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Being Therapeutic Area Coach for Programmers: Taking RECIST 1.1 Training as An Example

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ABSTRACT

RECIST 1.1 serves as the guideline for assessing tumor response, a vital efficacy endpoint in solid tumor clinical trials. Do you fully understand it and apply it without any question as a statistical programmer? This paper presents a novel approach to overcome the challenges when training junior programmers and making the learning curve steeper for senior programmers by illustrating RECIST 1.1 concepts and implementation in programming. We followed the response evaluation roadmap to demonstrate how to illustrate complicated and rigid concepts in a ravishing and impressive way. That is lucid even for non-medical and non-programming background audiences. Flowchart maker (*Diagrams.net*) is utilized to create diagrams. Simple, accurate, attractive, and convenient, that are our goals to deliver our train and help programmers to build up knowledge system and hardcore skills. Please note that the content of RECIST 1.1 is limited when demonstrating in this paper, and some programming special cases are based on our previous experience.

INTRODUCTION

RECIST 1.1

In different therapeutic areas, data collection and analysis methods are different, especially for oncology, which more and more pharmaceutical companies are working on. Therefore, the evaluation of efficacy in oncology studies, in particular for solid tumors, is pretty important. Nowadays, most clinical trials evaluating cancer treatments for the objective response in solid tumors use a set of rules called RECIST (version 1.1), which has become the de facto standard for assessment of response in solid tumors and served a critical role in drug development.

RECIST 1.1 is the abbreviation for Response Evaluation Criteria in Solid Tumors, version 1.1, including most of the criteria that are commonly used in the solid tumors' oncology clinical trials, where the response, assessment of the stable disease, or time to progression analyses are involved in the study endpoints list. Since all these outcomes are based on the assessment of the anatomical tumor burden and its change in the study follow-up, the main subject of the RECIST 1.1 Guideline is to introduce or interpret related conception.

In addition to RECIST v1.1, there are other associative criteria like mRECIST for Hepatic Cell Carcinoma, iRECIST for Immunotherapy. Our paper includes only RECIST 1.1.

PRINCIPLES

Three principles are set up for the training program.

Of programmers: The topic and content selected must be highly related to programmers' daily work.

By programmers: All the processes for the training must be done by programmers including but not limited to slides, reading material, handbooks, and presentations.

For programmers: The training must be designed for the programmers and help programmers build up basic knowledge on the related topic.

TRAINING DESIGN

BACKGROUND

Fresh graduates study proper theoretical knowledge about statistics, data analysis, utilizing SAS, or even learning the design of clinical trials. However, the erudition on related documents or criteria in the industry is very limited. As a result, when an inexperienced newcomer enters the pharmaceutical industry, the lack of particular basic knowledge in this area, such as CDISC-related documents, Good Programming Practice, or RECIST 1.1, will produce some troubles. In this case, appropriate training appears necessary. This situation is especially crucial for training or explanation on RECIST 1.1, which seems to be the “big bang” in a solid tumor study, especially for junior levels or students who have just graduated.

RECIST 1.1 is a very rigorous criterion with a lot of obscure concepts and complicated content. Therefore, many companies or organizations in the industry have carried out various instructions and training to help their employees build a basic structure on this part. There are two main methods for RECIST 1.1 learning. One is papers, and the other one is slides or presentations. RECIST 1.1 always accounts for a large proportion in both formats.

Papers

The first and most straightforward approach is papers. In the past five years, about 1,500 articles （Figure 1) on RECIST 1.1 have been written and published. Most of the articles involve the interpretation of RECIST 1.1, comparison between different versions, specific conceptual perception, logical derivation, and hands-on programming details.

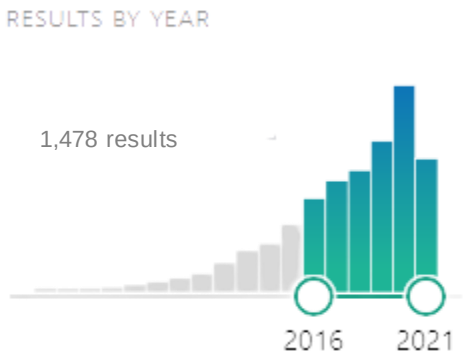

Figure 1 Paper Published in Last 5 Years

Among these, the official RECIST 1.1 guideline written by the RECIST 1.1 working group provides the most accurate, comprehensive, and full-scale introduction to RECIST 1.1. From this 20-page document, the history, primary structure, and details are thoroughly illustrated. The working group also answered many vital questions in the paper. It may not be the best paper for learning RECIST 1.1, but it must be on the necessary ones.

Other articles focus more on the detailed discussion of RECIST 1.1 or specific job-related applications, such as the derivation of Best Overall Response, decision making on imaging, and so forth. These articles can give users a more in-depth and more practical understanding of the specific concepts in RECIST 1.1 and enable readers to master the experience and skills of using it.

Articles

Advantages	Disadvantages
• Provide readers with detailed and accurate content. • Stimulate readers' associations and thinking. • Convenient to be reviewed and to be recalled. • Active learning	• Be cumbersome with so many wordings. • Be difficult to obtain valuable information easily. • Take more time and energy. • Not so interesting and fascinating.

Slides

In addition to articles, another standard method is the presentation with slides. Every organization and company will have its own slides for RECIST 1.1. Most of the slides are about introducing the RECIST 1.1, and a few of them will cover some biased examples of experiences towards certain functions. But, in general, the presentation or training is more about the general content included in the RECIST 1.1.

Slides

Advantages	Disadvantages
• Be simplified in content with the addon of the interpretation by speaker. • Be more interesting and attractive with inserting pictures and icons. • Easy to accept by learners • Easy for speaker to prepare.	• Difficult in revising since speech is not included in the slides. • Has limited ability to play the role as a reference file. • Can't make a deep impression on the concepts and logic. • Kind of passive learning, so learners may not be able to establish good associations or ignore some crucial details.

Others

Other forms such as video, audio, or animation are similar to slides. Although the fun and simplicity are improved, on the one hand, it is not convenient for employees to review, and on the other hand, they cannot give them more room for thinking.

Summary

Nowadays, many RECIST 1.1 articles, training, or workshops focus on the introduction or overview of RECIST 1.1. Most of them can let employees establish a basic knowledge and structure of RECIST 1.1. Of course, various essays explain in detail on some particular points of RECIST 1.1, such as the response derivation in SDTM or lesion measurement. These are worthy supplements and thoughtful guidance in daily work after learning RECIST 1.1.

But that is not enough. We have to admit, different functions or departments have different demands, so training should not be treated as the same. For instance, slides for the medical team may focus more on the judgment of tumor assessment (Figure 2) and the use of overall response rules. They may need to pay more attention to the concepts and logic frequently used in the daily work for programmers.

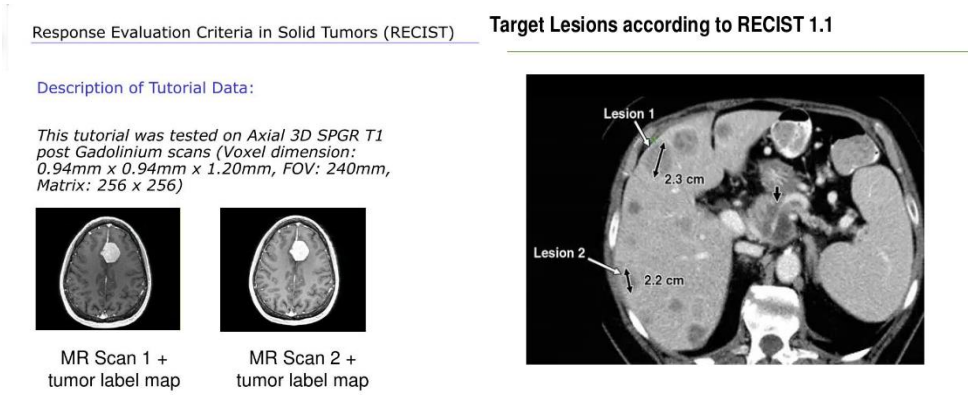

Figure 2. RECIST 1.1 training examples

Hence, we hope to find a way to **accurately, interestingly, simply, and thoroughly** display the vital concepts in RECIST 1.1 for programmers.

GOALS

When designing this training, we did many investigations, expecting our training to meet the programmers' needs. We hope to design our training in a novel way to better deliver knowledge on RECIST 1.1 to programmers. So, we set up four goals we hope to achieve according to the investigations' results.

Accurate: This is the cornerstone of training preparation and the most critical goal. We want to transmit precise and rigorous knowledge to the programmer. So we regard this goal as a principle to our training program.

Specific: RECIST 1.1 is an evaluation criterion so that many departments will use it. For example, the medical team will involve many tumor assessments, assessment methods, and the special consideration of lesion measurability. However, more attention should be paid to evaluating the tumor response for the statistical programmer or statisticians, so we must highlight what programmers are interested in and utilize in their daily work.

Attractive and Amusing: The traditional RECIST 1.1 related materials are formal and apply lots of texts or tables to show the concepts and criteria. We look forward to developing a more interesting presentation. Instead of words, we expect to use more charts, flows, figures, and tables to interpret the concepts in RECIST 1.1 in a fascinating way.

Convenience: The logic in RECIST 1.1 involved in programming is complicated, as well as some concepts. Hence it is difficult for the learner to memorize all the points through just one or two training sessions. Therefore, we hope to design our training materials with both simplicity and comprehensiveness. And finally, we can make it easier to access and review.

DESIGN

To achieve these goals, we first made our decision on the **style** of presentation. To reflect more differences between traditional slides and ours, an online drawing tool called *Diagrams.net* was used. We selected sketching as our main design style. Many icons and graphics were inserted into the slides to show most concepts in RECIST 1.1.

In the Overview page, we combine specific cartoon icons, graphics, and text to display the relation among Lesion, Time, Response, Progression, and Death so that we can present the learners with a splendid sight of RECIST 1.1 from the hilltop.

As for some logical concepts, we put flow diagrams, roadmap, and conceptual tables into use to help programmers with specific logic coding. For instance, in the Evaluation of Target Lesions page, we use cylinders with different colors to show the logic of determining response for target lesions.

We also use more vivid forms such as message boxes to describe formulas and some special cases.

Then we secondly select **specific contents**, including response evaluation roadmap, baseline lesions identification, target lesion evaluations, non-target lesion evaluations, new lesions, overall response, best overall response without confirmation, best overall response with confirmation from the programming point of view.

Response evaluation roadmap (Figure 3)

To give audiences a whole picture of RECIST 1.1, we designed a roadmap shown below to demonstrate the best overall response derivation process. As shown, four different colors were selected to indicate four steps to get best overall response (BOR). Obviously, three green parts pave the road to overall response by time points. Thus, an impressive concept is built up in mind.

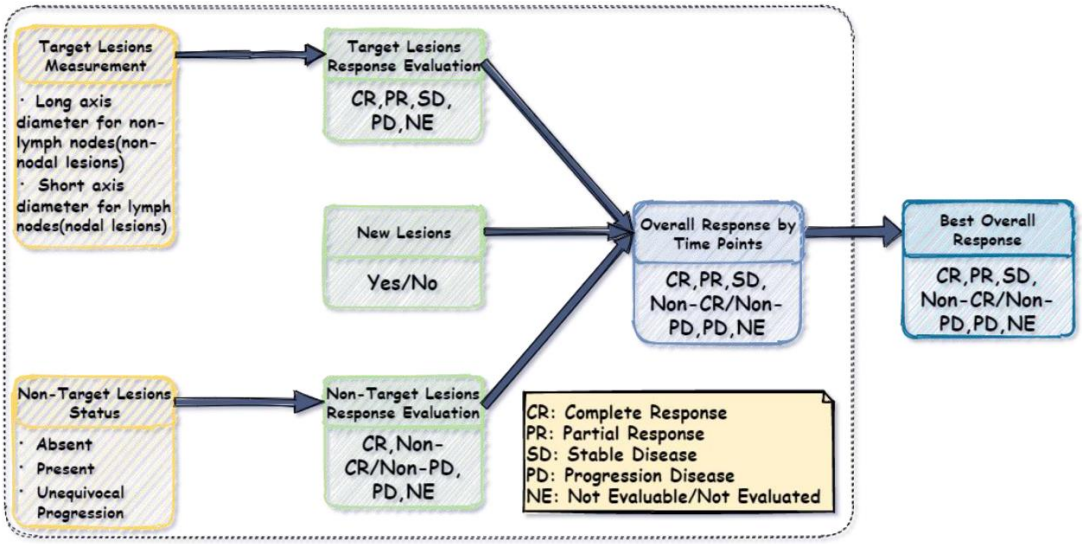

Figure 3 ***Response evaluation roadmap***

Baseline lesions identification (Figure 4)

Baseline identification is an essential starting point to perform the tumor evaluation. To illustrate the rigid concepts in a captivating and impressive way, we design the page as follows:

- Display three pairs of keywords: ‘target, non-target’, ‘measurable, non-measurable’, ‘nodal, non-nodal’ in the figure below
- Use cloud shape to indicate non-nodal lesions, which are measured in long diameter. Use ellipse to indicate nodal lesions, which are measured in short diameter.
- Sticky notes besides arrows are used for valuable notes to demonstrate how to select the target and non-target lesions.

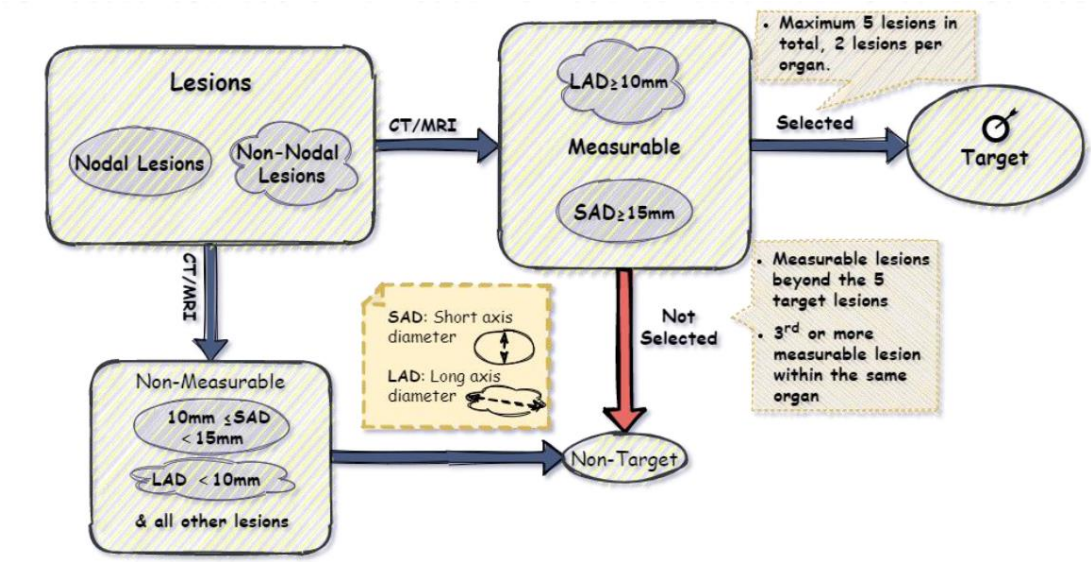

Figure 4 Baseline lesions identification

Target lesion evaluations (Figure 5)

The classical training usually displays a table to explain the definitions of CR, PR, SD, PD to illustrate the response evaluation of target lesions.

- We use three different colors to demonstrate three target lesion response derivation steps:
  - yellow → from individual lesion diameters to the sum of diameters.
  - green → from the sum of diameters to SOD on different time points.
  - blue → from the sum of diameters to lesion response.
- we designed a cylinder to indicate the definitions of CR, PR, SD, PD. 'Baseline' and 'Nadir' are highlighted in two different colors as two references. PD is calculated taking nadir as a reference, which is marked in purple, and PR is calculated taking baseline as a reference, which is marked in blue.
- A programming flow chart is displayed on the right-hand side. The green color indicates a helpful note that PD-PR order should be followed when deriving response evaluation.
- A special case is illustrated and marked as a star.

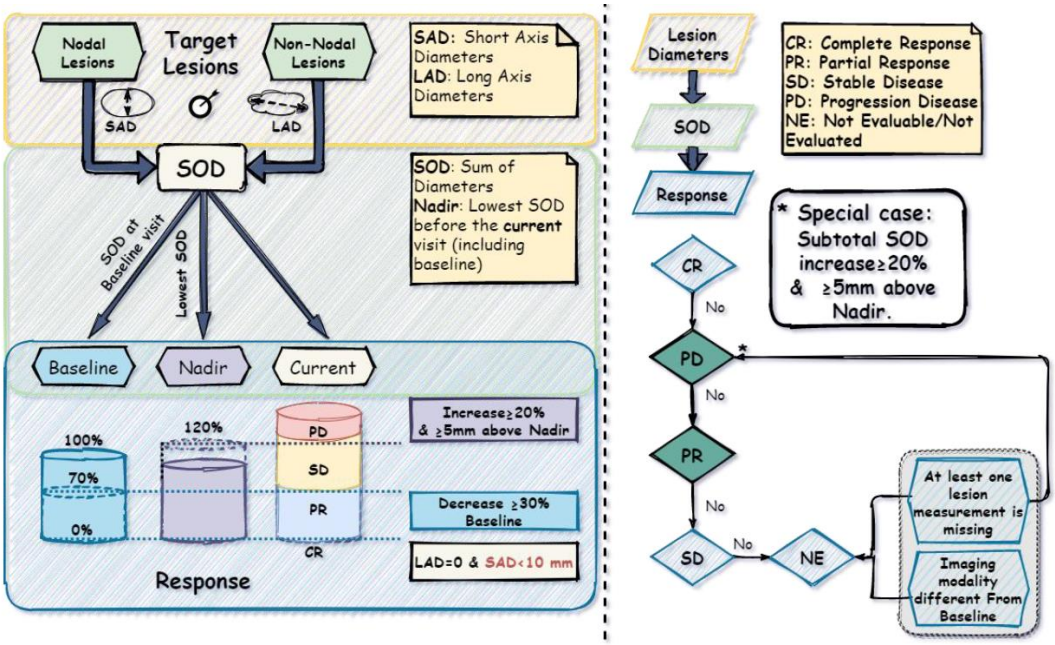

Figure 5 Target lesion evaluations

Non-target lesion evaluations and new lesions (Figure 6)

Here we illustrated non-target lesion response and new lesions qualitatively. Three categories were presented for non-target lesion response, and two categories were presented for new lesions, which are very straightforward.

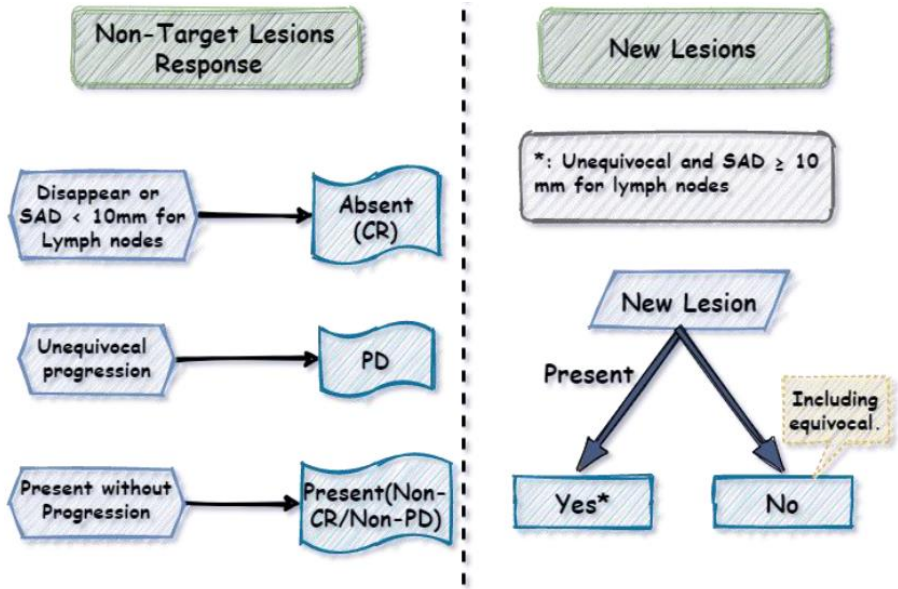

Figure 6 Non-target lesion evaluations and new lesions

Overall response (Figure 7)

The classical training usually displays a table to illustrate overall response calculation. We designed this part as follows:

- We check PD first, if PD is evaluated for any of new lesions, target lesions and non-target lesions, then overall response is PD.
- Target lesion plays a dominant role in overall response calculation.

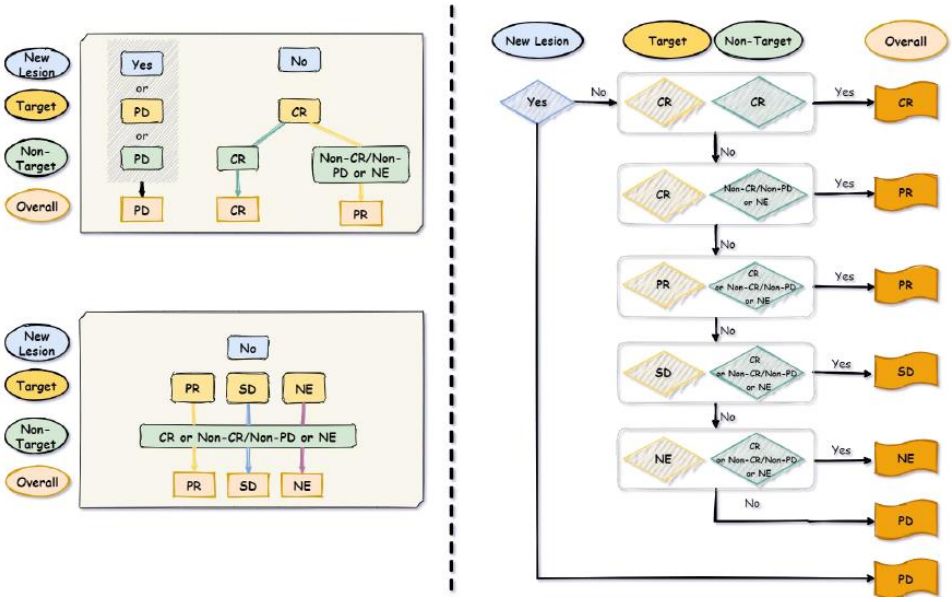

Figure 7 Overall response

Best overall response without/with confirmation (Figure 8/Figure 9)

To illustrate best overall response, the classic rigid training usually display a table to explain the definitions of BOR. We used different way to show this part.

- The comparison of BOR with confirmation and without confirmation was emphasized.
  - The first figure is straightforward demonstrating BOR without confirmation.
  - The second figure the highlighted three gray rectangles indicate the differences when deriving BOR with confirmation compared with the flowchart of BOR without confirmation. Obviously, CR and PR need to be confirmed by checking specific conditions.
- Special cases such as 'CR-NE-CR' are presented as valuable notes.

A question highlighted in red rectangle was designed to motivate audiences to think themselves regarding the difference between BOR with confirmation and without confirmation and guide the audiences to catch the key points of the knowledge.

Please be note that we use 'X' to demonstrate a case-by-case rule depend on company convention when illustrating duration of stable disease.

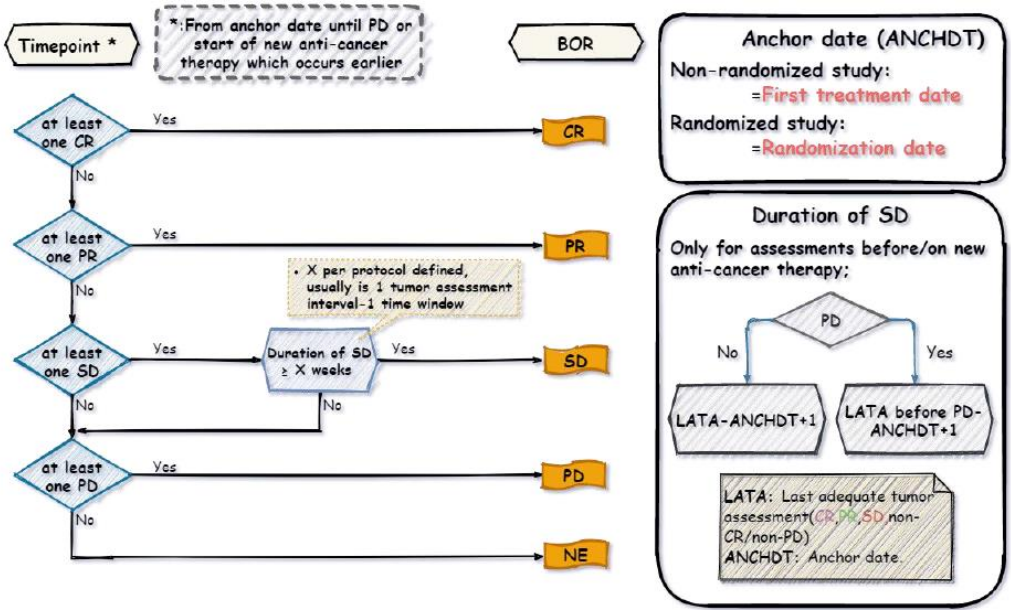

Figure 8 Best overall response without confirmation

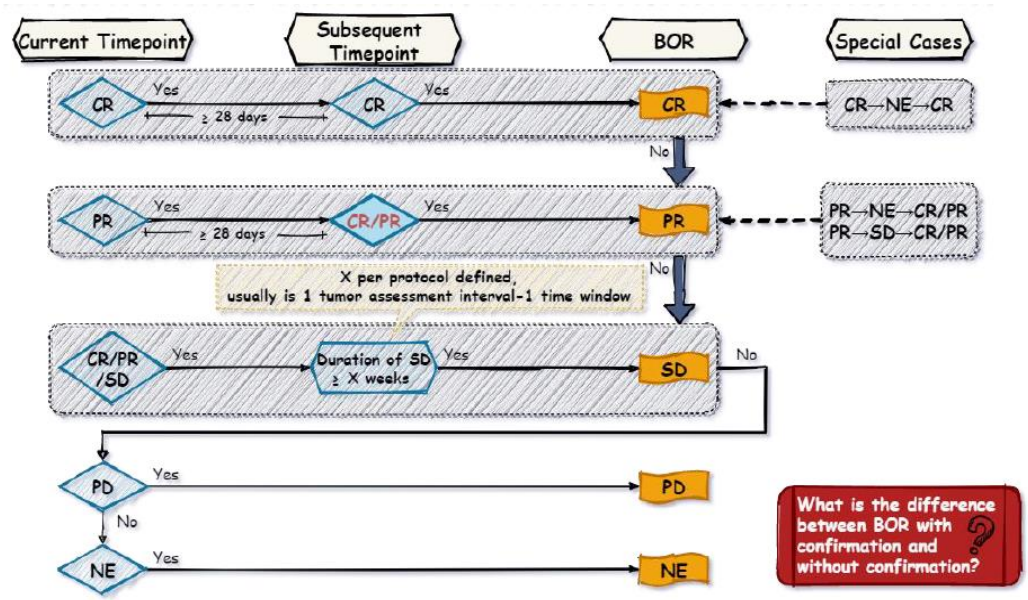

Figure 9 Best overall response with confirmation

FINAL OUTPUTS

Presentation:

In the presentation, despite explaining the content and details, usually covered in the traditional training, we focused on interpreting how to use our handbook. The design idea, the reading sequence, and key points are all included. Because our display format is novel and attractive, our colleagues concentrate more on the training.

Handbook:

We aggregated the slides used in presentations and published them into a handbook. Programmers can look it up at any time if necessary. Many logical diagrams and concept introductions are apparent, which can help learners review them in time when needed.

CONCLUSION

After the training, we conducted a survey to different levels of programmers to about 80 audiences in our department. Some juniors indicate this training is impressive and lucid compared with boring and rigid training, which can help them build up RECIST 1.1 knowledge system easily as a beginner in this area, and they also expect some examples or hands-on projects. Some seniors say this training is closely related to programming compared with the training from the medical department, and it is convenient for them to check knowledge when working on projects. Also, the training catches key points of RECIST 1.1 from a programmer's perspective.

All the positive comments show that the style of training and outputs can play a particular role in our daily work. However, some feedback pointed out some imperfections, and we wish to do better in the following training series.

DISCUSSION

RECIST 1.1 is the primary reference document on the efficacy evaluation of solid tumors. However, in a programmer's daily work, more knowledge is involved. Therefore, we additionally insert endpoint-related content that is commonly used in our study after the RECIST 1.1 part. Although this content does not directly come from the RECIST 1.1, it is closely linked with RECIST 1.1 and our daily work. Referring to the method or rule used in Beigene, we summarized and described endpoints with logic diagrams and roadmaps.

Since RECIST 1.1 itself is a combination of complicated concepts and rules, our handbook can only cover content with relative importance for statistical programmers. As a result, it is undeniable that our training has limitations in scope. Though it can meet daily use, programmers may need to consult extra materials, especially when they encounter special cases or complicated circumstances.

In addition, some rules in RECIST 1.1 are not monotonous. Rules and logic will be modified per protocols and Statistical Analysis Plan, such as durable stable disease. Therefore, we cannot exhaust all the possibilities.

Except for the differences between each company or each study, RECIST itself will also be updated. New trial designs, new drugs developing, and even new tumor imaging technologies may affect the details of RECIST. So, our handbook may also need to be updated accordingly.

REFERENCES

Reference

E.A. Eisenhauera, P. Therasseb, J. Bogaertsc, L.H. Schwartzd etc.2009. “New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)” European Journal of Cancer, 45:228–247.

Ankit Pathak. 2019. “From Lesion size to Best Response - Implementing RECIST through programming.” PharmaSUG 2019, BP-227. PharmaSUG.

Tool

Diagram.net: https://app.diagrams.net/

Github address: https://github.com/jgraph/drawio-desktop/releases/tag/v14.6.13

ACKNOWLEDGMENTS

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