If an invasion has been documented, the invasive cancer protocol[12] should be used.
- If imaging or clinical findings have been found, they increase the likelihood that stromal invasion is present.
- If a mastectomy is planned for the patient. There is no increase in morbidity if additional sampling of low lymph nodes or the SLN is performed. In cases where the nodes are negative and an invasive cancer is found, further surgical procedures for node sampling may be avoided.[13(p. 14)]

Nearly all tumour cells which are present in the lymph nodes of patients with DCIS are isolated tumour cells or have been artificially displaced from previous procedures. Isolated tumour cells have not been shown to have prognostic relevance if detected in patients with DCIS. The finding of a larger metastasis may indicate additional tissue sampling and review of slides to determine if an area of invasion is present.[13(p. 15)]

2 Materials and Methods

The following diploma thesis aims to identify differences in the understanding of the "R classification" in breast cancer diagnosis between various medical professions and where these differences derive from. The study design is a prospective study with anonymized results and is based on a literature review as well as data from a questionnaire.

2.1 Literature review

For the literature review, the "TNM Classification of Malignant Tumours"[1] as well as the "TNM Supplement"[2] of the UICC and the "AJCC Cancer Staging Manual"[4], their past publications as well as their current ones, were chosen, as were selected guidelines [3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15] which are currently used in breast cancer treatment. For this thesis, their definitions, mentions, and applications regarding the "R classification" were analysed.

2.2 Questionnaire

With the approval of the ethical committee of the Medical University of Graz under EK number 33-611 ex20/21, the questionnaire was created using the online survey tool "Lime Survey"[63] as a quantitative, fully structured written survey. The aim of this survey has been to anonymously receive the opinions of experts about their understanding of the "R classification".

The questions were designed after a literature review of the "TNM Classification of Malignant Tumours"[1] as well as the "TNM Supplement"[2] of the UICC and "AJCC Cancer Staging Manual"[4] as well as current guidelines[3, 15, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14] used for breast cancer treatment. Altogether, the questionnaire consists of 22 questions, including multiple choice, single choice, select all that apply, and one question where participants were given the opportunity to write in an alternative answer choice as free text. The questionnaire is divided into three sections: "General", "General TNM Classification", and "Specific Questions Regarding Breast Cancer Diagnosis". The sections range from six to nine questions each. The survey was piloted with seven people involved in the medical field before it was sent out to participants.

The questions, translated here from German to English, are depicted below. The original German questionnaire is in the appendix.

General

1. What medical profession do you work in?
    - Surgery/ Gynaecology
    - Radiation Therapy - Radiation Oncology
    - Pathology
    - Radiology
    - Oncology
    - Other:
2. How many years of professional experience do you have in your medical profession (including residency)?
    - 0-5 years
    - 6-10 years
    - 11-15 years
    - ≥16 years
3. Which of these guidelines/ classifications do you use in your clinical work? (multiple answers are possible)
    - Interdisciplinary S3 Guideline for Early Detection, Diagnosis, Therapy and Aftercare of Breast Cancer
    - St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer
    - Consensus- & Performance and Practice Guidelines of the American Society of Breast Surgeons - ASBrS
    - Clinical Practice Guidelines in Oncology in Breast Cancer of the National Comprehensive Cancer Network - NCCN
    - International Guideline for Management of Breast Cancer of the International Society of Breast Cancer - ISBrC
    - SSO/ASTRO/ASCO Consensus Guideline for DCIS as well as the SSO/ASTRO Consensus Guideline for invasive breast carcinoma of the American Society for Radiation Oncology - ASTRO
    - TNM Classification of Malignant Tumours of the UICC
    - AJCC Cancer Staging Manual

4. In your opinion, the “R classification” of the UICC provides information about
    - the residual tumour after therapy
        - yes
        - no
    - the prognosis
        - yes
        - no
    - the resection margin of the primary tumour alone
        - yes
        - no
    - the inclusion of distant metastasis
        - yes
        - no
5. Are you familiar with the following “R categories” of the TNM classification of malignant tumours of the UICC with their exact definitions? (*The following questions could each be answered with yes or no)*
    - RX
    - R0
    - R0>1mm
    - R0≤1mm
    - R1
    - R2
    - R2a
    - R2b
    - R2c
6. Which of the following “R categories” of the TNM classification of malignant tumours of the UICC do you use in your clinical routine? (*The following questions could each be answered with yes or no*)
    - RX
    - R0
    - R0>1mm
    - R0≤1mm
    - R1

- R2
- R2a
- R2b
- R2c

7. Do you consider the description of the “R categories” of the TNM classification of malignant tumours of the UICC to be clearly defined?
   - yes
   - no
8. How do you consider the description of the “R categories” of the TNM classification of malignant tumours of the UICC in practise?
   - satisfactory
   - non satisfactory
9. Who do you think should be responsible for the “R classification”?
   - Pathologist
   - Surgeon
   - Oncologist
   - The treating physician who is most familiar with the patient’s medical history
   - Together on an interdisciplinary basis in the tumour board

General TNM Classification

1. Is there any additional information required for a R0 category other than the assessment of the resection margin?
   - yes
   - no
2. Which “R category” would you assign to a breast surgical specimen of an invasive breast carcinoma with a largely tumour-free resection margin and a positive, completely removed sentinel lymph node, but no axillary dissection present?
   - RX
   - R0
   - R1
   - R2
   - no “R category” can be assigned

3. In your opinion, which “R category” is assigned if the surgical specimen is sent in in several parts?
    - RX
    - R0
    - R1
    - R2
    - no “R category” can be assigned
4. In your opinion, which “R category” is assigned if the surgical specimen shows a surface with multiple tears and resection margins that are in some parts difficult to assess?
    - RX
    - R0
    - R1
    - R2
    - no “R category” can be assigned
5. In your opinion, which “R category” can be assigned if no tumour can be detected in a surgical specimen after neoadjuvant therapy?
    - RX
    - R0
    - R1
    - R2
    - no “R category” can be assigned
6. In your opinion, which “R category” can be assigned if the scarred and now tumour-free area of the primary tumour is located at the edge of the resection in a surgical specimen after neoadjuvant therapy?
    - RX
    - R0
    - R1
    - R2
    - no “R category” can be assigned
7. In your opinion, which “R category” can be assigned, if in a surgical specimen after neoadjuvant therapy, in the mostly scarred area of the primary tumour, isolated

residual tumour cell nests are distributed at a distance of approximately 5mm and more, the scarred tumour area extends directly to the resection margin, and the minimum distance of the nearest residual tumour cell nest is 2mm?

- RX
- R0
- R1
- R2
- no “R category” can be assigned

Specific Questions Regarding Breast Cancer Diagnosis

1. R1 in breast surgery means (multiple answers possible)
   - ink on tumour in invasive carcinoma
   - invasive carcinoma fractions of a millimetre from the resection margin
   - invasive carcinoma less than 2mm from the resection margin
   - invasive carcinoma removed over 2mm, but DCIS at the resection margin
   - ink on tumour in DCIS (without invasive carcinoma)
   - DCIS (without invasive carcinoma) less than 2mm from the resection margin
2. Which “R category” would you assign to a neodadjuvantly treated breast carcinoma with a disseminated growth pattern in the entire specimen (the individual tumour cells do not reach the ink; “no ink on tumour”)?
   - RX
   - R0
   - R1
   - R2
   - no “R category” can be assigned
3. Which “R category” would you assign to a surgically treated breast cancer specimen with a largely tumour-free resection margin and a clinically discovered (and histologically verified) but not removed liver metastasis?
   - RX
   - R0
   - R1
   - R2
   - no “R category” can be assigned

4. In your opinion, which “R category” should be assigned for a surgical breast cancer specimen with DCIS if the incision margin is tumour-free but suspicious calcifications are discovered in the postoperative mammography?
    - RX
    - R0
    - R1
    - R2
    - no “R category” can be assigned
5. Should breast specimens with invasive carcinomas and narrow resection margins be assessed by frozen section?
    - yes
    - no
- Should these narrow resection margins be marked by the surgeon?
    - yes
    - no
6. Should breast specimens with neoadjuvantly treated invasive carcinomas with narrow resection margins be assessed by frozen section?
    - yes
    - no
- Should these narrow resection margins be marked by the surgeon?
    - yes
    - no
7. Should breast specimens with DCIS and narrow resection margins be assessed by frozen section?
    - yes
    - no
- Should these narrow resection margins be marked by the surgeon?
    - yes
    - no
- Should the narrow resection margin of a DCIS in a surgical mammary specimen be marked intraoperatively by specimen radiography?
    - yes
    - no

2.3 Participants

The study population consists of physicians from different medical professions, including surgeons/ gynaecologists, pathologists, radiation oncologists/ radiation therapists, oncologists, and radiologists. A web link to the survey was distributed via email through the "IAP Austria", the "Österreichische Gesellschaft für Senologie", the "Deutsche Gesellschaft für Senologie", the "Österreichische Gesellschaft für Gynäkologie und Geburtshilfe", the "Österreichische Gesellschaft für Radioonkologie, Radiobiologie und Medizinische Radiophysik", the "Österreichische Gesellschaft für Chirurgie" and the "Austrian Society of Surgical Oncology". The questionnaire was sent to these organisations with the request to distribute the survey to physicians participating in the treatment of breast cancer.

The survey was made available during the late summer of 2021. Each participant was asked to provide demographic information, including the number of years in practise and their speciality.

2.4 Statistical Analysis

When the survey closed, the collected answers of the participants' opinions were analysed using "SPSS version 26"[64]. This tool was also used to create diagrams and graphs to illustrate the results.

Frequencies and percentages are used to display responses to individual questions as well as Pearson's Chi-Square Test to analyse if there is a significant difference between the opinions of the various medical professions. The level of significance was set at $p<0,05$ for all statistical analyses.

3 Results

A total of 303 participants started the questionnaire, of which 172 fully answered it. The full respondents comprised 73 surgeons/ gynaecologists (S/G) (42%), 73 pathologists (P) (42%), 16 radiation oncologists/ radiation therapists (10%), 5 oncologists (3%), and 5 radiologists (3%). As mentioned before, 172 (56,8%) participants fully completed the survey, 30 (9,9%) partially answered it, and 101 (33,3%) solely opened it without starting. A total of 202 (66,7%) participants (as detailed in Figure 2), therefore, either fully (*n*=172; 85,2%) or partially (*n*=30; 14,8%) contributed to the findings of the study. A full response rate cannot be given due to the fact that there is overlap between members of the different organisations.

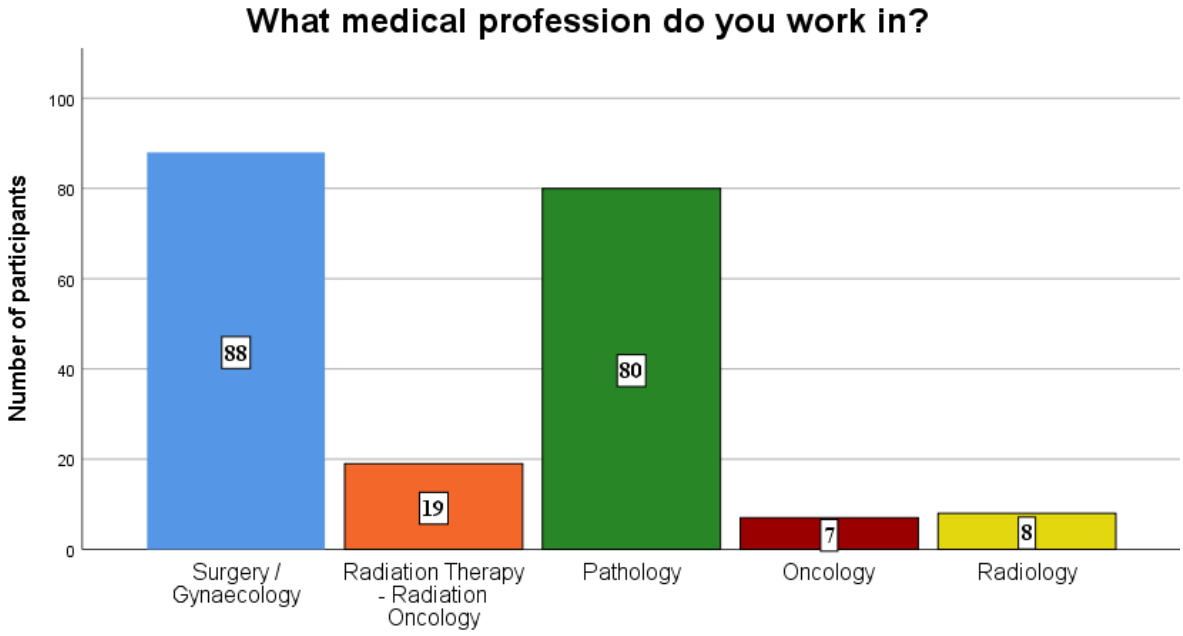

Figure 2: Number and medical profession participating in this questionnaire

3.1 Participant demographics

For statistical reasons, only the S/G and P questionnaires were analysed. Of the 168 relevant participants for this analysis, over half (*n*=88; 52,4%) classified themselves as S/G, with the remainder categorising themselves as P (*n*=80; 47,6%). Of these participants, 58,9% worked ≥16 years in their medical profession, including residency; 19,6% worked between 11-15 years; 11,3% 6-10 years and 10,1% ≤ 5 years (Table 1).

Years of professional experience (including residency)	Number of surgeons/ gynaecologists		Number of pathologists		Total number	
	absolute	relative	absolute	relative	absolute	relative
0-5 years	10	11,4%	7	8,7%	17	10,1%
6-10 years	5	5,7%	14	17,5%	19	11,3%
11-15 years	19	21,6%	14	17,5%	33	19,7%
≥16 years	54	61,3%	45	56,3%	99	58,9%
Total	88	100%	80	100%	168	100%

Table 1: Number and years of experience of the participants

3.2 General

In this part of the survey, questions about participants' general understanding, definition, and clinical practise of the "R classification" were asked.

Regarding the guidelines/ classifications which participants use in their clinical work, 135 participants chose the "Interdisciplinary S3 Guideline for Early Detection, Diagnosis, Therapy and Aftercare of Breast Cancer - S3" (80,4%), 104 the "St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer - St. Gallen" (61,9%), 5 the "Consensus- & Performance and Practice Guidelines of the American Society of Breast Surgeons - ASBrS" (3%), 30 the "Clinical Practice Guidelines in Oncology in Breast Cancer of the National Comprehensive Cancer Network - NCCN" (17,9%) and 24 participants selected the "SSO/ASTRO/ASCO Consensus Guideline for DCIS as well as the SSO/ASTRO Consensus Guideline for invasive breast carcinoma of the American Society for Radiation Oncology - ASTRO" (14,3%). Additionally, 154 participants selected the "TNM Classification of Malignant Tumours of the UICC" (91,7%) and 30 the "AJCC Cancer Staging Manual - AJCC" (17,9%). Moreover, two participants selected a non-existing guideline called the "International Guideline for Management of Breast Cancer of the International Society of Breast Cancer - ISBrC" that was used for validation. These results are presented in Table 2. Furthermore, Table 3 shows the distribution among the two analysed medical professions, with a total of 88 S/G and 80 P answering this question.

Guidelines/ classification	Number of participants [168]	
	absolute	relative
S3	135	80,4%
St. Gallen	104	61,9%
ASBrS	5	3%
NCCN	30	17,9%
ASTRO	24	14,3%
UICC	154	91,7%
AJCC	30	17,9%
ISBrC	2	1,1%

Table 2: Number of guidelines used in participants' clinical work

Guidelines/ classification	Number of surgeons/ gynaecologists [88]		Number of pathologists [80]	
	absolute	relative	absolute	relative
S3	81	92%	54	67,5%
St. Gallen	66	75%	38	47,5%
ASBrS	2	2,2%	3	3,8%
NCCN	23	26,1%	7	8,8%
ASTRO	19	21,5%	5	6,3%
UICC	75	85,2%	79	98,8%
AJCC	9	10,2%	21	26,3%
ISBrC	1	1,1%	1	1,3%

Table 3: Number of chosen guidelines among medical professions

When asked which kind of information the “R classification” of the UICC provides, 104 participants (62,3%) chose “the residual tumour after therapy”, 76 (45,8%) “the prognosis”, 106 (63,6%) “the resection margin of the primary tumour alone” and 51 (30,7%) “the inclusion of distant metastasis”. Figure 3 shows the distribution between S/G and P.

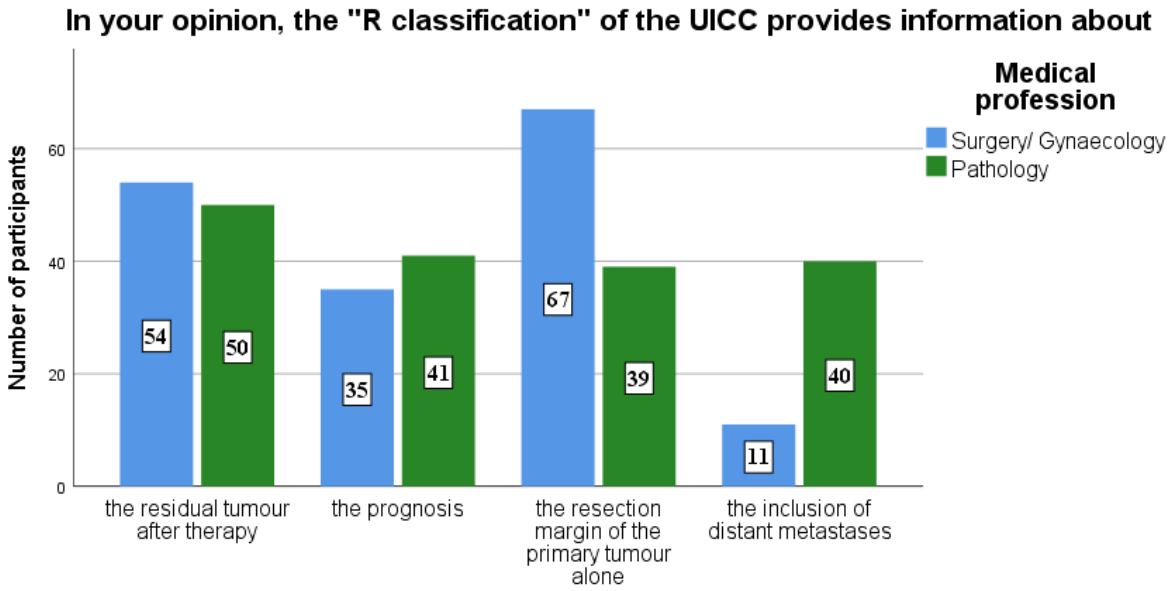

Figure 3: Medical profession and information provided by the "R classification"

67/87 (77%) S/G stated that the "R classification" provides information about the resection margin of the primary tumour alone, while only 39/80 (48,8%) P chose this option. Applying Pearson's Chi-Square Test, there was a significant difference between these professions (x^2=14,358, p<0,001). Regarding the inclusion of distant metastases, another significant difference (x^2=28,074, p<0,001) between the professions occurred with 40/79 (50,6%) P selecting this option and 11/87 (12,6%) S/G.

The answers to the questions as to whether the exact definitions of the "R classification" are known and used in clinical practise are listed in Figures 4 and 5. The "R0" category is known to nearly all of the participants (84/87 [96,6%] S/G and 79/80 [98,8%] P) as well as used in their clinical routine (85/85 [100%] S/G and 76/80 [95,5%] P).

It is similar with the "R1" category, where 84/87 (96,6%) S/G and 77/80 (96,3%) P are familiar with the definition and 82/84 (97,6%) S/G and 77/80 (96,3%) P use it in their clinical routine.

Only 43/86 (50%) S/G and 48/79 (60,8%) P stated to know the exact definition of "RX", while 62/85 (72,9%) S/G and 67/80 (83,8%) P declared to use it in their clinical routine.

In comparison to the "R2" category, 61/87 (70,1%) S/G and 67/79 (84,8%) P are familiar with the exact definition, and 48/83 (57,8%) S/G as well as 55/79 (69,9%) P use it in their clinical routine.

"R0>1mm" was known to 46/87 (52,9%) S/G and 47/79 (59,5%) P, while 30/83 (36,1%) S/G and 24/79 (30,4%) P use it in their clinical routine. "R0≤1mm" was known to 43/86

(50%) S/G and 48/79 (60,8%) P, and 31/84 (36,9%) S/G and 24/79 (30,4%) P use it in their clinical routine.

The “R2a” category was known to 11/87 (12,6%) S/G and 11/79 (13,9%) P and the “R2b” category to 11/87 (12,6%) S/G and 10/79 (12,7%) P. However, only 6/84 (7,1%) S/G and 1/79 (1,3%) P use both “R2a” and “R2b” in their clinical routine. The least chosen category was “R2c”, with only 5/87 (5,7%) S/G and 4/79 (5,1%) P being familiar with the exact definition and only 3/83 (3,6%) S/G and none of the 79 P using it in their clinical routine. The deviations in the absolute numbers of participants arose from the fact that not all participants answered all questions.

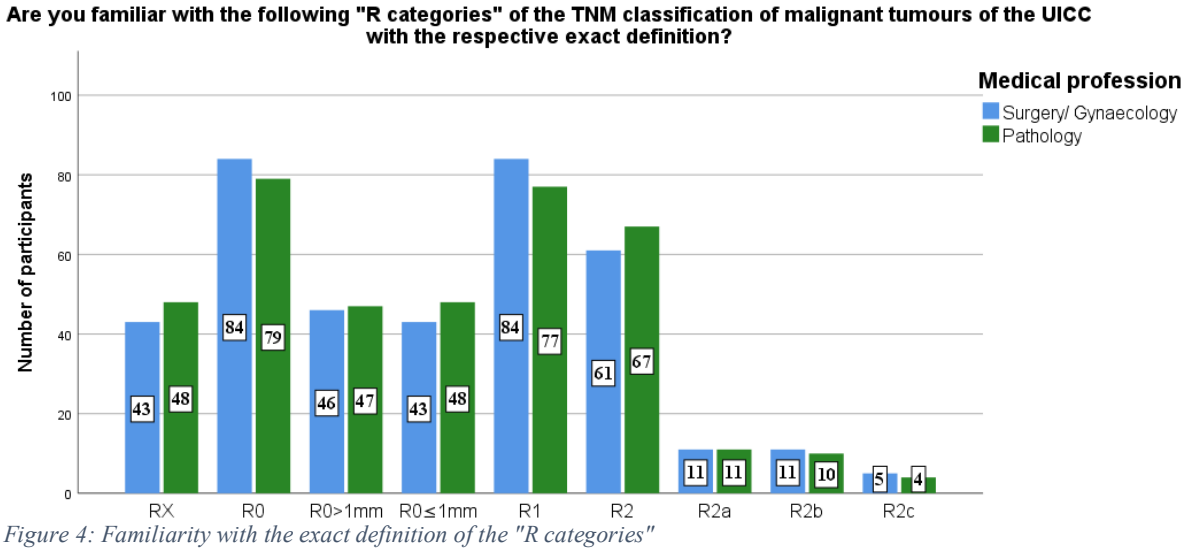

Figure 4: Familiarity with the exact definition of the "R categories"

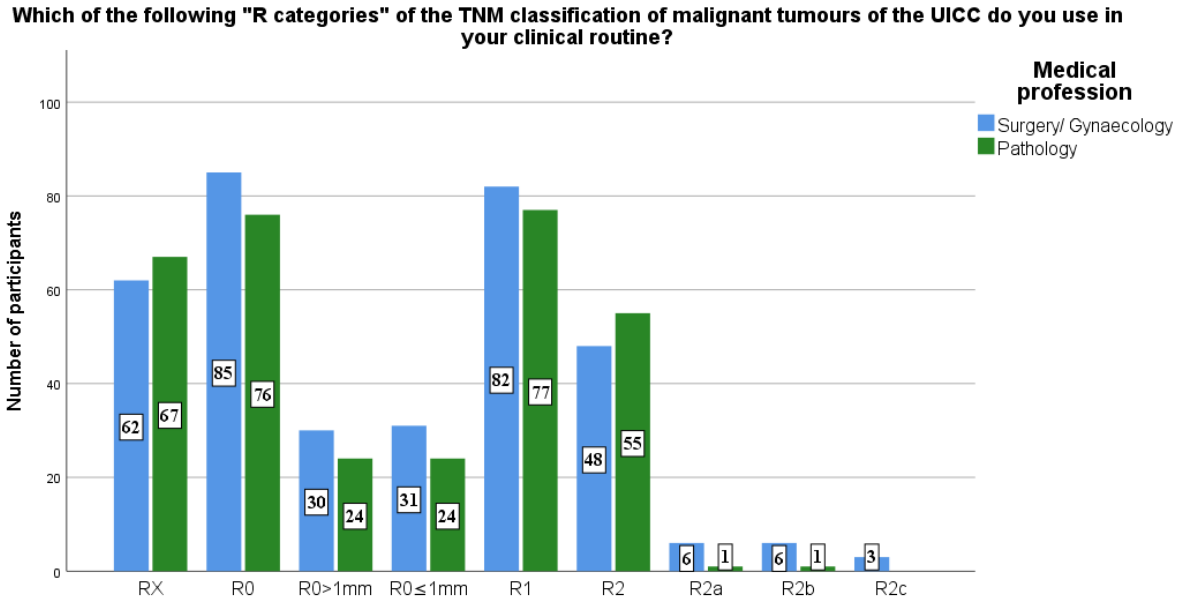

Figure 5: Usage of the "R categories" in clinical routine

Overall, 105 out of 161 participants (62,5%) consider the "R categories" of the TNM classification of the UICC as clearly defined. 104 of 165 participants (61,9%) consider the description of the "R categories" in practise satisfactory. The answers of S/G and P are depicted in Figure 6. As can be seen, 60/83 (72,29%) of the S/G consider the description of the "R categories" as clearly defined, while the same is only true for 45/78 (57,69%) of the P. Regarding the description of the "R categories", 64/85 (75,29%) of the S/G are satisfied with it in practise, contrary to 40/80 (50%) of the P, which is a significant difference (x^2=11,315, p<0,001).

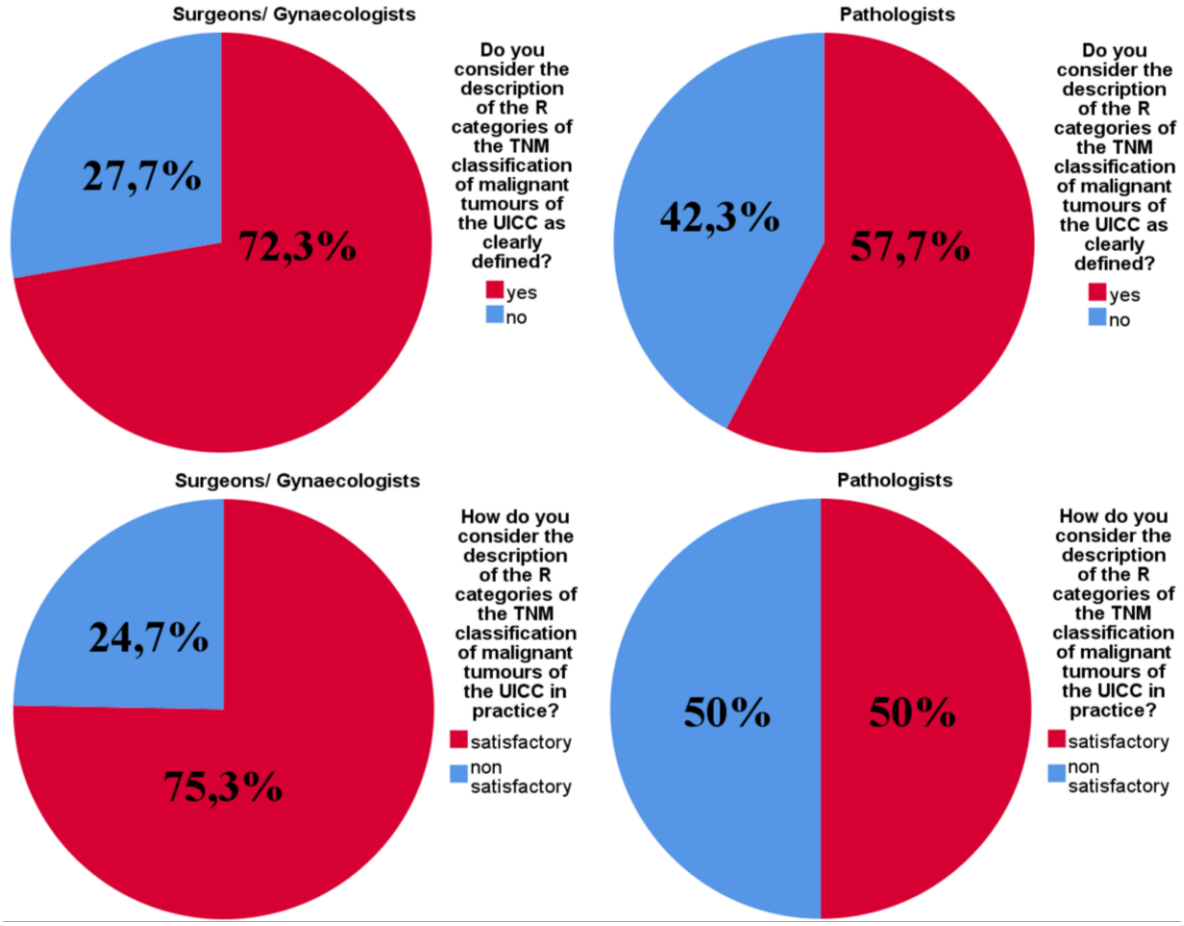

Figure 6: Answers from the medical professions regarding the exact definition and satisfaction of the "R categories"

The last question in this part addressed the issue of who should be responsible for the "R classification". Of 166 participants, 78 (46,4%) chose the pathologist, 6 (3,6%) the surgeon, and 82 (48,8%) selected the option that this decision should be reached together on an interdisciplinary basis in the tumour board, as depicted in Figure 7. Not a single participant chose the option of an oncologist or the treating physician who is most familiar with the patient's medical history. There was no significant difference (x^2=2,174, p=0,337) between S/G and P, as 44/86 (51,2%) of the S/G stated that the pathologist should be responsible for the "R classification", 38/86 (44,2%) thought that this decision should be made together on an interdisciplinary basis in the tumour board, and 4/86 (4,7%) wanted the surgeons to be responsible. Concerning the P, 44/80 (55%) wanted this decision to be made in the tumour board, 34/80 (42,5%) selected the pathologist themselves, and only 2/80 (2,5%), the surgeon.

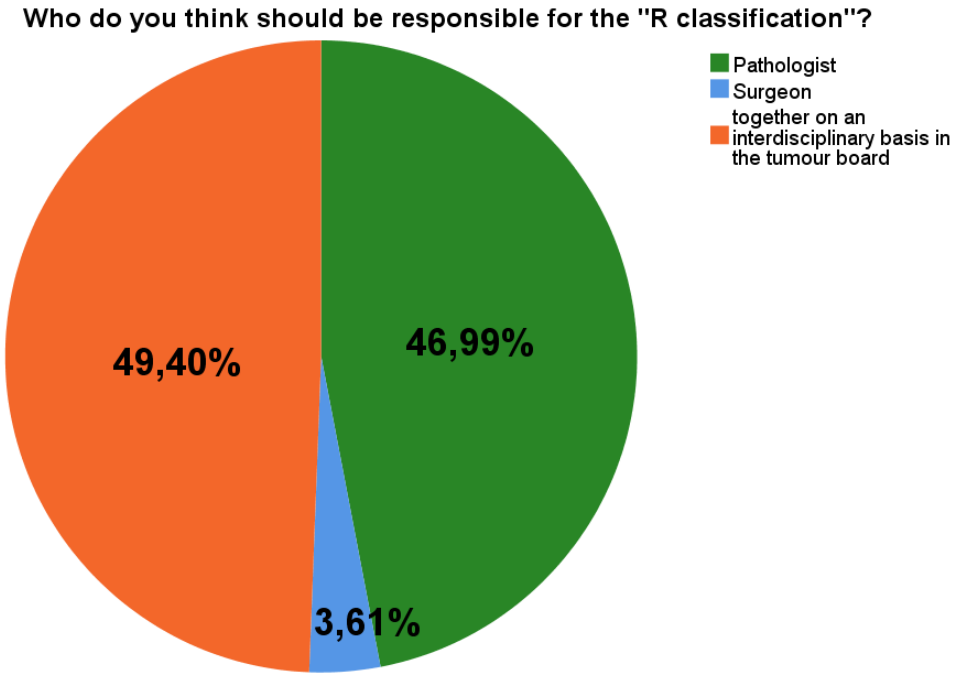

Figure 7: Selected options for who should be responsible for the "R classification"

3.3 General TNM Classification

In this part of the questionnaire, general questions concerning the "R classification" and its application were asked. To be more precise for the majority of questions, participants could select between assigning "RX", "R0", "R1", "R2", and "no R category can be assigned" to individual questions.

When asked if additional information is required for a "R0" category other than the assessment of the resection margin, 43/74 S/G (58,1%) answered "yes" and 31/74 (41,9%) chose "no". For the same question, 53/72 P (73,6%) opted for "yes" and 19/72 (26,4%) for "no". This is a significant difference (x^2=3,895, p=0,0484) and it is depicted in Figure 8.

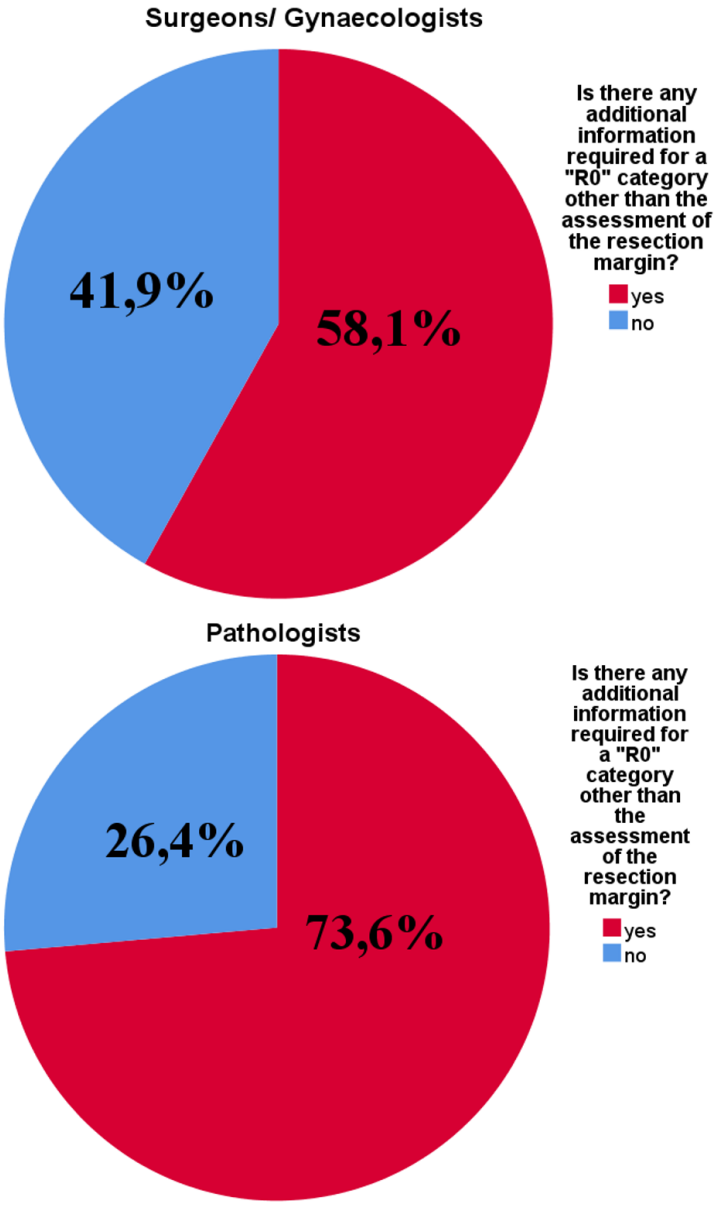

Figure 8: Answers from the medical professions regarding additional information for a "R0" category

Regarding the question of which “R category” could be assigned to a breast surgical specimen of an invasive breast carcinoma with a largely tumour-free resection margin and a positive, completely removed sentinel lymph node but no axillary dissection present, 68 of 75 S/G selected “R0” (90,7%), 5 “RX” (6,7%), and 2 (2,7%) chose that no “R category” could be assigned. On the other hand, 55 of 74 P chose “R0” (74,3%), 9 “RX” (12,2%), and 10 (13,5%) favoured that no “R category” could be assigned. The difference between S/G and P concerning the selected options is significant (x^2=7,844, p=0,0198). The answers are depicted in Figure 9.

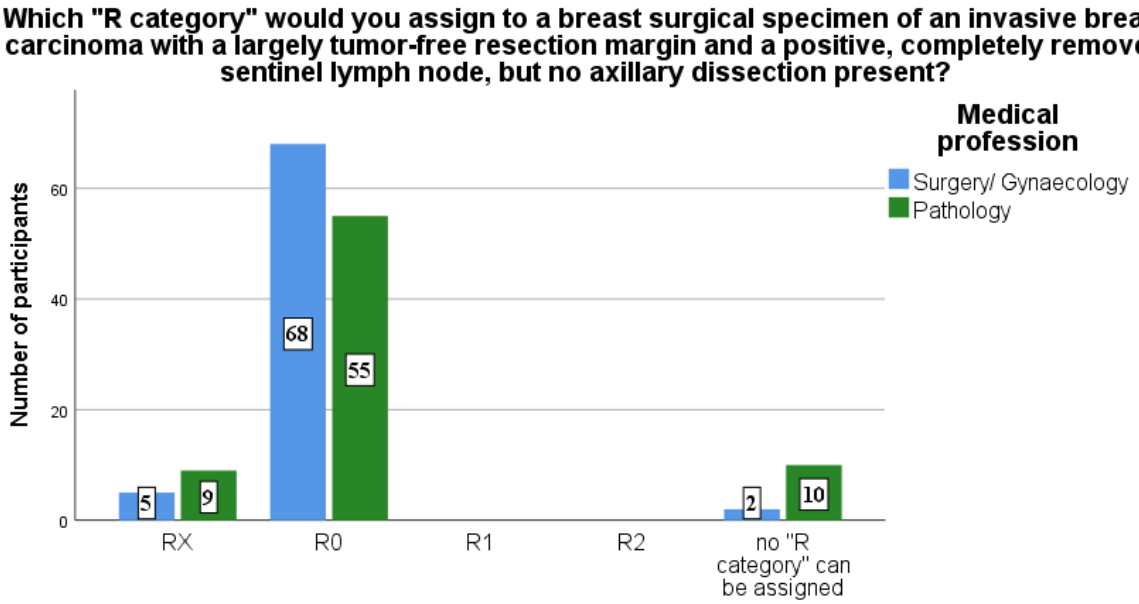

Figure 9: Chosen options concerning this question

When asked which “R category” should be given if the surgical specimen is sent in several parts, 35 of 75 S/G chose “RX” (46,7%), 19 “R0” (25,3%), and 21 (28%) answered that no “R category” could be assigned. Meanwhile, 50 of 75 P chose “RX” (66,7%), 6 “R0” (8%), 1 “R1” (1,3%), and 18 (24%) answered that no “R category” could be assigned. There is a significant difference (x^2=10,638, p=0,0139) between these medical professions and their answers regarding the categories, which is depicted in Figure 10.

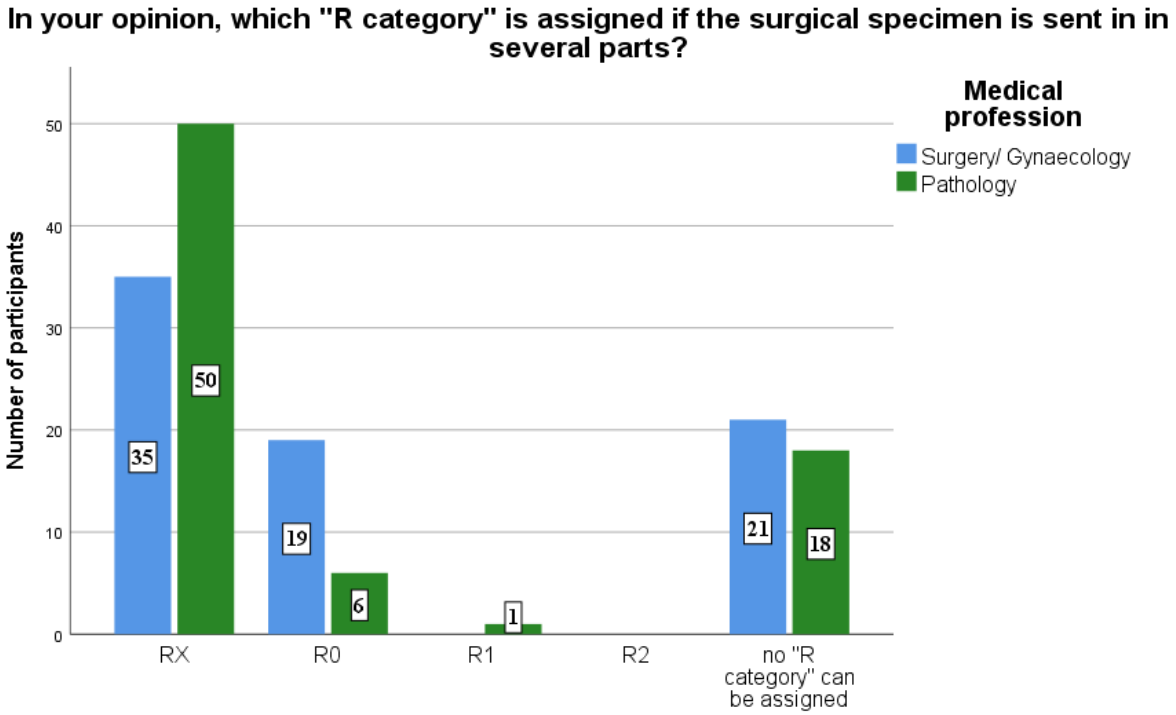

Figure 10: Answers for assigned "R category" if surgical specimens are sent in in several parts

Regarding the question of which “R category” should be assigned if the surgical specimen shows a surface with multiple tears and resection margins that are in some parts difficult to assess, 59 of 74 S/G chose “RX” (79,7%), 1 “R0” (1,4%), and 14 (18,9%) selected that no “R category” could be assigned. Similarly, 57 of 74 P chose “RX” (77%), 1 participant chose “R0” (1,4%), 1 participant chose “R1” (1,4%), and 15 (20,2%) answered that no “R category” could be assigned. The findings are not significant (x^2=1,069, p=0,785). They are depicted in Figure 11.

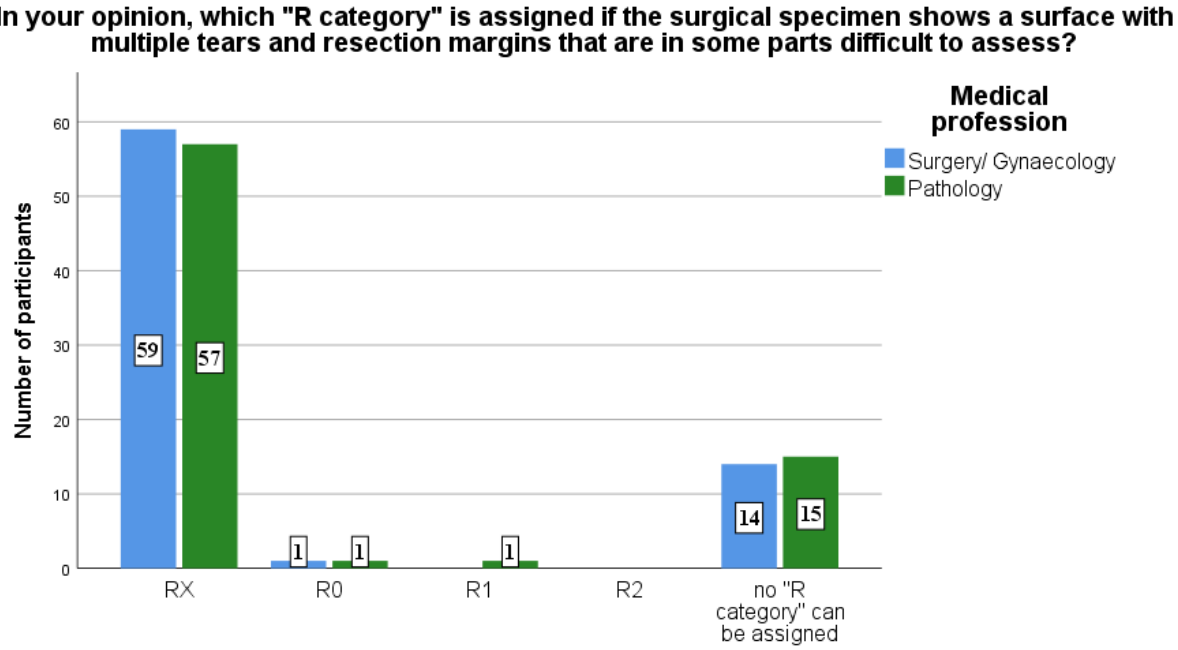

Figure 11: Answers for assigned "R category" if the surgical specimen shows a surface with multiple tears and resection margins that are difficult to assess

Concerning the question of which “R category” should be assigned if no tumour can be detected in a surgical specimen after neoadjuvant therapy, 45 of 74 S/G chose "R0" (60,8%), 3 “RX” (4,1%), and 26 (35,1%) felt that no “R category” could be assigned. P show similarities in their answers, given that 59 of 75 selected “R0” (78,7%), 1 “RX” (1,3%), and 15 (20%) chose that no “R category” could be assigned. The results are not significant (x^2=5,829, p=0,054). They are depicted in Figure 12.

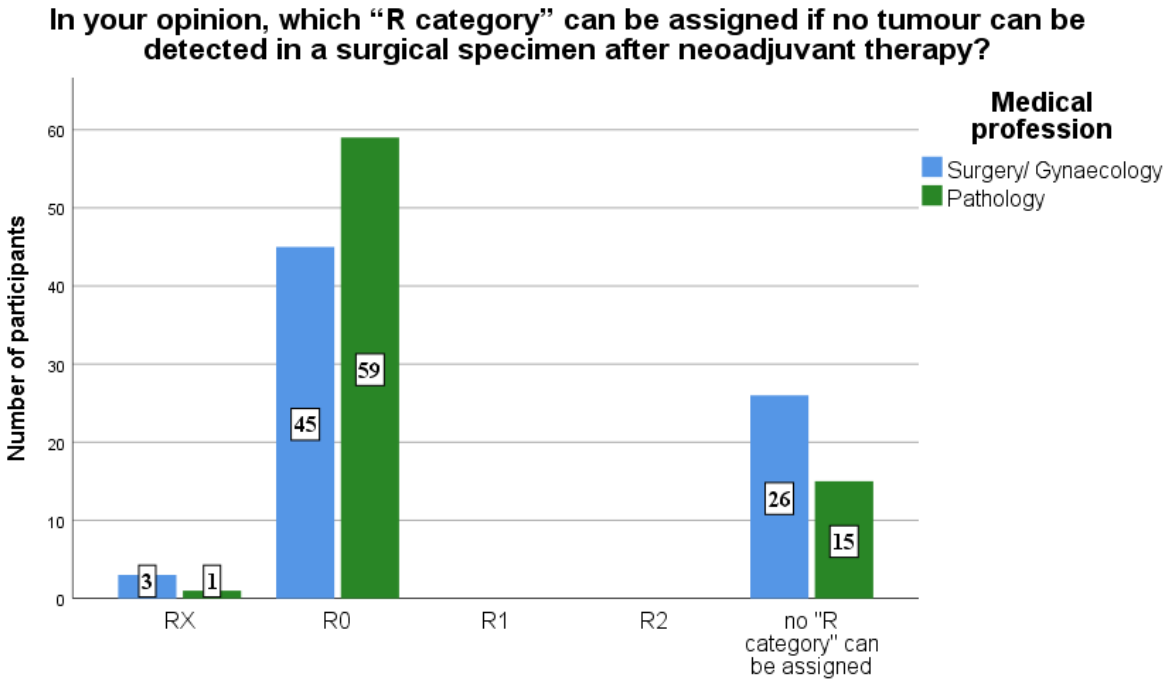

Figure 12: Opinions on which "R category" should be assigned if no tumour can be detected in a surgical specimen after neoadjuvant therapy

When asked which “R category” could be assigned if the scarred and now tumour-free area of the primary tumour is located at the edge of the resection in a surgical specimen after neoadjuvant therapy, 42 of 75 S/G selected “R0” (56%), 6 “RX” (8%), 10 “R1” (13,3%), 1 “R2” (1,3%), and 16 (21,3%) felt that no “R category” could be assigned. On the other hand, 51 of 75 P chose “R0” (68%), 11 “RX” (14,7%), and 13 (17,3%) decided that no “R category” could be assigned. With Pearson’s Chi Square Test (x^2=13,652, p<0,01) a significant difference in the selected options of these two professions could be detected. The answers are depicted in Figure 13.

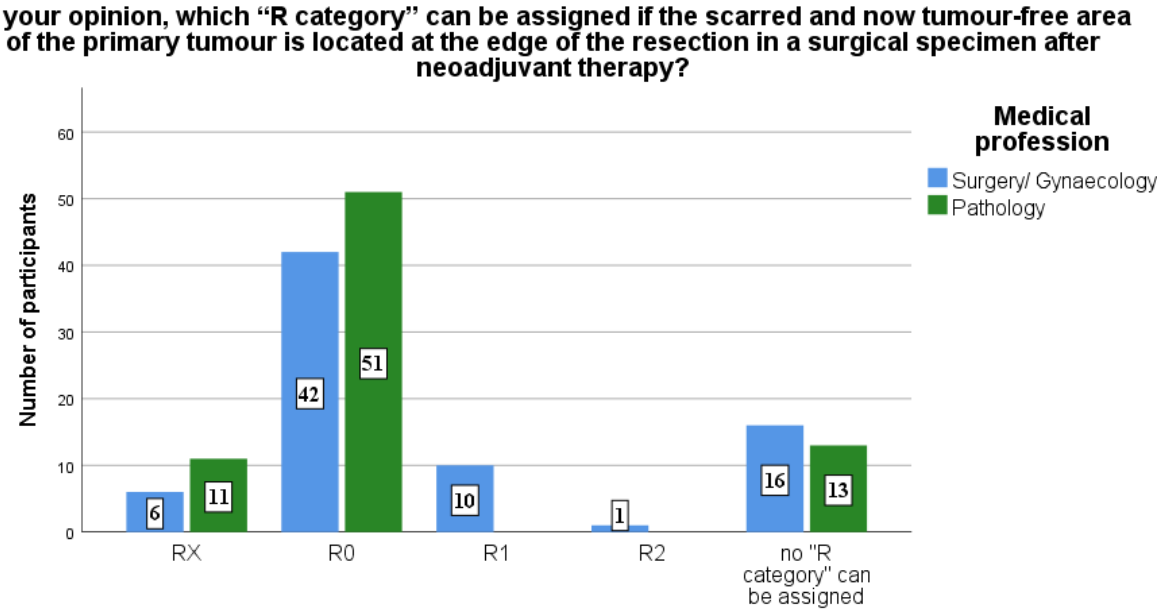

Figure 13: Chosen answers for this question

The last question in this part of the questionnaire examined which “R category” should be assigned if, in a surgical specimen after neoadjuvant therapy, in the mostly scarred area of the primary tumour, isolated residual tumour cell nests are distributed at a distance of approximately 5mm and more, the scarred tumour area extends directly to the resection margin, and the minimum distance of the nearest residual tumour cell nest is 2mm. For a better understanding, a graphic with a table of contents has been added to this question (Figure 14).

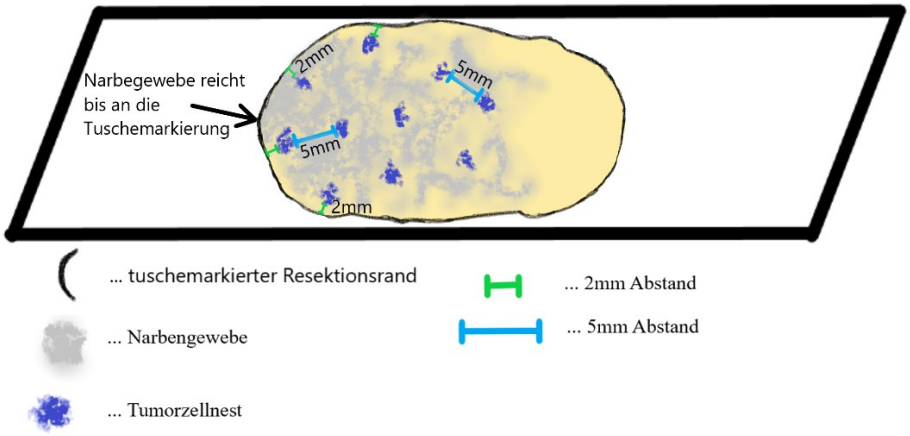

Figure 14: Graphic used in the part "General TNM Classification"

The findings suggest a significant difference (x^2=10,317, p=0,0354). Of 76 S/G, 43 selected “R0” (57,3%), 13 “RX” (17,3%), 11 “R1” (14,7%), 3 “R2” (4%) and 5 (6,7%) felt that no “R category” could be assigned. As for the P, 38 of 76 chose “R0” (50%), 21 “RX” (27,6%), 5 “R1” (6,6%), and 12 (15,8%) preferred that no “R category” could be assigned. The results are shown in Figure 15.

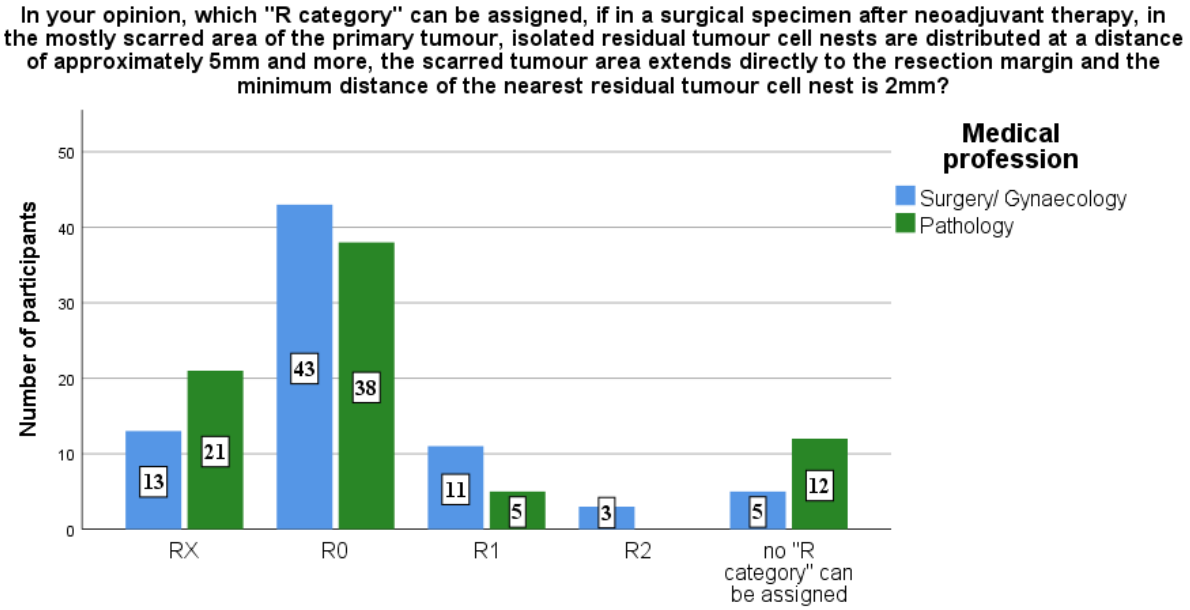

Figure 15: Chosen answers for this question

3.4 Specific Questions Regarding Breast Cancer Diagnosis

In the last part of the questionnaire, participants were asked to answer specific questions regarding the "R classification" in breast cancer diagnosis.

The first question was a multiple-choice one regarding the understanding of "R1" in breast surgery, and the participants' answers are depicted in Figure 16.

From a total of 73 S/G as well as 73 P, 62 S/G (84,9%) and 73 P (100%) selected the option that "R1" is equivalent to ink on tumour in an invasive carcinoma. Pearson's Chi Square Test shows that there is a significant difference (x^2=11,896, p<0,001) between these groups. In summary, 135 of 146 participants (92,5%) selected this option.

In contrast, 12 S/G (16,4%) and 7 P (9,6%) would understand "R1" as an invasive carcinoma fractions of a millimetre from the resection margin. This is not a significant difference between the medical profession and their chosen answers (x^2=1,513, p=0,219).

Another significant difference (x^2=6,527, p=0,0123) exists for the third option, where only 6 S/G (8,2%) and none of the P chose that "R1" means an invasive carcinoma less than 2mm from the resection margin.

22 S/G (30,1%) and 31 P (42,5%) stated that "R1" is equivalent to an invasive carcinoma which was removed over 2mm but with DCIS present at the resection margin. This is not a significant difference (x^2=2,399, p=0,121).

51 S/G (69,9%) and 56 P (76,7%) chose the option of ink on tumour in DCIS without an invasive carcinoma. There is no significant difference (x^2=0,875, p=0,35).

The last available option to take suggested that "R1" in breast surgery means DCIS without an invasive carcinoma less than 2mm from the resection margin and was chosen by 29 S/G (39,7%) as well as 14 P (19,2%). This implies another significant difference (x^2=7,417, p<0,01) in the opinions of these two professions.

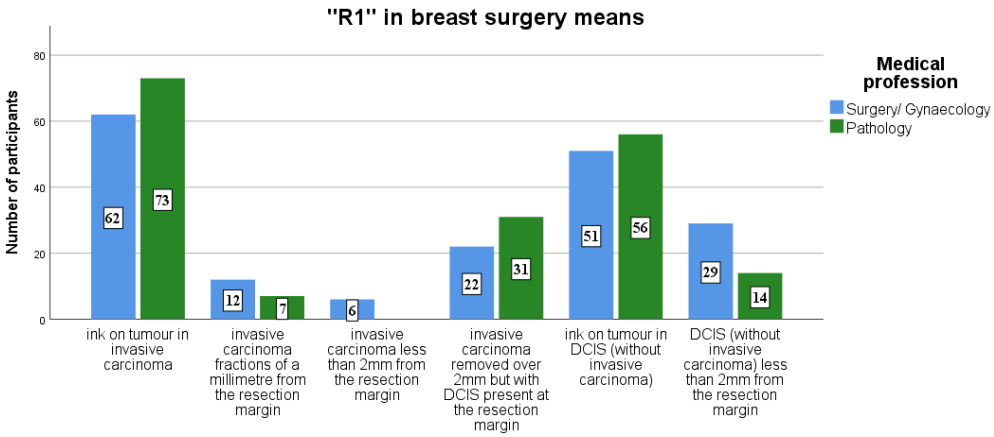

Figure 16: Multiple choice answers concerning the meaning of "R1" in breast surgery

The next question aimed to examine which “R category” could be assigned to a neoadjuvantly treated breast carcinoma with a disseminated growth pattern in the entire specimen, where the individual tumour cells do not reach the ink (“no ink on tumour”). For a better understanding, a graphic with a table of contents was added (Figure 17).

Figure 17: Graphic used in the part "Specific Questions Regarding Breast Cancer Diagnosis"

51 out of 73 S/G selected “R0” (69,9%), 9 “RX” (12,3%), 3 “R1” (4,1%), and 10 (13,7%) would not assign a “R category”.

Of the 73 P, 38 chose “R0” (52,1%), 20 “RX” (27,4%), 3 “R1” (4,1%), and 12 (16,4%) answered that no “R category” could be assigned. This resulted in no significant difference (x^2=6,253, p=0,1). The findings are depicted in Figure 18.

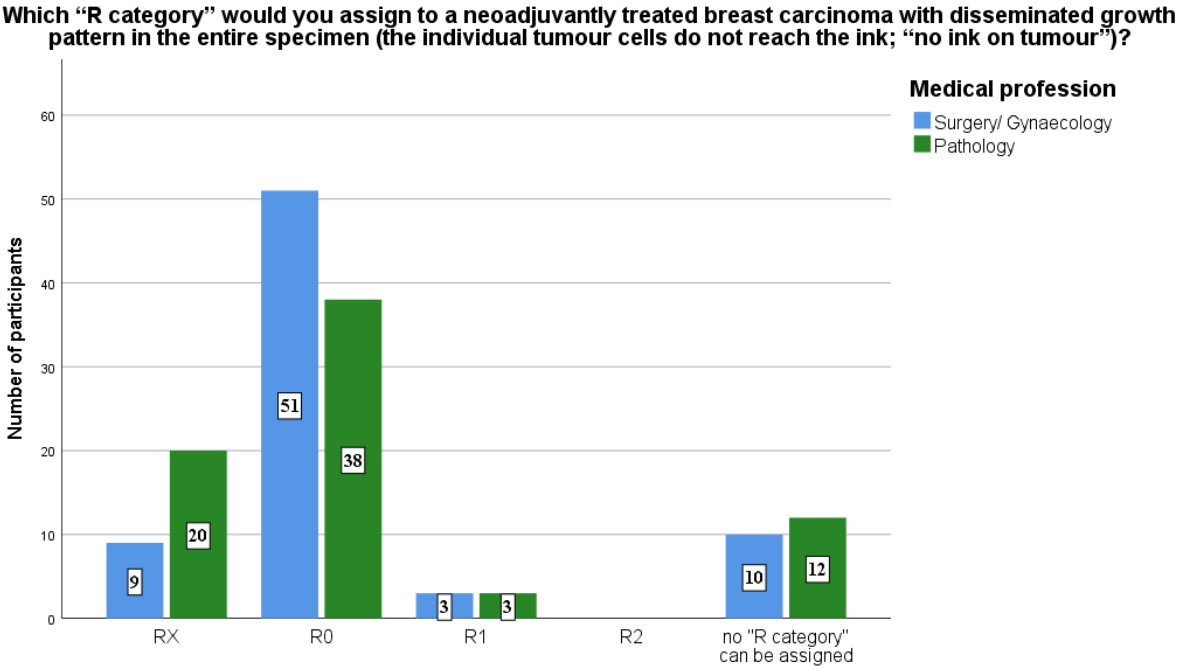

Figure 18: Choices from the question which "R category" in a neoadjuvantly treated breast carcinoma with disseminated growth pattern

There was a significant difference between S/G and P (x^2=27,043, p<0,001) regarding the question of which “R category” should be assigned to a surgically treated breast cancer specimen with a largely tumour-free resection margin and a clinically discovered and histologically verified but not removed liver metastasis. Of 73 S/G, 64 chose “R0” (87,7%), 1 “RX” (1,4%), 1 “R1” (1,4%), 3 “R2” (4,1%), and 4 (5,5%) would not give a “R category” in this case. In contrast, 36 of 72 P selected “R0” (50%), 1 “RX” (1,4%), 1 “R1” (1,4%), 25 “R2” (34,7%), and 9 (12,5%) chose not to assign a “R category”. These results are shown in Figure 19.

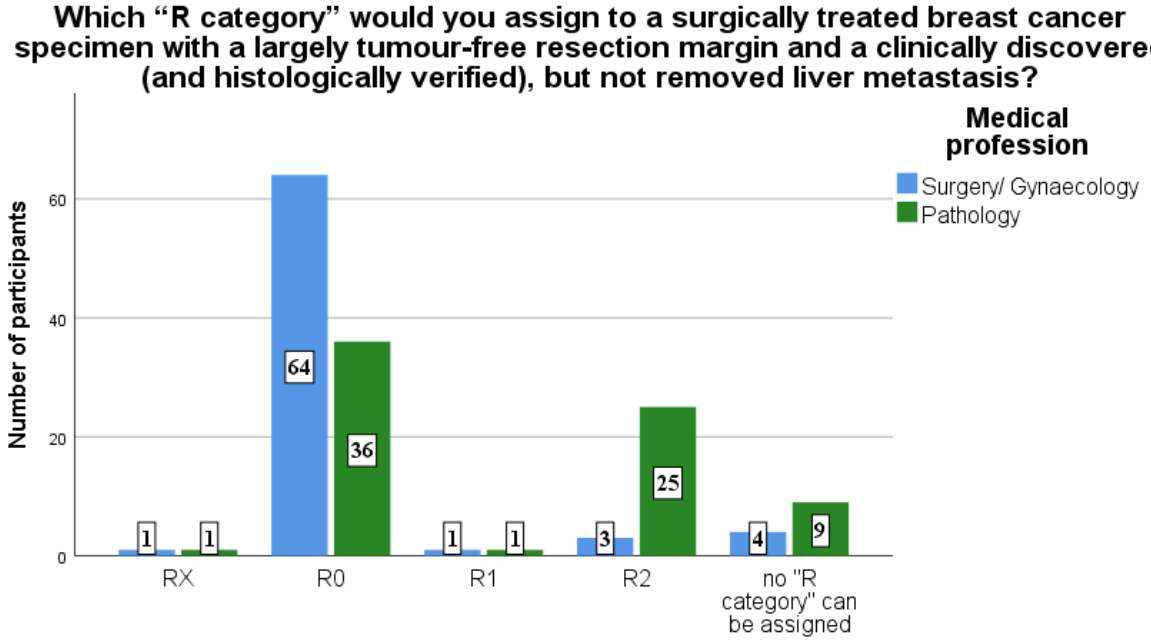

Figure 19: Answers from which "R category" should be assigned to a surgically treated breast cancer with a liver metastasis

Concerning the question of which “R category” should be assigned for a surgical breast cancer specimen with DCIS if the incision margin is tumour-free but suspicious calcifications were discovered in the postoperative mammography, the results of this significant difference (x^2=10,051, p= 0,0396) are shown below in Figure 20. 49 of 72 S/G (68,1%) chose “R0”, 7 “RX” (9,7%), 1 “R2” and 15 (20,8%) would not assign a “R category”. On the other hand, 37 of 73 P (50,7%) chose “R0”, 4 “RX” (5,5%), 1 “R1” (1,4%), and 31 (42,5%) selected that no “R category” could be assigned.

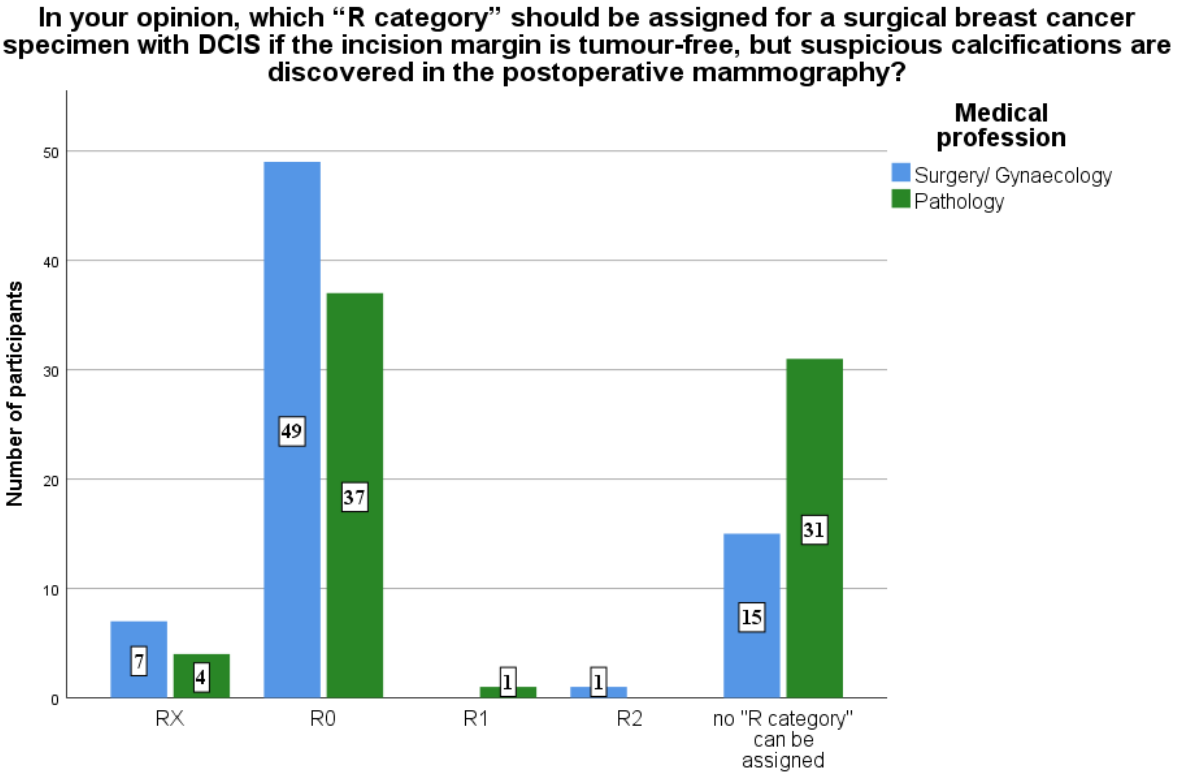

Figure 20: Answers of chosen "R category" for DCIS specimen with tumour-free margin, but suspicious calcifications in mammography

In Table 4, the results of the last question are represented. As can be seen, there are two significant differences, which are highlighted in bold. The first one addresses the question of whether breast cancer specimens with neoadjuvantly treated invasive carcinomas with narrow resection margins should be assessed by frozen section. As shown in Figure 21, 25 of 73 S/G (34,2%) and 11 of 73 P (15,1%) chose "yes" (x^2=7,226, p<0,01). The second one relates to the question of whether breast specimens with DCIS and narrow resection margins should be assessed by frozen section. 19 of 73 S/G (26%) and 8 of 73 P (11%) chose "yes" (x^2=5,498, p= 0,019), as shown in Figure 22.

		Surgeons/ Gynaecologists		**Pathologists**		**Total**	
		absolute	relative	absolute	relative	absolute	relative
Should breast specimens with invasive carcinomas and narrow resection margins be assessed by frozen section?	yes	32	43,8%	34	46,6%	66	45,2%
	no	41	56,2%	39	53,4%	80	54,8%
Should these narrow resection margins be marked by the surgeon?	yes	46	63%	53	72,6%	99	67,8%
	no	27	37%	20	27,4%	47	32,2%
Should breast specimens with neoadjuvantly treated invasive carcinomas with narrow resection margins be assessed by frozen section?* (p<0,01)	yes	25	34,2%	11	15,1%	36	24,7%
	no	48	65,8%	62	84,9%	110	75,3%
Should these narrow resection margins be marked by the surgeon?	yes	42	57,5%	49	67,1%	91	62,3%
	no	31	42,5%	24	32,9%	55	37,7%
Should breast specimens with DCIS and narrow resection margins be assessed by frozen section?* (p=0,019)	yes	19	26%	8	11%	27	18,5%
	no	54	74%	65	89%	119	81,5%
Should these narrow resection margins be marked by the surgeon?	yes	39	53,4%	45	61,6%	84	57,5%
	no	34	46,6%	28	38,4%	62	42,5%
Should the narrow resection margin of a DCIS in a surgical mammary specimen be marked intraoperatively by specimen radiography?	yes	42	57,5%	47	64,4%	89	61%
	no	31	42,5%	26	35,6%	57	39%

Table 4: Results from the question regarding the frozen section examination

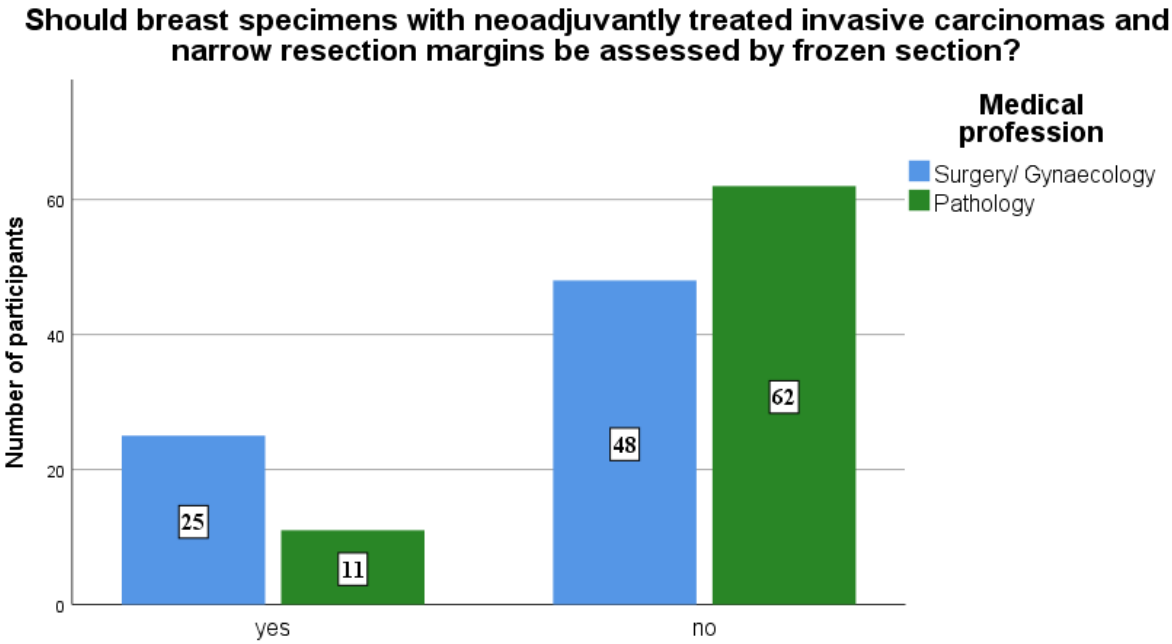

Figure 21: Answers from whether breast specimen with neoadjuvantly treated invasive carcinomas and narrow resection margins should be assessed intraoperatively

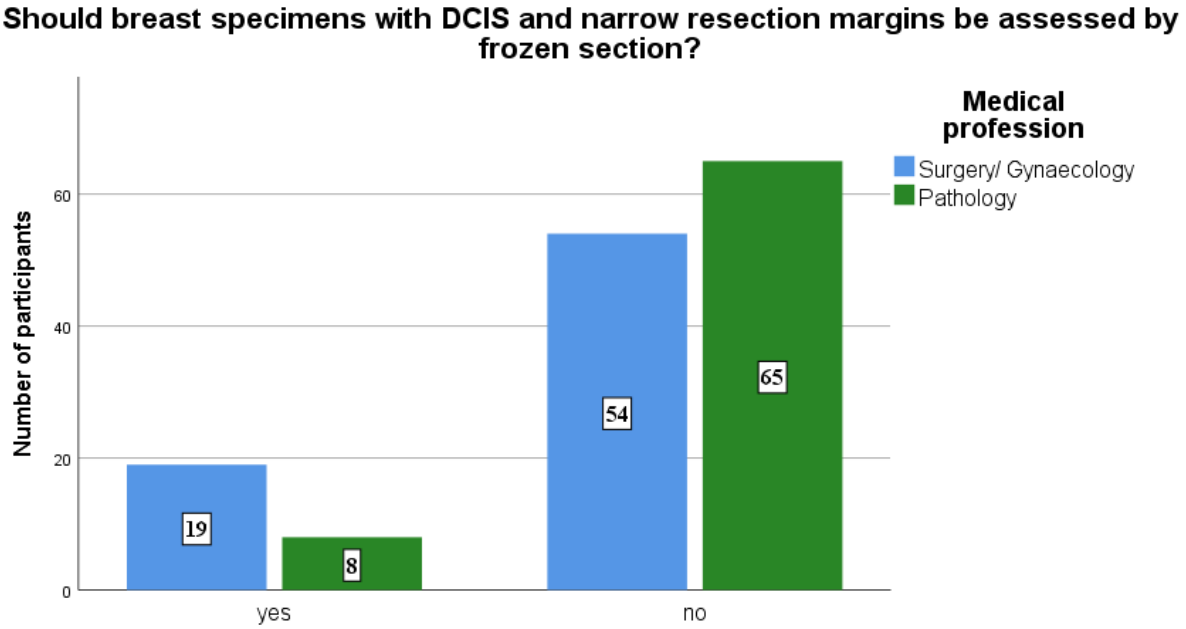

Figure 22: Answers from whether breast specimens with DCIS and narrow resection margins should be assessed intraoperatively

4 Discussion

The results suggest that there is a difference in the understanding of the "R classification" between surgeons/ gynaecologists (S/G) and pathologists (P). In the survey, 15 significant differences could be identified.

Overall, as seen in Table 2 (page 56) it can be said that the "TNM Classification of Malignant Tumours of the UICC" with a total of 154 participants (85,2% of the S/G and 98,8% of the P) is the most frequently used guideline, followed by the "Interdisciplinary S3 Guideline for Early Detection, Diagnosis, Therapy and Aftercare of Breast Cancer" with 135 participants (92% of the S/G and 67,5% of the P) and the "St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer" with 104 participants (75% of the S/G and 47,5% of the P).

Additionally, only one participant from each examined profession (S/G:1, P:1) has chosen the "International Guideline for Management of Breast Cancer of the International Society of Breast Cancer", which is a guideline fabricated to validate the answers of the participants. For example, if the majority of the participants would have chosen this option, their motivation should be questioned.

For our sample, the gathered data indicates two points. Firstly, guidelines published in German speaking countries, such as the S3 or St. Gallen guidelines, or in the European context, more precisely the UICC, are preferred over Anglo-American published guidelines. A similar finding to this interpretation has been made by Hoffman et al. (2016)[65(p.260)], who could show in their study that guidelines from the UICC, the S3, and the WHO are the most frequently used ones for the "R classification" of lung cancer. Secondly, almost all P stated that they use the UICC in their clinical work, while S/G prefer the S3. Additionally, S/G seem to work with several guidelines, as shown in Table 2 (page 56), and more explicitly in Table 5. This implies that there is a correlation between the use of guidelines and professional fields.

	Surgeons/ gynaecologists	**Pathologists**
UICC	85,2%	98,8%
S3	92%	67,5%
St. Gallen	75%	47,5%

Table 5: Percentages of the most used guidelines

Another interesting point is that generally both medical professions are most familiar with the exact definition of "R0" (97,6%), followed by "R1" (96,4%) and "R2" (77,1%). "RX" seems to be only the fourth-best-known category (55,2%). However, when asked which "R categories" are used in the clinical routine, "R0" (97,6%) and "R1" (97%) are the most frequent ones, but surprisingly, both medical professions use "RX" more often (78,2%) than "R2" (63,6%), as illustrated in Figures 4 and 5 (page 58). This finding is partially in contrast with Hoffmann et al. (2016) because his data[65(Abb.2 p.261)] suggest that "R0", "R1", and "R2" are better known than "RX" and that they are also more often used in the "R classification" of lung cancer.

Concerning the exact definition and satisfaction of the "R categories" as depicted in Figure 6 (page 59), the overall tendency was that 62,5% consider the categories as clearly defined and 61,9% are satisfied with the descriptions. However, there is a considerable difference between the two surveyed professions, which also resulted in a significant finding ($p<0,001$) for the question regarding the satisfaction of the "R categories" between S/G and P. 72,29% of the S/G consider the description of the "R categories" as clearly defined, and 75,29% are satisfied with them. In contrast to this, 57,69% of the P consider the description of the "R categories" as clearly defined, and only 50% are satisfied with them. It is possible that there is not only a difference between the medical professions but also that opinions are divided within P, given that only half of them (50%) are satisfied with the "R categories" as compared to S/G, where 75,29% are satisfied with them.

A further finding is that 91,7% of the participants stated that they use the "TNM Classification of Malignant Tumours of the UICC" in their clinical work. 62,3% of the participants believe that the "R classification" provides information about the residual tumour after therapy, which is less than expected when compared to the definition of the UICC, where it is stated that "the absence or presence of residual tumour after treatment is described by the symbol R"[1(p.10)]. Only 45,8% of the participants consider that the "R classification" provides information about the prognosis, although the UICC declares that the "R classification" is a "strong predictor of prognosis"[1(p.10), 2(p.15)].
Furthermore, 63,6% conclude that the "R classification" provides information about the resection margin of the primary tumour alone. While 77% of S/G chose that the "R classification" only provides information about the resection margin of the primary

tumour, only 48,8% of P opted for the same. Although nearly half of the P consider this to be accurate, this indicates that the opinions between these medical professions differ significantly ($p<0,001$). This interpretation is further supported by the finding that 12,6% of the S/G and 50,6% of the P are of the opinion that the "R classification" provides information about the inclusion of distant metastasis, which is also a significant difference ($p<0,001$) between the two medical professions. It also seems that there is not only a difference between the medical professions, but also within the medical profession of P, considering that their answers for both questions were equally divided (48,8% and 50,6%).
On this topic, the "TNM Classification of Malignant Tumours"[1] mentions that some employ the "R classification" only for the primary tumour and its locoregional extent, while others also include distant metastasis. It is recommended that the specific usage be indicated when used.[1(p.11)] The "TNM Supplement"[2] also indicates that the "R classification" is applied, especially in the USA, Canada, and the UK, only to the primary tumour and its locoregional extent, while others also include distant metastasis. Further, it is recommended, due to the prognostic relevance of the "R classification", that the distant metastasis be included[2(p.18)]. Hoffmann et al. (2016) discovered in their study[65(p.261)] that only half of the surveyed medical institutions include distant metastasis in the "R classification", while the other half only takes the locoregional extent into consideration. These findings can further be supplemented with the results gathered in the current study, as our study focused on medical professions rather than institutions as Hoffmann et al. (2016) did.

A further interesting finding emerged from the question of whether there is any additional information required for the "R0" category other than the assessment of the resection margin. Generally, 65,8% of the participants affirmed that additional information is needed to assign a "R0" category. However, there is a significant difference ($p=0,0484$) between the medical professions given that 58,1% of the S/G and 73,6% of the P stated that additional information is required to assign a "R0" category. This is depicted in Figure 8 (page 61).
To clarify this, in the "TNM Classification of Malignant Tumours" of the UICC, "R0" is defined as "no residual tumour"[1(p.10)]. The 5th edition of the "TNM Supplement" states that "R0 corresponds to clinical remission or resection for cure" and that it should be used in cases, where no residual tumour can be detected by any diagnostic means[2(p. 16)].

Furthermore, as pointed out by Wittekind et al. in "TNM residual tumour classification revisited"[29(p. 2513)], "R0" cannot be assumed in cases only because the resection margins are tumour-free, given that distant metastases could be present in the patient without the knowledge of the examining pathologist.

A possible reason for the different answers between the medical professions could be a missing clarification of the meaning of "R0". If mentioned at all in the guidelines, such as in the S3-Guideline[3], it is commonly described as "R0-Situation", "R0-Resektion" or "no ink on tumour". In the "St. Gallen Consensus guidelines"[15] as well as in the examined Anglo-American guidelines[5, 6, 7, 8, 9, 10, 11, 12, 13, 14], there is neither a reference to the "R classification" nor to its categories. According to the guidelines, no tumour cells at the resection margins, either invasive or DCIS cells, are defined as "no ink on tumour", and underline that these definitions are accepted, as depicted in the "2014 SSO-ASTRO Consensus Guideline for Breast-Conserving Surgery with Whole-Breast Irradiation in Stages I and II invasive breast cancer"[10]. A positive margin is defined as the presence of ink on either invasive or DCIS tumour cells, with a note that this would imply a potentially incomplete resection and a higher risk of ipsilateral tumour recurrence[10(p. 556)].

Regarding the understanding of the "R1" category, the participants were given a multiple-choice question with six possible answers, where they could choose what they think that "R1" in breast surgery means, as depicted in Figure 16 (page 68). For a better understanding, the answers are described separately.

The first option, that "R1" means ink on tumour in invasive carcinoma, has been the most chosen answer, as 92,5% of the participants, or more precisely, 84,9% of the S/G and 100% of the P, chose this. This suggests unity throughout the medical professions regarding this option. This is also displayed in the guidelines, as Moran et al. (2014)[10] define a negative margin as "no ink on invasive carcinoma or DCIS"[10(p.557)]. This definition is accepted in the "S3 Guideline"[3], the "St. Gallen Consensus Guideline"[15(p. 1546)] the "NCCN"[5(p. BINV-F 1)] and the "Consensus Guideline on Breast Cancer Lumpectomy Margins"[8(p. 1-3)] of the ASBrS.

The next option, "R1" means "invasive carcinoma fractions of a millimetre from the resection margin", has been chosen only by a few (16,4% of the S/G and 9,6% of the P). This is neither supported by the UICC[1] nor the AJCC[4], which both define "R1" as "microscopic residual tumour"[1(p. 11), 4(p. 29)]. The "TNM Supplement"[2] further specifies that

"R1" should only be applied if the tumour is transected; otherwise, "R0" has to be used[2(p. 18)]. The "S3-Guideline"[3] states that no re-resection is indicated in the case of a "R0 resection", even with close free margins[3(p. 93)] and for the assessment of the resection margin, for both invasive carcinoma as well as DCIS, it should be reported whether the tumour is directly present at the margin or not. If no tumour is present at the margin, the minimal distance has to be noted[3(p. 106)]. The "St. Gallen International Consensus Guidelines for primary therapy of early breast cancer 2019"[15] explains that wider margins as "no ink on tumour" are no longer recommended except for inflammatory breast cancer[15(p. 1546)]. The "NCCN Guidelines"[5] recommend as a margin status for invasive breast cancer "no ink on tumour"[5(pp. BINV-F 1-2)] and refer to the 2014 "SSO/ASTRO Margins Guideline for Stage I/II invasive cancers"[10], where it is further described that wider margin widths do not significantly lower the risk of ipsilateral tumour recurrence[10(p. 557)].

Regarding the third option, even fewer participants (8,2% of the S/G and none of the P) chose that "R1" in breast surgery means that invasive carcinoma can be found less than 2mm from the resection margin, which has been a significant finding (p=0,0123). Since only a few participants chose this option, the significance of this finding is questionable. As mentioned in the previous paragraph, the UICC[1, 2], AJCC[4], and the examined guidelines[3, 5, 8, 10, 15] also disagree with this opinion.

The following option, if "R1" means that an invasive carcinoma has been removed over 2mm but with DCIS present at the resection margin, was chosen by 30,1% of the S/G and 42,5% of the P. If tumour cells are present at the resection margin, both the definitions of the UICC[1] and the AJCC[4] agree with this option because the requirement of a "R1 microscopic residual tumour" is fulfilled. The "ink on tumour" standard, which is used in the examined guidelines[3, 5, 8, 10, 15], is also in accordance with these participants' opinions. Furthermore, in the "TNM Supplement"[2(p. 17)], it is stated that the presence of in situ carcinoma at the resection margin should additionally be noted as "R1(is)".

The next option, "R1" meaning ink on tumour in a sole DCIS tumour, has been chosen by 69,9% of the S/G and 42,5% of the P. This is in accordance with the definitions of the UICC[1, 2], and the AJCC[4], as well as the other examined guidelines[3, 5, 8, 11, 15], which use the "ink on tumour" standard.

Finally, the option that "R1" in breast surgery means DCIS without an invasive carcinoma less than 2mm from the resection margin has been chosen by 39,7% of the S/G and 19,2% of the P, which has been a significant difference (p<0,01). A possible explanation for this

finding could be that in the guidelines[3, 5, 8, 11, 15], it is stated that a reexcision should be performed if tumour cells are closer than 2mm to the resection margin. The definition of "R1", according to the UICC[1, 2] and AJCC[4], is "microscopic residual tumour", which would not be the case here. However, some participants may have chosen this option because the therapeutic consequences would be the same as with a "R1" classification.

Another finding is that the majority of participants (49,4%) seem to prefer to take the decision of which "R category" should be assigned on an interdisciplinary basis in the tumour board, as depicted in Figure 7 (page 60). It has to be pointed out that the second most chosen option has been the pathologist with 46,99%; therefore, a clear preference for this study could not be made between these options. Interestingly, only 3,61% wanted the responsibility in the hands of the surgeon, with 4 S/G and 2 P opting for this. Furthermore, none of the participants chose the oncologist or the treating physician who is most familiar with the patient's medical history. As for the last option, this is in contrast to the statement of the 5th edition of the "TNM Supplement", where it is written that a designated individual physician who has access to the most complete data should be responsible for TNM coding and, therefore, for the "R classification"[2(p. 12)]. This recommendation is further endorsed by Wittekind et al.[29(p. 2513)]. In this article, it is elaborated that the person may be a surgeon, oncologist, radiation oncologist, tumour registrar, or pathologist. Furthermore, it is stated that in several institutions in Germany, the "R classification" is assigned by a pathologist accompanied by data from the surgeon about the patient. Without the clinical information of the patient, the pathologist can only assess the resection margin and whether the locoregional tumour has been removed successfully or not.

In this section, the findings that emerged from specific examples are discussed. Participants were asked to assign a "R category" to 13 specific examples that were taken either directly or slightly adapted from the used guidelines. In the following, the results are discussed in detail.

For the question of which "R category" could be assigned to a breast surgical specimen on an invasive breast carcinoma with a largely tumour-free resection margin and a positive, completely removed sentinel lymph node but without an axillary dissection, the majority of the S/G (90,7%) chose "R0", 6,7% chose "RX", and 2,7% did not want to assign a "R

category". In contrast, 74,3% of the P chose "R0", 13,5% opted to not assign a "R category" and 12,2% would assign a "RX". This is a significant difference (p=0,0198), which is hardly surprising given that in the examined guidelines the role of an axillary dissection is disputed, especially if the SLN is positive. The 5th Supplement of the UICC[2] states that the "R classification" is not affected by the SLN unless it is transected. Due to the prognostic significance of a "R0" to a "R1" or "R2" category, a "R0(un)", as proposed in the Supplement[2(p. 19)] could be administered to facilitate the categorisation of such ambiguous cases. "R0(un)" is suggested in cases involving the assessment of lung carcinoma. For example, this category could be assigned in cases with no macroscopic or microscopic residual disease but where nodal assessment has been based on fewer than the ordinarily required number of nodes or stations in a lymphadenectomy specimen or in lung cancer specimens when the highest mediastinal lymph node is positive. This seems crucial given "General Rule No. 4", which declares that if there is doubt concerning the correct TNM categories, the less advanced one should be administered[2(p. 5)].

The question of which "R category" should be assigned if the surgical specimen is sent in in several parts resulted in a significant difference (p=0,0139). 46,7% of the S/G and 66,7% of the P chose "RX", which is striking insofar as the 5th Supplement of the UICC[2] clearly declares that a precise assessment of the resection line cannot be made if the tumour is removed in two or more parts, thus "RX" should be administered. In contrast, the answers to the question of which "R category" should be assigned if the surgical specimen shows a surface with multiple tears and resection margins that are in some parts difficult to assess align with the recommendations of the 5th Supplement of the UICC regarding "RX" [2(p. 19)]. 79,9% of the S/G and 77% of the P chose "RX". Interestingly, the second most chosen answer for both questions has been the option that no "R category" can be assigned; in the first question, 39 participants out of 150 (26%) and in the second question 39 participants out of 148 (26,4%) chose this option. This suggests that there is some hesitation concerning the assignment of the "RX" category.

A further finding emerged from the questions regarding the "R classification" after neoadjuvant treatment. For the first question, which "R category" should be assigned if no tumour can be detected in a surgical specimen after neoadjuvant therapy, 60,8% of the S/G and 78,7% of the P answered with "R0".

Moreover, concerning the question of which "R category" could be assigned if the scarred and now tumour-free area of a primary tumour is located at the edge of the resection margin, a significant difference ($p<0,01$) emerged. Here, 56% of the S/G and 68% of the P chose "R0", which is slightly less than in the question before. "RX" was chosen by 8% of the S/G and 14,7% of the P, while 21,3% of the S/G and 17,3% of the P felt that no "R category" could be assigned. Interestingly, 13,3% of the S/G opted for "R1" and a single S/G (1,3%) for "R2".

For both questions, the suggestion in the 5th edition of the UICC TNM Supplement[2] is "R0". It seems that the answers to the first question are in accordance with the literature, given that it is stated there that in the "R classification", only viable tumour at the resection margin is considered, while scars, fibrotic tissue or nodules, granulation tissue or mucin lakes do not qualify as "R1" [2(p. 19)]. However, the participants' answers in the second question seem to deviate more from the recommendations found in the literature than in the first question.

Regarding the question of which "R category" could be assigned if in a surgical specimen after neoadjuvant therapy, in the mostly scarred area of the primary tumour, isolated residual tumour cell nests are distributed at a distance of approximately 5mm and more, the scarred tumour area extends directly to the resection margin, and the minimum distance of the nearest residual tumour cell nest is 2mm, a significant finding ($p=0,0354$) emerged. The majority, 57,3% of the S/G and 50% of the P, favoured "R0". Interestingly, 17,3% of the S/G and 27,6% of the P would assign a "RX". 6,7% of the S/G and 15,8% of the P would not assign a "R category". 14,7% of the S/G as well as 6,6% of the P preferred a "R1", and 4% of the S/G would give a "R2" category.

Furthermore, the answers concerning which "R category should be assigned to a neoadjuvantly treated breast carcinoma with a disseminated growth pattern in the entire specimen, but the individual tumour cells just do not reach the ink and would therefore be classified as "no ink on tumour" were quite similar. In this question, the majority of the participants, 69,9% of the S/G and 52,1% of the P, opted for "R0". 12,3% of the S/G and, interestingly, 27,4% of the P chose "RX".

According to the official recommendations, "R0" appears to be the preferable choice for those questions, especially in consideration of "General Rule No. 4" of the 5th edition from the TNM Supplement[2(p. 5)], which declares that if there is doubt concerning the correct

TNM categories, the less advanced one should be administered[2(p. 5)]. A possible explanation for the findings of the first question could be that in this example, the isolated tumour cell nests are distributed at a distance of approximately 5mm, and there are tumour cell nests at a minimum distance of 2mm to the resection margin, which could mean that there could also be additional tumour cell nests left in the patient. The same explanation might apply to the second question, regarding the disseminated growth pattern in the entire specimen. Considering that there is no proof of additional residual tumour in the patient and "General Rule No. 4"[2(p. 5)], a "R1" or "R2" classification is less likely. Whether the assignment of a "R category" should be waived in such cases or "RX" should be applied could be discussed. Alternatively, a "R0(un)" as proposed in the 5th Supplement of the UICC[2(p. 19)] could be designated in these cases. As mentioned before, this category was initially proposed in ambiguous cases of lung carcinoma where the nodal assessment was based on less than the ordinarily expected number of nodes or stations in a lymphadenectomy specimen or in lung cancer specimens when the highest mediastinal lymph node is positive. However, this category could also be a possibility for the assessment of ambiguous cases of breast carcinoma.

A significant yet alarming finding ($p<0,001$) were the answers to the question of which "R category" should be assigned to a surgically treated breast cancer specimen with a largely tumour-free resection margin and a clinically discovered (and histologically verified) but not removed liver metastasis. Although the question was similar to an example in the 5th edition of the TNM Supplement, where it is stated that if at a colectomy a histologically confirmed liver metastasis is found, it would be considered as "R2(liver)"[2(p. 16)], only 4,1% of the S/G and 34,7% of the P selected "R2". The vast majority of the participants, 87,7% of the S/G and 50% of the P, chose "R0". A possible explanation for this surprising result may be that even the literature contains contradictory statements regarding this topic. For example, in the 8th edition of the "TNM Classification of Malignant Tumours" of the UICC, it is stated that it should be indicated whether the "R classification" is applied to the primary tumour and its locoregional extent alone or more broadly, including distant metastasis[1(p. 11)]. In the 5th edition of the TNM Supplement, however, it is highlighted that, in regard to prognostic relevance, distant metastasis should be included in the "R classification"[2(p. 18)]. In contrast to this, in the 8th edition of the "AJCC Cancer Staging Manual", in the description of the "R2" category, it is stated that "R2" is the macroscopic

residual tumour at the primary cancer site or regional nodal sites, with a note that this category should not be used to indicate metastatic disease identified but not resected at surgery[4(p. 29)].

Moreover, the answers for the question of which "R category" should be assigned for a surgical breast cancer specimen with DCIS if the incision margin is tumour-free but suspicious calcifications are discovered in the postoperative mammography are divided, which resulted in a significant difference (p=0,0396) between the two examined professions. The majority of the participants, 68,1% of the S/G and 50,7% of the P, opted for "R0". Yet, the second most chosen answer was "no R category can be assigned", with 20,8% of the S/G and 42,5% of the P. A possible explanation for this result might be that there is no recommendation in the literature for which "R classification" should be assigned in these cases. However, in the "S3 guideline" [3(p. 108)] as well as in the "ASTRO guidelines"[10, 11] a reexcision is recommended in cases of DCIS with an EIC where microcalcifications are present in the postoperative mammography.

Finally, two more significant findings among S/G and P emerged when asked about their opinions regarding the frozen section procedure. Firstly, a significant difference (p<0,01) exists as to whether the resection margins of neoadjuvantly treated invasive carcinomas should be assessed by frozen section. While 34,2% of the S/G answered "yes", only 15,1% of the P opted for the same. In total, 24,7% of the participants were in favour of this. Secondly, the question of whether breast specimens with DCIS and narrow resection margins should be assessed by frozen section resulted in a significant difference (p=0,019). 26% of S/G and 11% of P chose "yes", and in total, 18,5% of the participants wanted an assessment by frozen section. In addition, when questioned whether invasive breast carcinomas with narrow resection margins should be assessed by frozen section, 43,8% of S/G and 46,6% of P chose "yes", in total 45,2% of the participants; while this is not a significant finding, it underlines those opinions regarding the frozen section procedure are divided even in the professional groups.
Interestingly, the recommendations in the literature endorse frozen section procedures[3(p. 107)] due to better reoperation and reexcision rates[66]. Yet, it is not clearly defined in which cases this technique should be used, which might explain the above divided-results.

4.1 Limitations

Given that the answer rate for the intended examined professions varied considerably and therefore sample sizes ranged from small to large, only data collected from the S/G and P was used to draw results. For this reason, some differences between the medical professions could not be discussed, specifically between radiation oncologists/ radiation therapists, oncologists, and radiologists, because the sample was too small to be representative of the population.

Moreover, a response rate could not be calculated, because the surveys were sent to medical societies and not to medical practitioners themselves. If a society agreed to distribute the survey, they sent it directly to their members. Due to the fact that practitioners might be part of not only one but several medical societies, there might be overlaps.

Finally, the "TNM Supplement" was not included in the question regarding which guidelines or classifications are used by the participants. Considering that the recommendations for the inclusion of distant metastasis vary between the "TNM Classification of Malignant Tumours"[1] and the 5th edition of the "TNM Supplement"[2], this might make a difference.

5 Conclusion and Outlook

We hypothesised that there are different understandings between the various medical professions regarding the "Residual Tumour Classification" and focused specifically on breast cancer. In this study, we reviewed numerous guidelines[3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15] as well as the "TNM Classification of Malignant Tumours"[1], the "TNM Supplement"[2] of the UICC and the "AJCC Cancer Staging Manual"[4] regarding their interpretation of the "R classification" and created an anonymised questionnaire to gather the opinions of the "R classification" in various medical professions dealing with breast cancer.

The study could show that there exist considerable differences regarding the interpretation of the "R classification" among the examined medical professions as well as within the same medical profession. Further research is needed to find and understand where these differences come from and if they have an impact on the choice of treatment. Future studies with a focus on the use of guidelines and the interpretation of the "R classification" might reveal a correlation. In addition, further research including other medical professions with larger sample sizes could be advantageous.

Moreover, the study indicated that "RX" is used more often than its exact definition is known. This is concerning insofar as it might affect treatment, and further research in this area is needed to determine its origins.

A further point highlighted by the study is the problem arising from the use of the "R classification" for the assessment of the resection margin. Its use to determine the resection margins, for example, labelled as "R0-resection" or "R1-resection"[3], is insofar inadequate because the pathologist can only assess the resection margin and has no knowledge about the presence or absence of distant metastasis. As pointed out in the literature section, the latter needs to be considered when assigning a "R category". Regarding the reviewed literature as well as the results of the study, it can be recommended to emphasise the use of an existing resection margin classification such as the "Margin status following tumor resection"[4(p. 30)] of the AJCC. Alternatively, a new "resection margin classification" could be implemented, which would be comparable to the "R classification" but limited to the pathological viewpoint of the resection margin.

Lastly, the questionnaire showed that the majority of the participants (82 out of 166) would prefer to assess the “R classification” together on an interdisciplinary basis in the tumour board. This could be implemented, especially if the pathologist is only responsible for the assessment of the resection margin, as suggested above. Another possible alternative would be that the treating physician, who knows the patient’s complete medical history, is responsible for the ”R classification”, as suggested by Wittekind et al.[29]. Both options ensure that this decision is taken in consideration of the full patient’s data, which contributes to its prognostic relevance.

6 Bibliography

1. Brierley JD, Gospodarowicz MK, Wittekind C editors. TNM Classification of MALIGNANT TUMOURS. 8th ed. Oxford, Hoboken: Wiley Blackwell; 2017.
2. Wittekind C, Brierley J, Lee A, Eycken Ev editors. TNM Supplement. 5th ed. Oxford: Wiley & Sons Ltd; 2019.
3. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.3, 2020, AWMF Registernummer: 032-045OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/ (abgerufen am: 21.11.2020)
4. Amin MB, Edge SB, Brookland RK, Jessup JM, Greene Fl, Brierley JD, et al. editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
5. National Comprehensive Cancer Network (NCCN). Breast Cancer (Version 1.2021). [Accessed 2021 January 21]. Available from (with login): https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
6. American Society of Breast Surgeons. *Performance and Practice Guidelines for Breast-Conserving Surgery/Partial Mastectomy* (Version February 22, 2015.) Available from: https://www.breastsurgeons.org/resources/statements. [Accessed 5.2.2021.]
7. American Society of Breast Surgeons. *Performance and Practice Guidelines for Mastectomy* (Version November 25, 2014.) Available from: https://www.breastsurgeons.org/resources/statements. [Accessed 5.2.2021.]
8. American Society of Breast Surgeons. *Consensus Guideline on Breast Cancer Lumpectomy Margins* (Version December 20, 2017). Available from: https://www.breastsurgeons.org/resources/statements. [Accessed 5.2.2021.]
9. American Society of Breast Surgeons. *Performance and Practice Guidelines for Axillary Lymph Node Dissection in Breast Cancer Patients* (Version November 25, 2014). Available from: https://www.breastsurgeons.org/resources/statements. [Accessed 5.2.2021.]
10. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast

Irradiation in Stages I and II Invasive Breast Cancer. Int J Radiat Oncol Biol Phys. 2014;88:553-564.

11. Morrow M, VanZee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. Pract Radiat Oncol. 2016;6:287-295.
12. College of American Pathologists. *Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of the Breast* (Version: Breast Invasive Resection 4.4.0.0 February 2020). Available from: https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates. [Accessed January 25, 2021].
13. College of American Pathologists. *Protocol for the Examination of Resection Specimens From Patients With Ductal Carcinoma In Situ (DCIS) of the Breast* (Version: Breast DCIS Resection 4.3.0.2 February 2020). Available from: https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates. [Accessed January 25, 2021].
14. American Society of Breast Surgeons. *Consensus Guideline on the Management of the Axilla in Patients With Invasive/In-Situ Breast Cancer* (Version September 24, 2019). Available from: https://www.breastsurgeons.org/resources/statements. [Accessed 5.2.2021.]
15. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Annals of Oncology. 2019;30:1541-1557.
16. Spiessl B, Scheibe O, Wagner G. TNM Klassifikation der malignen Tumoren. 3rd ed. Berlin: Springer-Verlag Berlin Heidelberg New York; 1979.
17. International, Union, against, Cancer. TNM Klassifizierung der malignen Tumoren und Allgemeine Regeln zur Anwendung des TNM-Systems. 2nd ed. Berlin: Springer-Verlag Berlin Heidelberg GmbH; 1976.
18. Hermanek P, Sobin LH editors. TNM Classification of Malignant Tumours. 4th ed. Geneva: Springer Verlag Berlin Heidelberg New York London Paris Tokyo; 1987.

19. Beahrs OH, Henson DE, Hutter RVP, Myers MH editors. Manual for staging of Cancer. 3rd ed. Philadelphia: J. B. Lippincott Company; 1988.
20. Harmer MH, Copeland MM, Costachel O, Gentil F. Die Klassifizierung der malignen Tumoren nach dem TNM System. Berlin: Springer-Verlag Berlin Heidelberg New York; 1970.
21. Hermanek P, Henson DE, Hutter RVP, Sobin LH editors. TNM Supplement. Berlin: Springer-Verlag Berlin Heidelberg; 1993.
22. Sobin LH, Wittekind C editors. TNM Classification of Malignant Tumours. 5th ed. New York: Wiley-Liss; 1997.
23. Wittekind C, Henson DE, Hutter RVP, Sobin LH editors. TNM Supplement. 2nd ed. New York: Wiley-Liss; 2001.
24. Veronesi U, Farante G, Galimberti V, Greco M, Luini A, Sacchini V, et al. Evaluation of resection margins after breast conservative surgery with monoclonal antibodies. Eur Surg Oncol. 1991;17:338-341.
25. Schlimok G, Funke I, Pantel K, Strobel F, Lindemann F, Witte J, et al. Micrometastatic Tumour Cells in Bone Marrow of Patients with Gastric Cancer: Methodological Aspects of Detection and Prognostic Significance. Eur J Cancer. 1991;27:1461-1465.
26. Quirke P, Dixon MF. The prediction of local recurrence in rectal adenocarcinoma by histopathological examination. International Journal of Colorectal Disease. 1988;3:127-131.
27. Compton C, Fenoglio-Preiser CM, Pettigrew N, Fielding LP. American Joint Committee on Cancer Prognostic Factors Consensus Conference. Cancer. 2000;88:1739-1757.
28. Wittekind C, Meyer HJ, Bootz F editors. TNM Klassifikation maligner Tumoren. 6th ed. Heidelberg: Springer Medizin Verlag Heidelberg; 2002.
29. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM Residual Tumor Classification Revisited. Cancer. 2002;94:2511-2516.
30. Wittekind C, Greene FL, Henson DE, Hutter RVP, Sobin LH editors. TNM Supplement. 3rd ed. New York: Wiley-Liss; 2003.
31. Sobin LH, Gospodarowicz MK, Wittekind C editors. TNM Classification of Malignant Tumours. 7th ed. Oxford: Wiley-Blackwell; 2009.

32. Wittekind C, Compton CC, Brierley J, Sobin LH editors. TNM Supplement. 4th ed. West Sussex: Wiley-Blackwell; 2012.
33. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ. Manual for Staging of Cancer. Chicago: American Cancer Society; 1977.
34. Beahrs OH, Myers MH editors. Manual for staging of cancer. 2nd ed. Philadelphia: J. B. Lippincott Company; 1983.
35. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ editors. Manual for staging of Cancer. 4th ed. Philadelphia: J. B. Lippincott Company; 1992.
36. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A editors. AJCC CANCER STAGING MANUAL. 7th ed. Chicago: Springer New York; 2010.
37. Flemming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP, et al. editors. AJCC Cancer Staging Manual. 5th ed. Philadelphia: Lippincott - Raven; 1997.
38. Greene FL, Balch CM, Page DL, Haller DG, Fleming ID, Morrow M, et al. editors. AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002.
39. German Guideline Program in Oncology (GGPO). German Guideline Program in Oncology (GGPO) [Internet]. Berlin: Office des Leitlinienprogrammes Onkologie c/o Deutsche Krebsgesellschaft e.V.; 2019 [updated 2019 Oct 21; cited 2020 Nov 21] Available from: https://www.leitlinienprogramm-onkologie.de/english-language/.
40. St. Gallen Oncology Conferences (SONK). st. gallen oncology conferences [Internet]. Rorschacherstrasse 150 CH-9006 St. Gallen / Switzerland: Stiftung St. Gallen Oncology Conferences; 2021 [cited 2021 Jan 21] Available from: https://www.oncoconferences.ch/about-us/
41. National Comprehensive Cancer Network. About NCCN [Internet]. Plymouth Meeting Pensilvania: National Comprehensive Cancer Network; 2021 [cited 2021 Feb 2nd] Available from: https://www.nccn.org/about/default.aspx.
42. Waddel BE, Stomper PC, DeFazio JL, Hurd TC, Edge SB. Postexcision Mammography Is Indicated After Resection of Ductal Carcinoma-In-Situ of the Breast. Ann Surg Oncol. 2000;7:665-668.
43. Cody HS, VanZee KJ. Point: Sentinel Lymph Node Biopsy Is Indicated for Patients With DCIS. J Natl Compr Canc Netw. 2003;1:199-206.

44. MacDonald HR, Silverstein MJ, Mabry H, Moorthy B, Ye W, Epstein MS, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins Am J Surg. 2005;190:521-525.
45. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ J Clin Oncol. 2009;27:1615-1620.
46. VanZee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years Ann Surg. 2015;262:623-631.
47. American Society of Breast Surgeons. About ASBrS [Internet]. 2021 [updated 2021; cited Feb 12th, 2021] Available from: https://www.breastsurgeons.org/about/.
48. Landerscape J, Attai D, Atisha D, Beitsch P, Bosserman L, Boughey J, et al. Toolbox to Reduce Lumpectomy Reoperations and Improve Cosmetic Outcome in Breast Cancer Patients: The American Society of Breast Surgeons Consensus Conference. Ann Surg Oncol. 2015;22:3174-3183.
49. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. The New England Journal of Medicine. 2002;347:1233-1241.
50. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwing L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy Eur J Cancer. 2010;46:3219-3232.
51. Buchholz TA, Sommerfield MR, Griggs JJ, El-Eid S, Hammond MEH, Lyman GH, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. J Clin Oncol. 2014;32:1502-1506.
52. National Comprehensive Cancer Network Guidelines Version 2.2017 Invasive Breast Cancer: Margin Status in infiltrating carcinoma. 2017; BINV-F. Available at (with login): http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

53. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer The ACOSOG Z1071 (Alliance) Clinical Trial. JAMA. 2013;310:1455-1461.
54. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14:609-618.
55. American Society for Radiation Oncology. Society History [Internet]. Arlington2021 [cited 2021 11.04.21] Available from: https://www.astro.org/About-ASTRO/History/Society-History.
56. Fisher B, Wolmark N, Fisher ER, Deutsch M. Lumpectomy and Axillary Dissection for Breast Cancer: Surgical, Pathological, and Radiation Considerations. World J Surg. 1985;9:692-698.
57. Holland R, Veling SHJ, Mravunac M, Hendriks JHCL. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer. 1985;56:979-990.
58. Houssami N, Macaskill P, Marinovich ML, Morrow M. The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2014;21:717-730.
59. Correa C, McGale P, Taylor C, Wang Y, Clarke M, Davies C, et al. Overview of the Randomized Trials of Radiotherapy in Ductal Carcinoma In Situ of the Breast. J Natl Cancer Inst Monogr. 2010:162-177.
60. Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, et al. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2016;23:3811-3821.
61. College of American Pathologists. Historical Timeline [Internet]. 2021 [cited 2021 22.06.] Available from: https://www.cap.org/about-the-cap/historical-timeline.
62. College of American Pathologists. Protocols and Guidelines [Internet]. 2021 [cited 2021 22.06.] Available from: https://www.cap.org/protocols-and-guidelines.

63. LimeSurvey GmbH. LimeSurvey [Internet]. 2021 [cited 2021 June 17th] Available from: https://www.limesurvey.org/de/.
64. IBM. IBM SPSS Statistics 26 [Internet]. 2021 [cited 2021 December 20th] Available from: https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-26.
65. Hoffmann H, Junker K, Kugler C, Schnabel PA, Warth A. Anwendung und Interpretation der R-Klassifikation beim Lungenkarzinom. Pathologe. 2016;37:258-268.
66. Jorns JM, Visscher D, Sabel M, Breslin T, Healy P, Daignaut S, et al. Intraoperative Frozen Section Analysis of Margins in Breast Conserving Surgery Significantly Decreases Reoperative Rates. Am J Clin Pathol. 2012;138:657-669.

7 Appendix

Teil A: Allgemeines

Für Rückfragen stehe ich Ihnen gerne zur Verfügung!

Philipp Fischer cand. med.

philipp.fischer@stud.medunigraz.at

+43

A1. In welcher medizinischen Fachrichtung sind Sie tätig?

- ☐ Chirurgie/ Gynäkologie
- ☐ Strahlentherapie- Radioonkologie
- ☐ Pathologie
- ☐ Onkologie
- ☐ Radiologie
- ☐ Sonstiges

Sonstiges

A2. Wie viele Jahre Berufserfahrung bringen Sie in Ihrer Fachrichtung (inklusive Facharztausbildung) mit?

- ☐ 0-5 Jahre
- ☐ 6-10 Jahre
- ☐ 11-15 Jahre
- ☐ ≥16 Jahre

A3. An welchen dieser Leitlinien/ Klassifikationen orientieren Sie sich in Ihrer klinischen Tätigkeit? (Mehrfachnennung möglich)

- ☐ Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms
- ☐ St. Gallen International Consensus Guidelines in early breast cancer
- ☐ Consensus- & Performance and Practice Guidelines der American Society of Breast Surgeons - ASBrS
- ☐ Clinical Practice Guidelines in Oncology in Breast Cancer des National Comprehensive Cancer Network - NCCN
- ☐ International Guideline for Management of Breast Cancer der International Society of Breast Cancer - ISBrC
- ☐ SSO/ASTRO/ASCO Consensus Guideline für DCIS sowie die SSO/ASTRO Consensus Guideline für invasives Mammakarzinom der American Society for Radiation Oncology - ASTRO

TNM Klassifikation der malignen Tumoren der UICC ☐

AJCC Cancer Staging Manual ☐

A4. Die R-Klassifikation der UICC gibt Ihrer Ansicht nach Auskunft über

	ja	nein
den residuellen Tumor nach einer Therapie	☐	☐
die Prognose	☐	☐
den Resektionsrand des Primärtumors alleine	☐	☐
den Miteinbezug von Fernmetastasen	☐	☐

A5. Ist Ihnen die folgende R-Kategorie der TNM Klassifikation maligner Tumore der UICC mit der jeweiligen exakten Definition bekannt?

	ja	nein
RX	☐	☐
R0	☐	☐
R0>1mm	☐	☐
R0≤1mm	☐	☐
R1	☐	☐
R2	☐	☐
R2a	☐	☐
R2b	☐	☐
R2c	☐	☐

A6. Welche der folgenden R-Kategorien der TNM Klassifikation maligner Tumore der UICC verwenden Sie in Ihrem klinischen Alltag?

	ja	nein
RX	☐	☐
R0	☐	☐
R0>1mm	☐	☐
R0≤1mm	☐	☐

	ja	nein
R1	☐	☐
R2	☐	☐
R2a	☐	☐
R2b	☐	☐
R2c	☐	☐

A7. Empfinden Sie die Beschreibung der R-Kategorien der TNM Klassifikation maligner Tumore der UICC als klar definiert?

ja ☐

nein ☐

A8. Empfinden Sie die Beschreibung der R-Kategorien der TNM Klassifikation maligner Tumore der UICC in der Praxis als

zufriedenstellend ☐

nicht zufriedenstellend ☐

A9. Wer sollte Ihrer Meinung nach die R-Klassifikation erstellen?

Patholog*in ☐

Operateur*in (Chirurg*in/ Gynäkolog*in) ☐

Onkolog*in ☐

die*der behandelnde Ärztin*Arzt, welche*r mit der medizinischen Historie der*des Patient*in am besten vertraut ist ☐

gemeinsam interdisziplinär im Tumorboard ☐

Teil B: Allgemeine TNM Klassifikation

Für Rückfragen stehe ich Ihnen gerne zur Verfügung!

Philipp Fischer cand. med.

philipp.fischer@stud.medunigraz.at

+43

B1. Bedarf es außer der Beurteilung des Schnittrandes für eine R0 Kategorie noch weiterer Informationen?

ja ☐

nein ☐

B2. **Welche R-Kategorie würden Sie vergeben, bei einem Mammaoperationspräparat eines invasiven Mammakarzinoms mit weit tumorfreien Resektionsrand und einem positiven, komplett entfernten Sentinellymphknoten, jedoch ohne vorliegenden axillären Dissektat?**

- ☐ RX
- ☐ R0
- ☐ R1
- ☐ R2
- ☐ es kann keine R-Kategorie vergeben werden

B3. **Welche R-Kategorie wird Ihrer Meinung nach vergeben, wenn das OP-Präparat in mehreren Teilen eingeschickt wird?**

- ☐ RX
- ☐ R0
- ☐ R1
- ☐ R2
- ☐ es kann keine R-Kategorie vergeben werden

B4. **Welche R-Kategorie wird Ihrer Meinung nach vergeben, wenn das OP-Präparat eine mehrfach eingerissene Oberfläche zeigt mit zum Teil schlecht beurteilbaren Resektionsrändern?**

- ☐ RX
- ☐ R0
- ☐ R1
- ☐ R2
- ☐ es kann keine R-Kategorie vergeben werden

B5. **Welche R-Kategorie kann Ihrer Meinung nach vergeben werden, wenn in einem OP-Präparat nach einer neodadjuvanten Therapie kein Tumorgewebe mehr nachweisbar ist?**

- ☐ RX
- ☐ R0
- ☐ R1
- ☐ R2
- ☐ es kann keine R-Kategorie vergeben werden

B6. **Welche R-Kategorie kann Ihrer Meinung nach vergeben werden, wenn in einem OP-Präparat nach neoadjuvanter Therapie das vernarbte und mittlerweile tumorfreie Gebiet des Primärtumors am Resektionsrand liegt?**

- RX ☐
- R0 ☐
- R1 ☐
- R2 ☐
- es kann keine R-Kategorie vergeben werden ☐

B7. **Welche R-Kategorie kann Ihrer Meinung nach vergeben werden, wenn in einem OP-Präparat nach neoadjuvanter Therapie, im größtenteils vernarbten Gebiet des Primärtumors vereinzelt residuale Tumorzellnester im Abstand von ca. 5mm und mehr verteilt liegen, das vernarbte Tumorareal unmittelbar an den Resektionsrand heranreicht und der minimale Abstand des nächstgelegenen residuellen Tumorzellnests 2mm beträgt?**

- RX ☐
- R0 ☐
- R1 ☐
- R2 ☐
- es kann keine R-Kategorie vergeben werden ☐

Teil C: Spezielle Fragen in Hinblick auf die Mammabefundung

Für Rückfragen stehe ich Ihnen gerne zur Verfügung!

Philipp Fischer cand. med.

philipp.fischer@stud.medunigraz.at

+43

C1. **R1 in der Mammachirurgie bedeutet (Mehrfachnennung möglich):**

- ink on tumour bei invasivem Karzinom ☐
- invasives Karzinom Bruchteile eines Millimeters vom Resektionsrand entfernt ☐
- invasives Karzinom unter 2 mm vom Resektionsrand entfernt ☐
- invasives Karzinom über 2mm entfernt, aber DCIS am Resektionsrand ☐
- ink on tumour bei DCIS (ohne invasiven Tumor) ☐
- DCIS (ohne invasiven Tumor) unter 2 mm vom Resektionsrand entfernt ☐

C2. **Welche R-Kategorie würden Sie bei einem neoadjuvant therapierten Mammakarzinom mit disseminierten Wachstumsmuster im gesamten Präparat vergeben (die einzelnen Tumorzellen erreichen knapp nicht die Tuschemarkierung; "no ink on tumour")?**

- RX ☐
- R0 ☐
- R1 ☐
- R2 ☐
- es kann keine R-Kategorie vergeben werden ☐

C3. **Welche R-Kategorie würden Sie bei einem operierten Mammakarzinom mit einem weit tumorfreien Resektionsrand und einer klinisch entdeckten (und histologisch verifizierten), aber nicht operierten Lebermetastase vergeben?**

- RX ☐
- R0 ☐
- R1 ☐
- R2 ☐
- es kann keine R-Kategorie vergeben werden ☐

C4. **Welche R-Kategorie ist Ihrer Meinung nach anzuwenden, bei einem Mammaoperationspräparat mit DCIS, wenn der Schnittrand zwar tumorfrei ist, aber in der postoperativen Mammographie suspekte Kalzifikationen entdeckt werden?**

- RX ☐
- R0 ☐
- R1 ☐
- R2 ☐
- keine R-Kategorie inklusive Kommentar und Diskussion im Tumorboard ☐

C5.

	ja	nein
Mammapräparate mit invasiven Karzinomen und knappen Resektionsrändern sollten zur intraoperativen Gefrierschnittuntersuchung gelangen?	☐	☐
Sollten diese knappen Resektionsränder bereits von der*dem Operateur*in markiert werden?	☐	☐
Sollten Mammapräparate mit neoadjunvant therapierten invasiven Karzinomen mit knappen Resektionsrändern zur intraoperativen Gefrierschnittuntersuchung gelangen?	☐	☐
Sollten diese knappen Resektionsränder bereits von der*dem Operateur*in markiert werden?	☐	☐

	ja	nein
Mammapräparate mit DCIS mit knappen Resektionsränder sollten zur intraoperativen Gefrierschnittuntersuchung gelangen?	☐	☐
Sollten diese knappen Resektionsränder bereits von der*dem Operateur*in markiert werden?	☐	☐
Sollte ein knapper Resektionsrand eines DCIS bei einem Mammaoperationspräparat durch die Präparatradiographie intraoperativ markiert werden?	☐	☐

C6. Sollten alle Segmentresektate mit einem DCIS oder invasiven Mammakarzinom intraoperativ präparatradiographiert werden?

ja ☐

nein ☐

Vielen Dank, dass Sie an dieser Umfrage Teilgenommen haben!