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RESEARCH PAPER

Cyber Cloud Oncology

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Abstract

Breast cancer treatment is experiencing a groundswell transformation directed by a better understanding of tumour cell metabolism. Observation of metabolic tumor cell variations led to precision medicine. In addition, a "new wave" of rapid drug development spurred by the 2016 U.S. government's Moonshot program is in the backdrop and, in part, placed an overwhelming burden on clinical oncologists and patients. In 2016, the U.S. government announced the Cancer Moonshot intending to make ten years' worth of progress in cancer prevention, diagnosis, and treatment in just five years. In the 5-year interval 2017–2021, the FDA issued an unprecedented 161 new approvals of therapeutic agents for various indications in adult patients with solid tumors.

Cancer chemotherapy now involves a complex balance between new drug development, clinical trial observations, FDA drug approvals, next-generation sequencing of tumour and blood samples, and "consensus opinion" between medical, surgical, and radiation oncologists. New "precision" medicine selects precise treatment options that benefit patients based on the genomic makeup of their tumour. Genomic profiling provides information about a diagnosis and prognosis and often predicts response or resistance to therapy, years before routine imaging studies change. New technologies, including liquid biopsy and next-generation sequencing (NGS), have identified oncogenic drivers and unique drugs capable of targeting and inhibiting/modifying newly discovered oncogenic driver pathways. Herein is presented a helpful method for keeping track of and rapidly updating physicians on newly developed effective treatments and therapeutic consensus opinion, which often lacks contemporary harmonization between official oncology societies. Physicians and supporting healthcare workers contribute the most to patients when equipped with knowledge of the newest, least toxic, and most effective therapies.

Keywords: breast, cancer, algorithm, RAPIT, treatment, drug, PDF, cloud, computer oncology, guidelines

Citation
Glenn Tisman (2022), Cyber Cloud Oncology. *Digital Medicine and Healthcare Technology* 2022(0), 1–19.

DOI
https://doi.org/10.5772/dmht.08

Published
20 September 2022

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https://drive.google.com/drive/folders/1hJZH-2vZvz_THsSppchRTQYrna0bj9xM?usp=sharing

1. Introduction: Practice changing breast cancer therapies increase exponentially

A brief search of the Internet for the phrase "breast cancer practice changing" brings to the fore several study results presented at ASCO 2022 termed "practice changing." Some such trials include the following:

(A) The results of the DESTINY-Breast04 trial reveal the use of trastuzumab-deruxtecan (ENHERTU) in patients with HER2 (1+ or 2+) = (HER2-low). These patients were previously considered ineligible for treatment with this drug. Results showed that the median PFS for the HR-positive cohort was higher in the T-DXd group than in the group administered the treatment of physician's choice (TPC) (10.1 vs. 5.4 months, respectively).

(B) The TROPiCS-02 trial explored the use of sacituzumab-govitecan (Trodelvy) in ER-positive patients. This drug will be beneficial for patients who continue to have good performance status despite multiple prior lines of therapy and who need an additional treatment option.

(C) The MAINTAIN trial appears beneficial for patients with HR-positive/HER2-negative metastatic breast cancer who have experienced disease progression on a CDK4/6 inhibitor, suggesting treatment with a different CDK4/6 inhibitor may be effective.

The newest NCCN Guidelines for HER2-Negative Breast Cancer, focusing on systemic therapy, included the following practice-changing updates:

(D) For HER2-negative, hormone receptor-positive, *BRCA*-mutated early breast cancer, adjuvant olaparib (with endocrine treatment) can be considered in patients with residual disease.

(E) For HER2-negative, hormone receptor-positive early breast cancer with high-risk characteristics, two years of adjuvant abemaciclib is considered in conjunction with endocrine therapy.

(F) For triple-negative early breast cancer with high-risk characteristics, adjuvant pembrolizumab is a preferred option (following neoadjuvant pembrolizumab).

Additionally, the 2022 NCCN breast cancer guidelines for the locoregional management of early-stage breast cancer revised at least eight new recommendations for radiotherapy. These changes can be reviewed by assessing this manuscript's accompanying file entitled "**Breast Cancer Algorithms.PDF**." The identical file is revealed within two links (one for iCloud access and one for GDrive access), and the new recommendations are found by searching this RAPIT PDF for "**radiation recommendations**."

https://www.icloud.com/iclouddrive/02aqQr7bCQEiLcL5dF-nMlNPA#Cyber.

https://drive.google.com/drive/folders/1hJZH-2vZvz_THsSppchRTQYrnaobj9xM?usp=sharing

The new therapies noted above are but a limited sampling among many, which may be helpful to physicians and their patients, unaware of reports of the most current and potentially practice-changing and life-extending therapy.

1.1. A simple method for storing, updating, and sharing the new advances of rapidly changing medical oncology therapeutics

Fifty years ago, the half-life of new medical knowledge was variable and measured in months to a few years. Progress in biological sciences, laboratory instrumentation, and the health care industry continues to grow at an accelerated rate. New molecular biology discoveries and understanding of how genetic mutations affect tumour growth accelerated the development of more effective drugs. The speed of new drug development based on tumour cell metabolism is breathtaking. Today, the half-life of newly discovered medical information is measured in just weeks to a few months.

Occasionally, new clinical trials provide high drug efficacy signals with manageable toxicity. Under such circumstances, physicians should be informed and quickly share that information with their patients who may be eligible for treatment with the more effective and potentially less toxic drugs.

Today, while immersed in a patient's clinical and laboratory data, medical practitioners try their best to be aware and keep track of the newest medical and drug announcements that apply to their specialties. Keeping up to date is a complex but necessary activity to assure the administration of a rapidly changing standard of care.

Our group has developed a simple mechanism using standard computer technology to rapidly update, organize, and distribute new cancer medicine standards while expanding efficacious therapeutic options.

Over time we found, as previously reported studies, that learning techniques used by medical personnel and medical students revealed that a considerable number of them used visual-spatial memory techniques [1]. The use of algorithms

falls within that category and has always been a popular teaching tool. However, textbook and journal manuscripts using this technique are almost instantly outdated when they reach the end-user's eyes. For example, the National Comprehensive Cancer Network (NCCN) guideline updates for the newest oncology therapies typically do not include the latest FDA drug approvals. The NCCN guideline process is a lengthy procedure that may take up to a year to be ready for universal distribution to practicing physicians [2], which may delay some recommendations for the most effective therapy.

2. *Distribution of new medical information*

Some vendors use short video interviews or summary lectures by expert researchers to rapidly distribute the newest medical information gleaned from oncology specialty meetings. These videos may last a few minutes to a few hours, and they are worth watching, for the most part, assuming one has the time. The next challenge involves remembering where the user filed that video with its information and accessing that video for a second time when one's practice calls for the use of the data.

Today's clinician's learning is diminished by bureaucratic demands for physician documentation, addressing insurance company reimbursement appeals, and the essential humanistic needs as well as empathy for the cancer patient and his family. These requirements have made substantial demands on physicians' learning time.

This communication aims to share our relatively simple technique developed by our group over the past few years to help understand, keep track of, rapidly update and distribute a set of cloud-based breast cancer treatment algorithms.

Mostly, these treatment algorithms incorporate consensus treatment recommendations stored in our shared cyber cloud and personal computers (PC, Mac, or mobile devices). The primary updated cloud recommendations are to be edited by designated physicians. However, the updates may be downloaded by all or restricted to groups or specific individuals.

2.1. An example of breast cancer information consensus development

A popular source for new breast cancer therapy recommendations with expertise in breast cancer therapy meets bi-annually in St. Gallen, Switzerland, to discuss and form a consensus on best practice guidelines for managing breast cancer. The 2021 meeting included 3300 participants.

Seventy-four expert panelists from all continents discussed and commented on previously elaborated consensus questions and many vital questions on early breast cancer diagnosis and treatment contributed by the audience. Live panel discussions

and real-time panel voting results drew a worldwide audience of thousands. A brief summary of the Consensus Discussion on Customizing Therapies for Women with Early Breast Cancer appears in the Journal Cancer Care [3]. I recommend a quick read of the summary report of voting by the St. Gallen expert panel on various aspects of early breast cancer therapies. From that summary of panelists voting on multiple treatment recommendations, it is evident that a significant majority for a consensus agreement on various clinical scenarios is not always attainable. The complete overview of the meeting recommendations is available for review [4]. Clinicians should be aware that proper adjustments and modifications to recommendations should be made according to the potential complications and tumor-specific characteristics of their patients.

Since implementing the U.S. government ***Moonshot*** program, the new cancer drug approval rates has been overwhelming for many clinical oncologists. Recent results from many clinical trials frequently offer patients enhanced quality of life and overall survival with acceptable toxicity. However, waiting for official medical oncology groups to insert the newest clinical trial findings into official treatment guideline algorithms is often an impediment to delivering updated patient care. Universal acceptance of new therapies is often modified due to patient age, financial reimbursement (patient *financial toxicity*), regional customs, and social-political issues. These modifiers vary from country to country and between centers of excellence within the same country.

2.2. Rapid Algorithmic PDF Information Transfer (RAPIT)

The WIKIPEDIA definition of a PDF file is outlined in reference [5].

For convenience, we defined the acronym RAPIT (Rapid Algorithmic PDF Information Transfer) as a simple, routine PDF file. RAPITs are uploaded into Apple's iCloud from a Mac computer or into Google's GDrive. Using a PDF editor, we created four RAPITs entitled: (1) **Breast Cancer Algorithms.pdf**, a 39 page PDF containing breast cancer treatment algorithms, (2) **Medscape Updated Drug Protocols.pdf,** a PDF containing updated Medscape breast cancer chemotherapy protocols, (3) **NCCN Drug Protocols.pdf** and (4) **NCCNDrugs v. 4.2022.pdf** an 11 page review of chemotherapy protocols. Regarding the four RAPITs, I was designated (by myself) as the RAPITs' official editor and the only one permitted to change/edit each PDF RAPIT file.

The four RAPITs plus a single README.txt file were transferred to a single folder and either uploaded to Apple's iCloud or Google's GDrive (within the cloud). Different URL link addresses were assigned to the iCloud folder, one to the GDrive folder. That process automatically produced the following **original URL links** to the respective folders in both Apple's iCloud and Google's GDrive. See below:

For Apple's iCloud: https://www.icloud.com/iclouddrive/02aqQr7bCQEiLcL5dF-nMlNPA#Cyber and for Google's GDrive: https://drive.google.com/drive/folders/1hJZH-2vZvz_THsSppchRTQYrna0bj9xM?usp=sharing.

The folders containing four RAPITs (PDF files) and a README.txt file may be downloaded at any time by anyone given the original URL link (see above). If the original RAPITs' editor updates anyone of the five iCloud or GDrive files in the future, the updated files can be downloaded by anyone in possession of the **original URL links**. The speed at which a newly published practice-changing therapeutic finding can be incorporated into a shared RAPIT PDF file sitting in the iCloud or GDrive is measured in just a few minutes.

Our new treatment discovery process entails scrutiny of meeting abstracts, academically confirmed clinical trials, review of videos made at oncology society meetings, FDA-announced new drug approvals, and quick updates distributed by oncology societies.

RAPITs housed in the iCloud in algorithmic format afford users "one place shopping" where they know the newest findings can easily be found, searched, and inserted into an instructive, visual-spatial structure, making it easier to recall therapeutic patterns.

The "Breast Cancer Algorithms.pdf" RAPIT contains treatment algorithms for most breast cancer clinical presentations and includes a listing of the most pertinent updates. Each algorithm displayed within a RAPIT PDF file contains links to abstracts and manuscripts of cancer chemotherapy drug trial results. A second RAPIT displays updated chemotherapy protocols from Medscape [6], and the third and fourth RAPITs reveal NCCN V 2.2018 and V 2.2022 chemotherapy protocols for the treatment of breast cancers [7]. These three drug RAPITs were cross-checked vs. the latest version of the Physicians' Cancer Chemotherapy Drug Manual 2022 by Edward Chu, MD, FACP, and Vincent T. DeVita, Jr., MD [8].

While this manuscript awaits publication, it contains nine samples of the newest, generally accepted treatment algorithms **figures 1–9 as of today, 7/4/2022**. When the final version of this manuscript passes through the press, it is not unreasonable to expect that the original four RAPITs in the cloud will have undergone several editorial updates. Though the printed figures 1–9 are now frozen within this manuscript, the **actual URL links** will always allow downloading the latest updated iCloud and GDrive RAPIT versions (both yield identical files).

Thus, future updated information will always be available by downloading the original folder (housed within the iCloud or GDrive) containing the four RAPITs.

Editors of RAPITs may update data within minutes based on new therapeutic announcements from clinical trials, FDA approvals, national and international

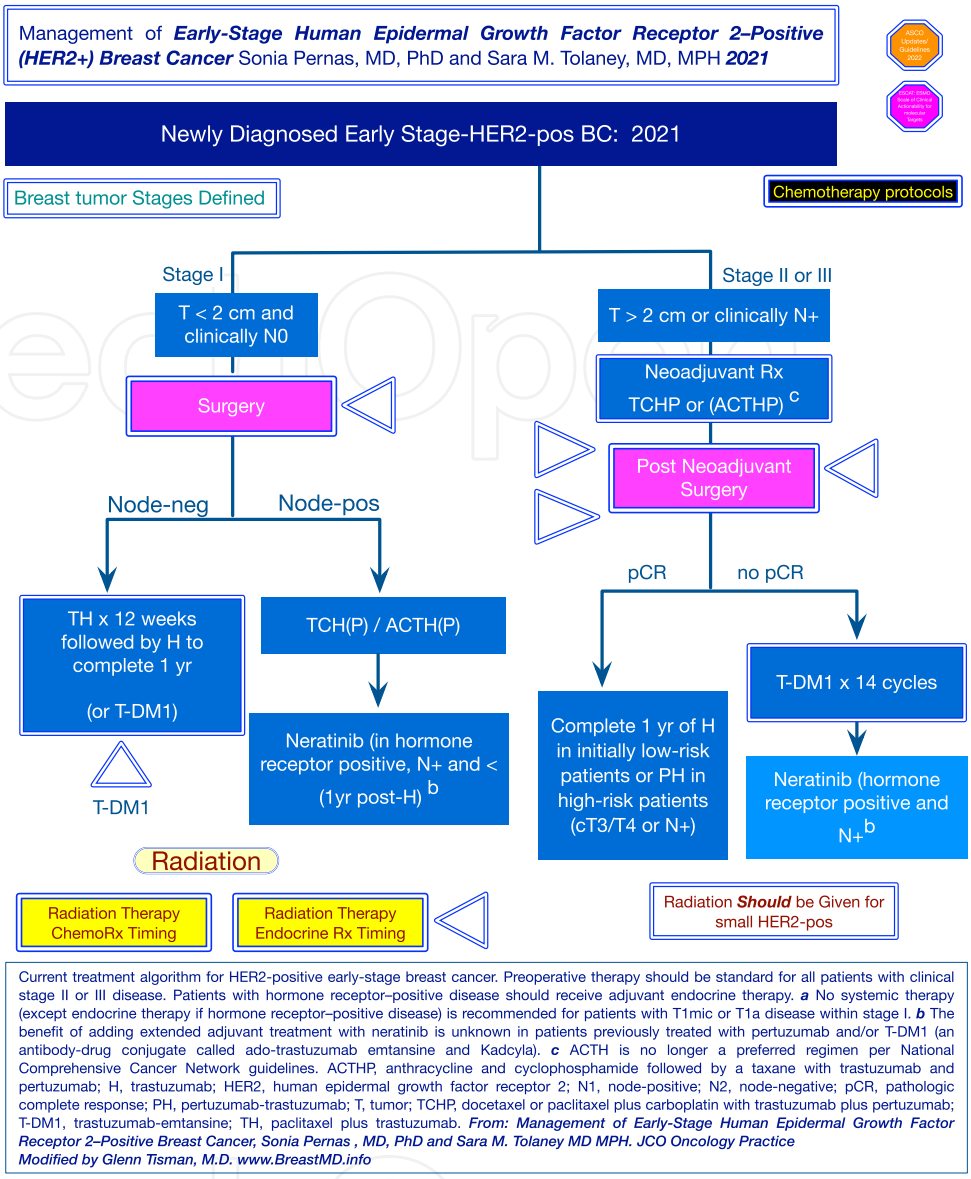

Figure 1. Annotated and referenced algorithm for newly diagnosed early stage-HER2-pos breast cancer.

medical society meetings, oncology literature, and other research meetings. They can be updated during a meeting if there is WIFI access. These updates come with the usual caveats for applying the newest therapies, and these caveats accompany popup notes when necessary.

The RAPIT author's responsibility is to warn that newly incorporated data should always be considered preliminary; however, that data could be lifesaving for many patients, who have become refractory to older therapies.

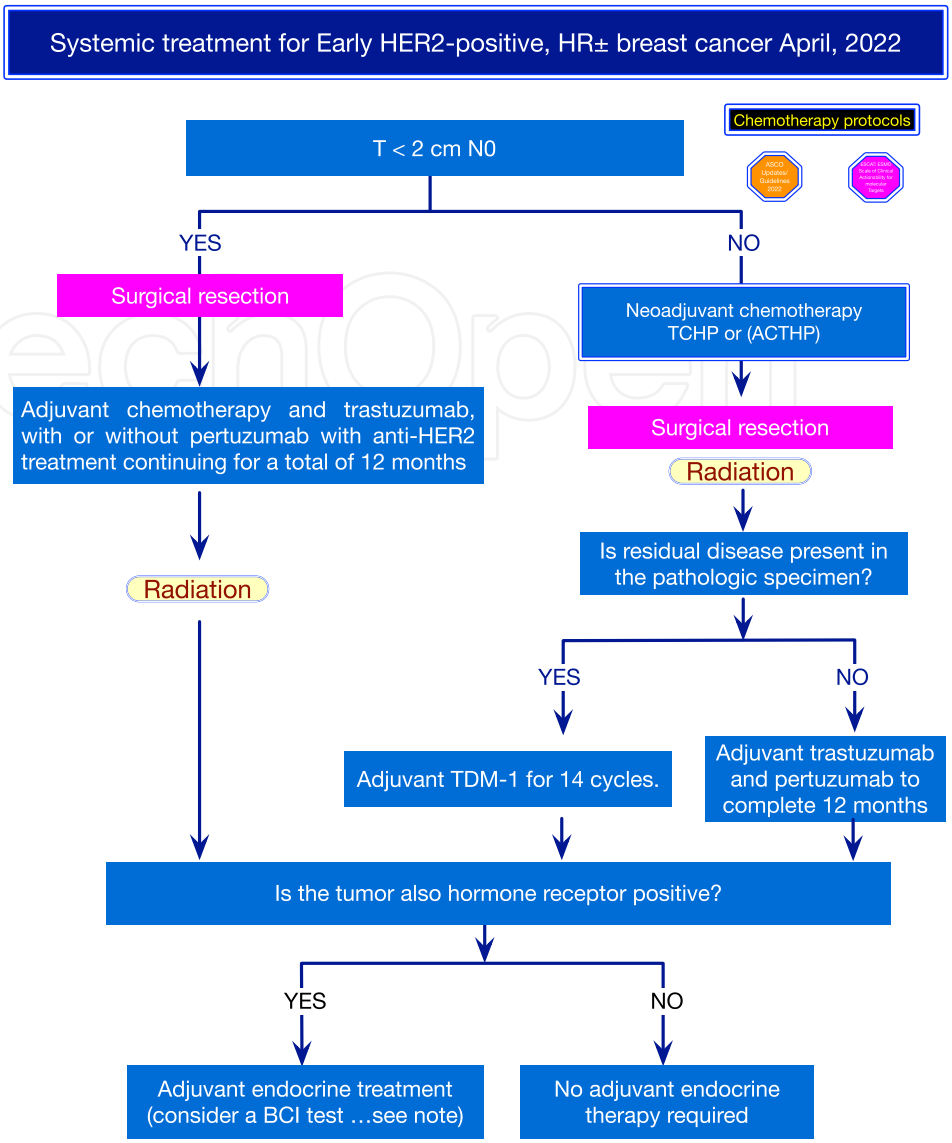

Figure 2. Annotated and referenced algorithm for newly diagnosed early stage-HER2-pos breast cancer.

2.3. Preliminary testing of the RAPIT technique

Current testing of this methodology confirms the speed of updating algorithms for potentially practice-changing new information is approximately 3 min. RAPITs may accommodate large numbers of algorithms (one or as many as necessary, 100+). Updates may be distributed to large numbers of algorithms on different pages of the RAPIT PDF by simply using inherent PDF searches to find older algorithm nodes needing change. As a PDF file, the RAPIT can rest on a single user's computer, or mobile device, or within a cyber cloud. A RAPIT can be printed, sent by message, or emailed to a fellow physician, pharmacist, medical student, nurse, or anyone

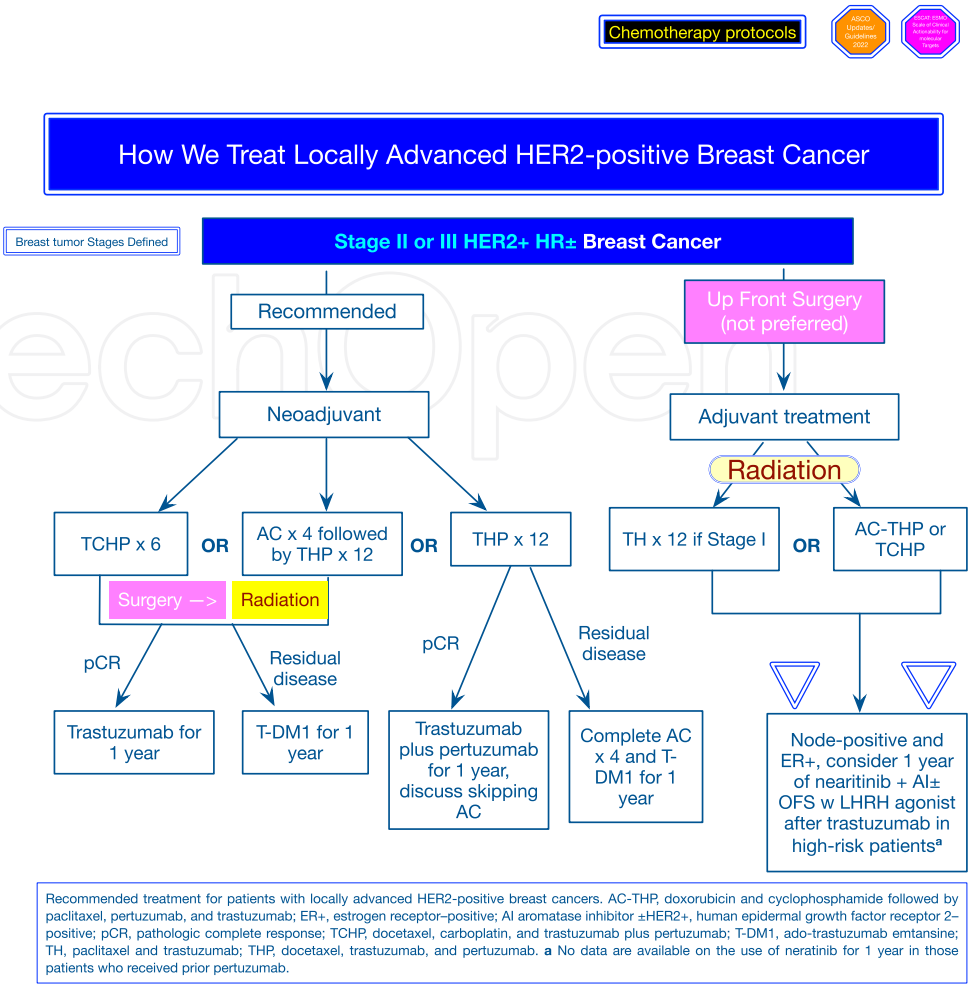

Figure 3. Annotated and referenced algorithm for newly diagnosed and locally advanced stage-HER2-pos breast cancer.

responsible for patient care. Once downloaded onto a computer, or mobile phone, or iPad, their contents may comfortably be searched and reviewed.

Having the original RAPIT housed within a cloud enables other physicians involved in patient care to use the same guidelines by downloading the identical RAPIT URL link.

Suppose the editor of the RAPIT wishes to incorporate a changed or new therapy. In that case, users may update by downloading the updated file using the same linked URL address used before the update. Shared URL links do not change after editing a RAPIT.

The cloud is a helpful medium permitting the concerned medical professional to refresh and download updated RAPIT algorithms as necessary. With the editor's permission, end-users (instructors/students/patients referred specialists) can

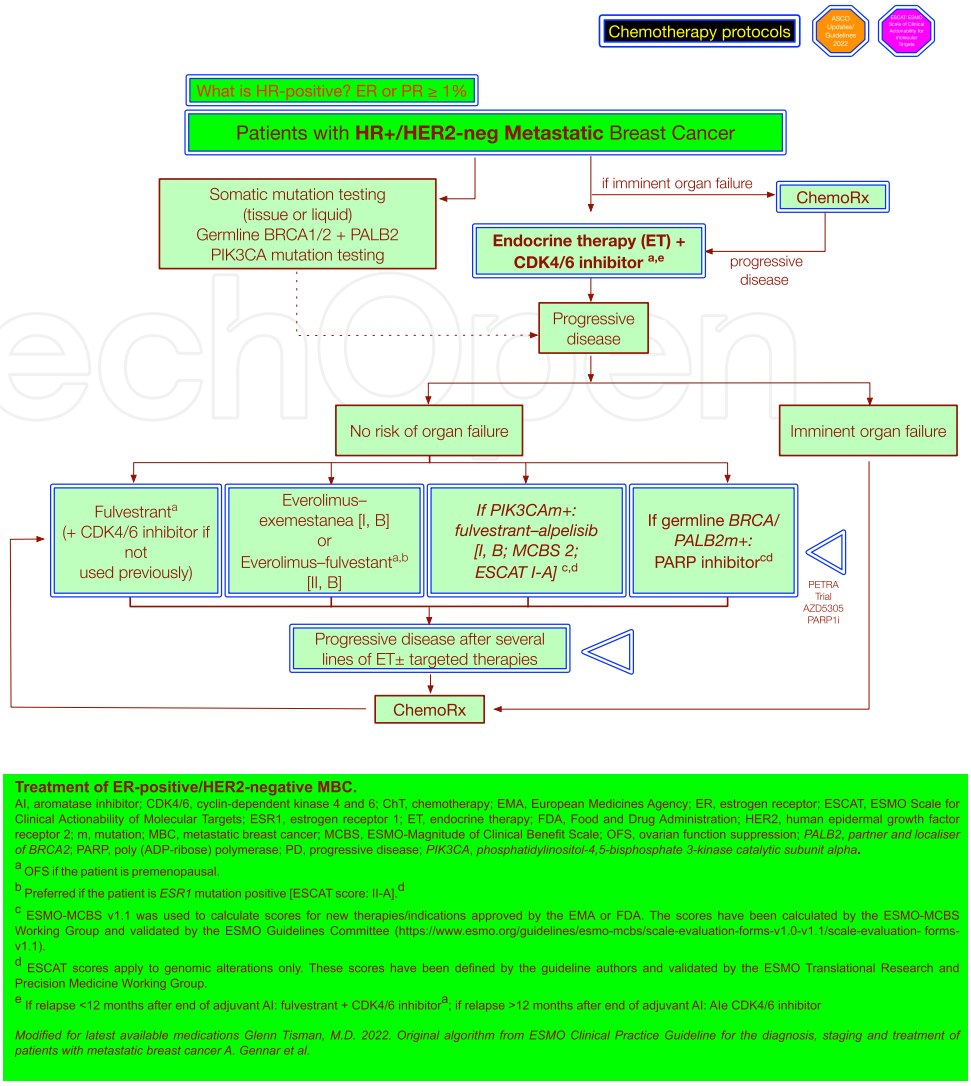

Figure 4. Annotated and referenced algorithm for patients with HR+/HER2-neg metastatic breast cancer.

download a copy of the principal or original RAPIT PDF file and change or add to the downloaded copy with personally added notes using a PDF editor (ADOBE ACROBAT or Preview as examples). If users have their own cloud space, they are free to upload their own modified RAPIT version to their iCloud, GDrive, or computer. They may mail a copy of the edited RAPIT to associates, students, etc., and send associates a link to their modified RAPIT from their cloud. The ability to edit a RAPIT may or may not be restricted by the original editor, and the editor may control who is allowed to view the RAPIT.

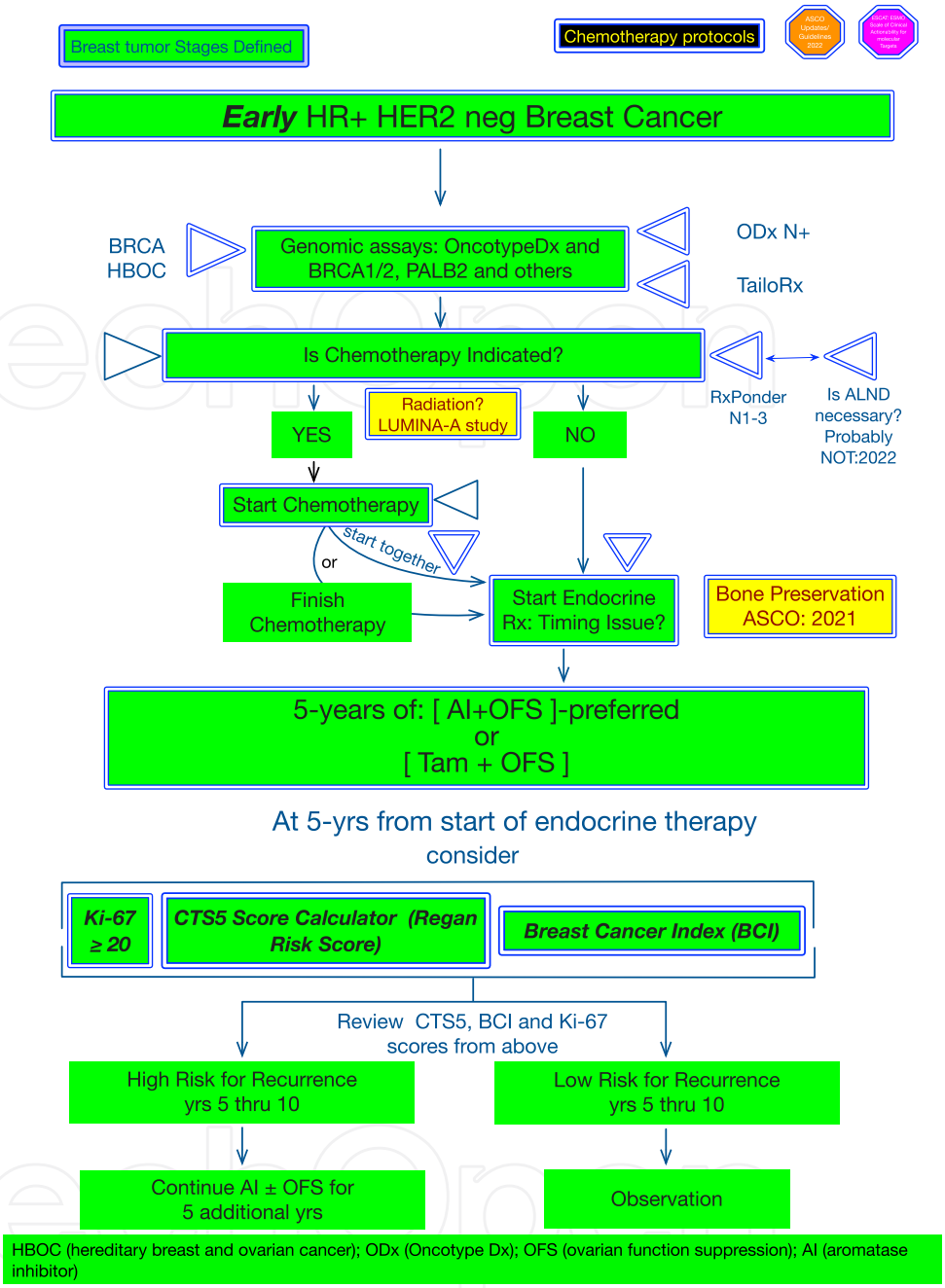

Figure 5. Annotated and referenced algorithm for patients with early HR+/HER2-neg breast cancer.

2.4. Construction of a new RAPIT

The example RAPIT "Breast Cancer Algorithms.pdf" URL included with this manuscript can be downloaded by tapping the URL link: https://www.icloud.com/iclouddrive/02aqQr7bCQEiLcL5dF-nMlNPA#Cyber for

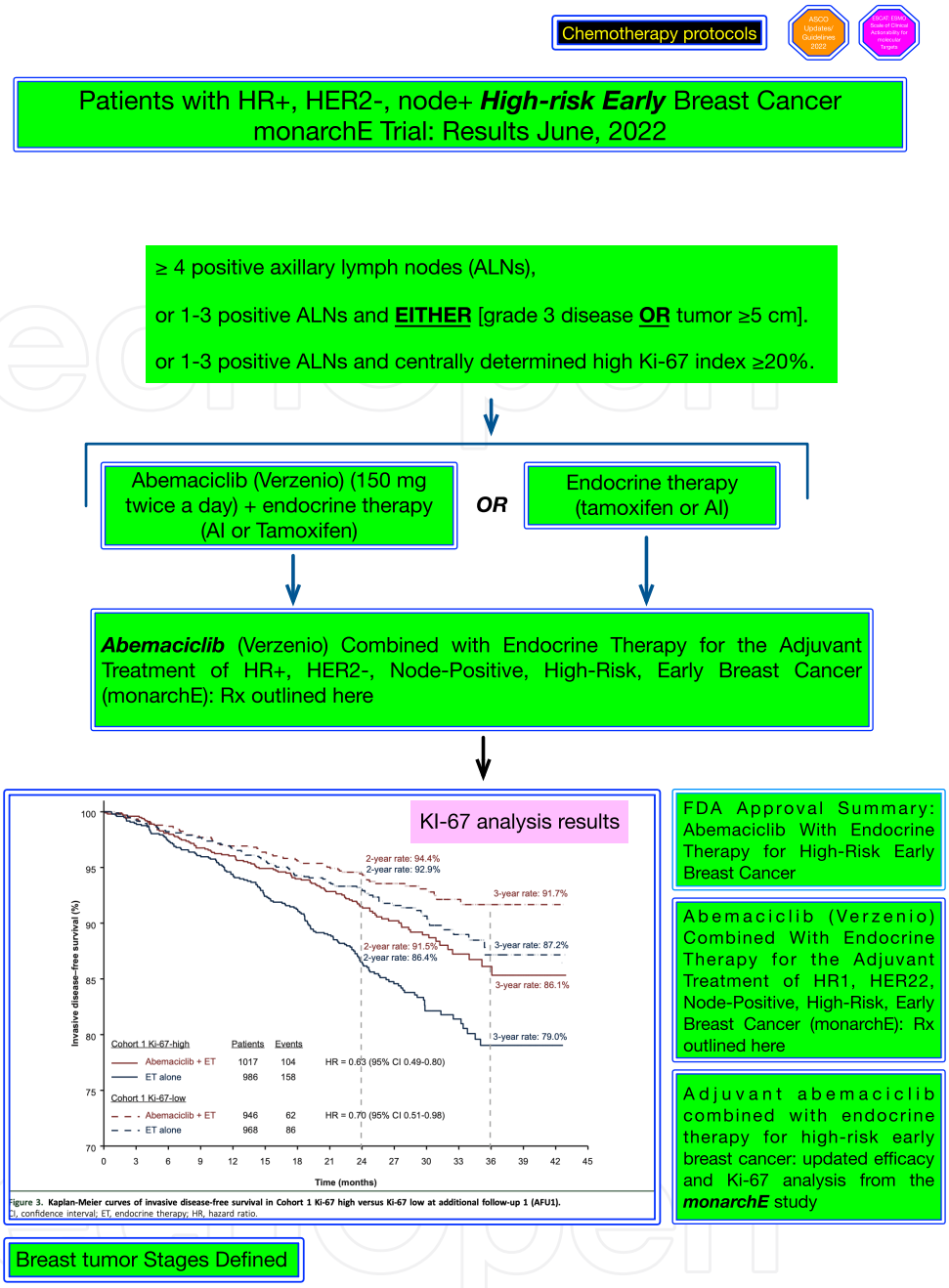

Figure 6. Annotated and referenced algorithm for HR+, HER2-, node+ high-risk early breast cancer, the monarchE Trial.

iCloud or https://drive.google.com/drive/folders/1hJZH-2vZvz_THsSppch RTQYrnaobj9xM?usp=sharing for GDrive.

Because of its graphic nature, it was constructed using the **OmniGraffle** software program. I highly recommend trying the free trial of OmniGraffle, a software product for Mac computing that we use for producing our RAPITs from scratch. This

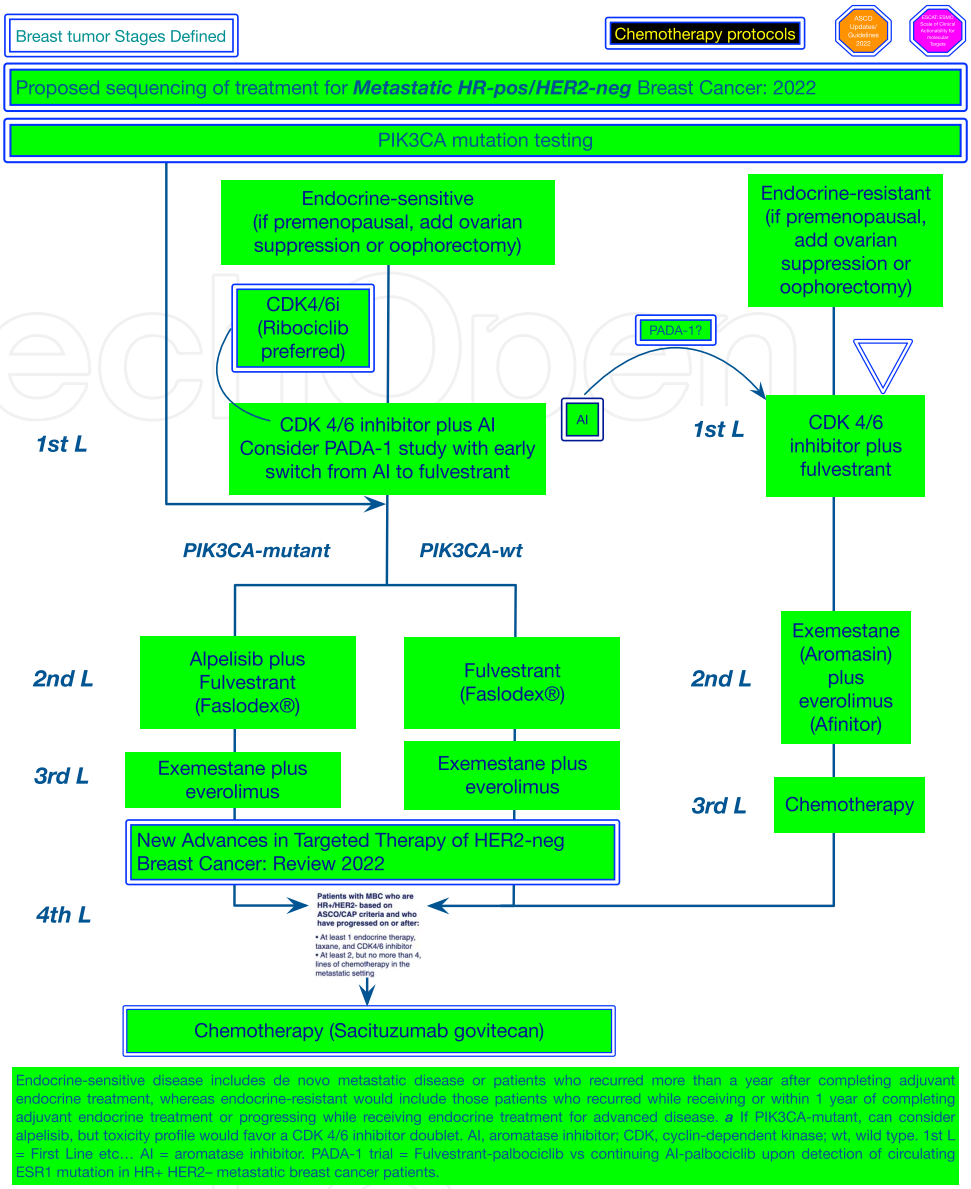

Figure 7. Annotated and referenced algorithm for Metastatic HR-pos/HER2-neg breast cancer.

software costs approximately 90.00 dollars in the U.S. with an educational discount. Though I have not tried it yet, I suspect that using any PDF generating software should work but may be more cumbersome when drawing algorithms. OmniGraffle is time-saving and quickly learned and thus preferred.

For IBM PC users, a comparable software product called Lucidchart may produce similar results; however, we have no experience with that product. Both products offer free trials through the Internet.

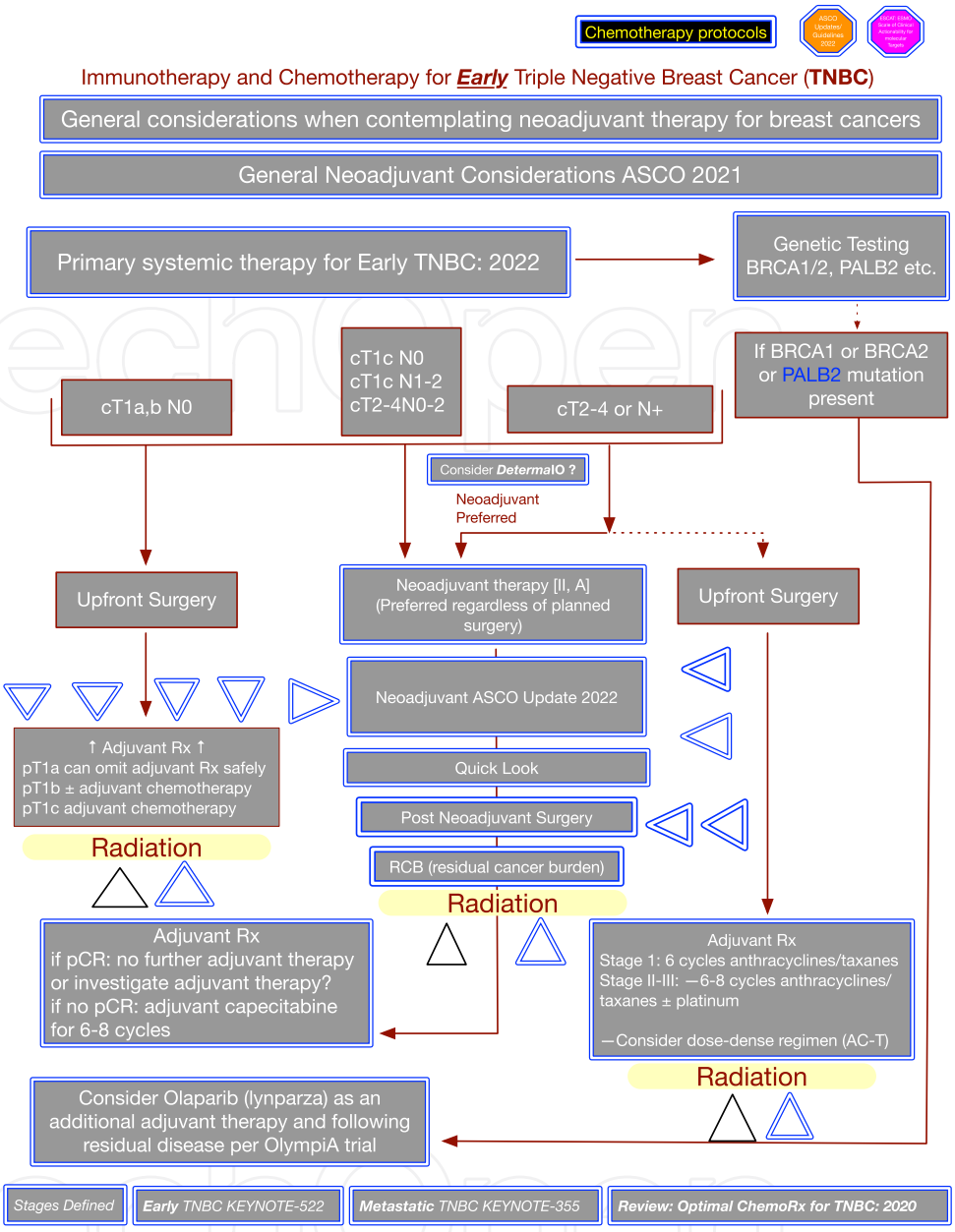

Figure 8. Annotated and referenced algorithm for early Triple Negative Breast Cancer (TNBC).

2.5. Advantages and cautions when using treatment algorithms to guide clinical practice

We have noted an apparent advantage to using RAPITs; users become informed of the latest in-house changes and national and international consensus guidance by going to **A SINGLE LOCATION!** Participating physicians don't have to wait for large specialty societies to vote for sanctioned official guidance changes that

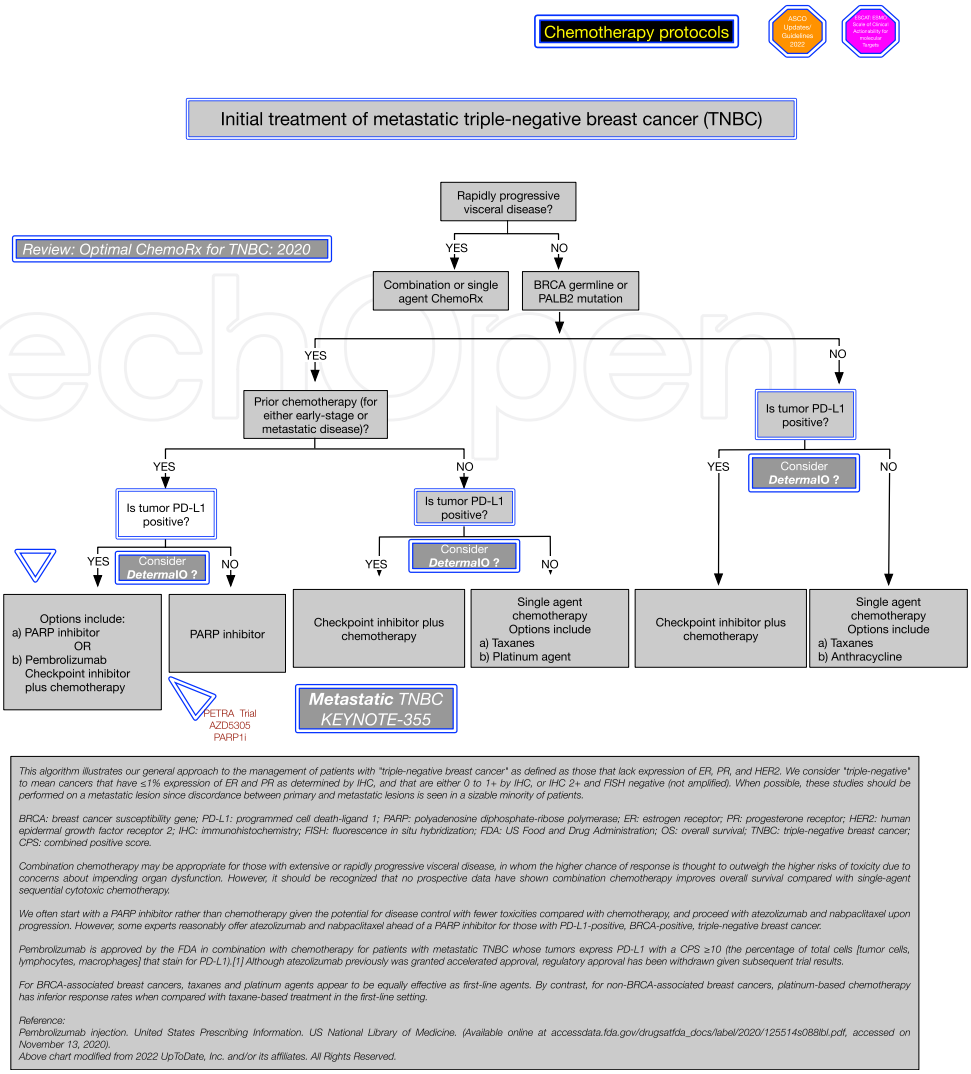

Figure 9. Annotated and referenced algorithm for treatment of metastatic triple-negative breast cancer (TNBC).

frequently become outdated soon after their announcement. And as we and others have discovered, it is not unusual that intra- and inter-society guideline recommendations often differ. For example, a literature review by Zagouri comparing ESMO and NCCN breast cancer guidelines reported differences in breast cancer screening guidelines, genetic risk evaluation, surgery, systemic therapy, radiotherapy, and follow-up recommendations [9].

More recently, in an assessment entitled "Expert review on systemic treatment in the St. Gallen International Breast Cancer Conference 2021," Mingxi Lin *et al.* concluded, "The expert recommendations of the 17th St. Gallen conference could guide clinicians, and the recommendations might suit most patients in common clinical situations. However, clinicians should be aware that proper adjustments

should be made according to the patient's socioeconomic status, complications, and tumor characteristics." [10]. These findings should alert physicians that may find it imperative to follow a particular treatment algorithm to a T.

A recent issue concerning the use of adjuvant chemotherapy for small TNBC breast cancers was the topic discussed in a paper by Li *et al.* entitled "A Novel Risk-Scoring System to Identify the Potential Population Benefiting from Adjuvant Chemotherapy for node-negative TNBC Patients with Tumor Size Less Than 1 cm" [11]. In that paper, their group presents the following therapeutic difficulty, and I quote:

"There are different opinions about whether TNBC patients with tumor size less than 1 cm need chemotherapy. NCCN (Version 6, 2021) guidelines recommend that TNBC patients with stage T1aN0M0 do not need adjuvant chemotherapy and use the word "consideration" for T1bN0M0 patients. In the 17th St. Gallen International Breast Cancer Conference, according to the experts' voting results, 45.6% of experts support that the appropriate tumor size threshold of lymph node-negative TNBC breast cancer for adjuvant therapy should be 5 mm. At the same time, the European Society of Oncology (ESMO) guidelines indicate that patients with TNBC should receive adjuvant chemotherapy except for low-risk T1aN0M0 tumors. Based on the guideline of the CSCO (Version 2022), all TNBC patients with the T1a-bN0M0 stage should receive standard adjuvant chemotherapy. In the records of the SEER database, more than 50% of patients in T1b received chemotherapy, and it was the highest proportion among T1mi, T1a, and T1b stages. For T1a stage patients, only 23.3% of cases were treated with chemotherapy. T1mi patients had the lowest chemotherapy acceptance rate, accounting for 9.0% of all patients. In our center, approximately 80.0% of patients receive chemotherapy, which is related to different guidelines and principles in different countries. Clinicians in China are more active in the implementation of chemotherapy."

Li's group concluded: "Tumor size should not be the only criterion for chemotherapy treatment decision-making."

Our "Breast Cancer Algorithms.pdf" RAPIT was updated with Li's findings for small TNBC tumors within minutes.

As previously discussed, there may be significant differences between recommended treatment algorithms displayed in a RAPIT. There are frequent differences between the consensus opinion of experts and oncology societies, and when these guidelines are voted upon, there is rarely 100% agreement between academicians. "At times, we can all agree to disagree."

2.6. A note on machine learning

An obvious disadvantage of this technique is that someone/group will have to continually update a RAPIT when it becomes apparent that a new clinical trial or laboratory discovery suggests pertinent findings that benefit patients. I suspect machine learning may be used soon to streamline and flag data for consideration.

3. Conclusions

This paper briefly touches on some undesirable issues within the current consensus procedures for forming diagnostic and treatment guidelines. In essence, an overwhelming majority of experts rarely agree on final guidance, and perhaps that is what should be expected from groupthink. Final, accepted consensus guidelines developed by ESMO, NCCN, and the St. Gallen conferences frequently vary.

The time involved in research meetings, debating, voting, and finally codifying and distributing therapeutic recommendations is, in my opinion, much too long (counted in many months to longer than a year in many cases). Cultural, patient tumor genetics, patient finances (*financial toxicity*), and regional socialization of medicine often play significant roles in the availability and administration of therapeutics. Thus, the final consensus opinion is difficult or impossible to harmonize between regional academic institutions and large international oncology societies.

There is a need for a system to disseminate the newest patient care discoveries rapidly and universally through an accelerated process for patients. Patients should be given access to promising therapies in clinical trials revealing exceptional signals of efficacy in the absence of significant toxicity.

The RAPIT fast cyber-cloud updating system discussed herein is relatively simple and employs a central cloud space available in almost every oncology practice office. We currently use Apple's iCloud or Google's GDrive to distribute our cloud files, and both clouds are compatible with Apple and Microsoft cloud technology. Cloud technology seems useful for universal distribution and personal redistribution of RAPITs. It requires simple, inexpensive software tools and standard computer technology.

Conflict of Interest

Glenn Tisman, MD, has no conflict of interests.

Acknowledgements

I am indebted to MS Julia Hopkins for her help with the use of cloud computing technology.

Instructions for downloading and viewing all accompanying treatment algorithms and chemotherapy protocols referred to in this document

The following URL address accesses the pertinent files on Apple's iCloud

https://www.icloud.com/iclouddrive/02aqQr7bCQEiLcL5dF-nMlNPA#Cyber

The link above directs you to the five following files:

(1) Breast Cancer Algorithms.pdf – 39 pages
(2) Medscape Updated DrugProtocols.pdf – 25 pages
(3) NCCN Drug Protocols.pdf – 3 pages
(4) NCCNDrugs v. 4.2022.pdf – 11 pages
(5) README FIRST.txt – 1 page

The following URL https://drive.google.com/drive/folders/1hJZH-2vZvz_THsSppchRTQYrna0bj9xM?usp=sharing contains the identical 5-files that are within a folder housed in Google's GDrive. *A special caveat to those using GDrive with respect to opening these files while they reside within GDrive. The largest file entitled "Breast Cancer Algorithms.pdf" cannot be fully opened* ***WITHIN*** *GDrive and requires initial downloading to the user's own computer or mobile device drive. The downloading menu choice appears by right-clicking the file's name. All files from either iCloud or GDrive should INITIALLY be downloaded before opening for best results.*

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3 Thomssen C, Balic M, Harbeck N, Gnant M. St. Gallen/Vienna 2021: a summary of the Consensus discussion on customizing therapies for women with early breast cancer. *Breast Care (Basel) [Internet]*. 2021;**16**(2):135–143. Available from: doi: 10.1159/000516114.

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