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LETTER TO THE EDITOR

Cancer in young adulthood – classifying the intensity of treatment

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Background

Only 5% of all cancers are diagnosed in young adulthood [1], commonly defined as those aged 18–39, and studies of survivorship issues in this age group therefore often include several cancer diagnoses to reach a sufficient sample size. In order to take into account the impact of treatment on various aspects, such as health-related quality of life (HRQOL), it is essential to be able to compare treatments across diagnoses.

The Intensity of Treatment Rating Scale (ITR) 2.0 and the revised version 3.0 [2,3], were developed for pediatric oncology to enable comparisons of treatment intensity across protocols for different cancer types. These ITRs include cancer diagnoses most common in childhood and were developed to grade treatment intensity based on medical chart data. Treatment intensity is divided into four levels from least to most intensive based on diagnoses, stage, and treatment modality. However, in large-scale studies, medical chart data are not always available and thus, Tobin *et al.* further developed a methodology, based on ITR 3.0, to be used in registry-based studies [4].

Young adults, typically defined as 18–39 years of age, experience a different panorama of malignant diseases than both children and older adults, and their treatments differ from that of childhood cancer [1]. The ITR 2.0 and 3.0 have been used in studies including young adults, but only for selected diagnoses/treatments [5,6], and a corresponding tool for this particular population is lacking. This complicates the possibility to make comparisons and adjust for treatment intensity across diagnoses.

The aim of the present study was to adapt the ITR 3.0 to enable the measurement of treatment intensity in young adults during and after cancer treatment, and to evaluate its psychometric properties.

Material and methods

The present methodology was based on the process used to develop and revise ITR 2.0 and 3.0 [2,3], including several rounds of input from physicians, specialized in the field to create a preliminary version of the ITR and subsequent testing by a separate group of specialized physicians. The present study entailed the following three phases: adaptation of the ITR 3.0 to six diagnoses common in young adulthood, testing the feasibility and accuracy of the preliminary ITR Young Adult (ITR-YA), and examination of known-groups validity of the ITR-YA.

The Fex-Can cohort study

Adaptation of the ITR 3.0 was conducted as a part of the population-based cohort study Fertility and Sexuality following Cancer (Fex-Can) [7]. The study includes 1010 young adults (67% response rate) diagnosed during the period January 2016 through August 2017, who are followed the first five years after being diagnosed with cancer at ages 18–39 years. The diagnoses included in the Fex-Can Cohort study were selected based on the impact of the diseases and/or treatments on fertility and sexuality, and include breast cancer (women only), cervical cancer, ovarian cancer, lymphoma, testicular cancer and brain tumors. Patient-reported outcomes including HRQOL were collected approximately 1.5 years after diagnosis. Clinical data on disease and treatment were retrieved from the National cancer quality registers for the included diagnoses. Ethical approval

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was obtained from the Regional Ethical Review Board in Stockholm.

Adaptation of ITR 3.0

The original ITR 3.0 separates four levels of treatment intensity; least, moderately, very and most intensive [3], which were modified according to the cancer types, stage and current treatments for young adults. The adaptation was performed in collaboration with five specialized physicians representing the Swedish cancer quality registries of the diagnoses included in the Fex-Can Cohort study (cervical and ovarian cancer represented by the same physician) [8–12]. The adaptation included five rounds of discussions, a methodology similar to that used when ITR 2.0 and ITR 3.0 were developed [2,3]. First, a draft was developed, including types and numbers of treatment modalities for the four ITR levels. For those diagnoses represented in ITR 3.0 (germline tumors, lymphoma and brain tumors), that information was added to the first draft. The register representatives added details on diagnosis, stage and treatment for every level, based on the treatments recommended in the national guidelines for each diagnosis. Within every diagnosis, the contents of each level were modified in several rounds. Final changes were made to harmonize treatments between the diagnoses in collaboration with all the representatives to create a preliminary version of the ITR-YA. All patients included in the Fex-Can Cohort study were subsequently classified according to the preliminary version of the ITR-YA by one oncologist trained to classify all included diagnoses (Supplement 1).

After five rounds of discussions, the preliminary version of the ITR-YA was agreed upon by the group of representatives from the National quality registers. To emphasize the impact of treatment during a long period, and for patients with progressive or metastatic disease, the term 'extensive' was added to each level of the ITR-YA: Least intensive/extensive (level 1), Moderately intensive/extensive (level 2), Very intensive/extensive (level 3), and Most intensive/extensive (level 4) (Supplement 1).

Feasibility and accuracy of the ITR-YA

To examine the feasibility and accuracy of the preliminary version of the ITR-YA, a panel of 15 oncologists and hematologists working clinically at different hospitals around Sweden, otherwise not involved in this study, completed an online survey. The participating physicians were specialists in breast cancer oncology ($n = 4$), uro-oncology ($n = 3$), haematology/lymphomas ($n = 3$), gynaecological oncology ($n = 1$) and brain tumors ($n = 4$). The majority were women (60%) and 9/15 (60%) had worked more than 15 years in their specialty. Respondents were requested to apply the preliminary ITR-YA to classify 12 patient cases into the four ITR-YA levels using short descriptions of diagnosis, stage, treatment and treatment effect (based on data from the quality registers). The 12 patient cases represented the six cancer diagnoses, and each diagnosis was represented by patients from two different levels. In addition, respondents could comment on the ITR-YA in an open-ended question. A similar method for assessing inter-rater reliability has been used in the development of ITR 2.0 and 3.0 [2,3].

All 15 physicians were able to classify the 12 patient cases, which indicates the feasibility of the preliminary ITR-YA. Inter-rater reliability of the oncologists' ratings of the 12 patient cases indicated a high level of agreement between the physicians' ratings (0.83, range 0.64–1.0). For two of the patient cases, lower than expected rates of correct classification resulted in two changes to the preliminary ITR-YA. The first case was a patient with breast cancer who was misclassified by 40% of physicians due to misinterpretation of tamoxifen as GNRH-agonist, which was handled by adding 'not tamoxifen and/or aromatase inhibitor only' to GNRH-agonist at levels 2 and 3. The second case concerned a patient with a benign brain tumor treated with surgery only who was misclassified by 47%, which was handled by clarifying the different treatment options of the levels. In addition, physicians' written comments resulted in a revised lay-out of the ITR-YA where the different options in each level were clearly separated by 'OR' and a line break (Table 1) (Supplement 1).

Known-groups validation

Known-group validation was based on previous studies showing that treatment intensity and disease stage affect HRQOL [13–16]. To perform the known-group validation, we used data on treatment intensity and HRQOL from patients included in the Fex-Can Cohort study [7]. HRQOL was measured with the EORTC QLQ-C30 instrument [17], which includes five functional scales, three symptom scales, six single-item scales and a global health status scale. Known-groups validity was examined by testing if patients' ratings of two functional domains, physical (PF) and role functioning (RF), differed by level of treatment intensity. PF consists of five items regarding the level of help patients needs or the trouble they have in physical activities, while RF assesses a patient's ability to perform daily activities.

Statistical analyses

The accuracy of the ITR-YA was examined by calculation of inter-rater reliability using the kappa coefficient. Kappa coefficients were interpreted according to Cohen: 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement [18]. Known-groups validity was assessed by comparing means of PF and RF subscales of the EORTC QLQ-C30 between the four levels of the ITR-YA using the Kruskal-Wallis test, due to skewed distribution. Clinical significance was examined according to the established recommendations regarding the interpretation of EORTC QLQ-C30 values (scales 0–100). These specify that differences of 5–10, 10–20, and >20 correspond to minimally important, moderately important or considerable differences [19]. The SPSS version 25 software was used for statistical analyses and the p-value was set at 0.05.

Table 1. Intensity Treatment Rating Young Adult (ITR-YA) based on participants of the Fex-Can Cohort study: patients aged 18–39 years at diagnosis with one of six cancer types.

	Level 1 least intensive/ extensive treatments	Level 2 moderately intensive/ extensive treatments	Level 3 very intensive/extensive treatments	Level 4 most intensive/extensive treatments
Breast cancer	Surgery only ± tamoxifen and/or aromatase inhibitor	One of the following treatments: chemotherapy, radiotherapy or GNRH-agonist (not tamoxifen and/or aromatase inhibitor only), ± surgery	Two or more of the following treatments: chemotherapy, radiotherapy or GNRH-agonist (not tamoxifen and/or aromatase inhibitor only), ± surgery	Treatment of relapsing disease **OR** Metastatic disease at diagnosis
Cervical cancer	Surgery only (not bilateral SOE)	Surgery with bilateral SOE **OR** Neuroendocrine tumors: surgery + chemotherapy	Surgery + external beam radiotherapy + concurrent chemotherapy **OR** External beam radiotherapy + concurrent chemotherapy + brachytherapy	Treatment of relapsing disease **OR** Metastatic disease at diagnosis
Ovarian cancer	Surgery only (with unilateral SOE)	Stages I-II Surgery followed by chemotherapy	Stage III Extensive optimal surgery followed by one or more treatments (e.g., chemotherapy ± maintenance treatment)	Not optimal surgery/inoperable at diagnosis **OR** Treatment of relapsing disease **OR** Metastatic disease at diagnosis (stage IV)
Lymphoma	Indolent Non-Hodgkin lymphoma without treatment (watch and wait) or treated with surgery, antibiotics or immunotherapy only **OR** Indolent Non-Hodgkin lymphoma stage I (only radiotherapy)	Indolent Non-Hodgkin lymphoma stage II–III treated with moderate intensity (immuno-) chemotherapy (not anthracycline-containing) **OR** Hodgkin lymphoma: stage I-IIa and response to first line therapy	Stage II–III indolent Non-Hodgkin lymphoma treated with intensive anthracycline-containing (immuno-) chemotherapy with response to first-line therapy **OR** Aggressive Non-Hodgkin lymphoma all stages with response to first-line therapy **OR** Hodgkin lymphoma stage IIb, III and IV with response to first-line therapy	Hodgkin and Non-Hodgkin lymphomas that are non-responders (SD or PD) to first-line (immuno-) chemotherapy **OR** Relapse and treatment with second line therapy **OR** Responders to first-line treatment with consolidating stem cell transplantation
Testicular cancer	Stage I only surgery (orchiectomy)	Stage I surgery (orchiectomy) with adjuvant chemotherapy (typically 1 cycle)	Surgery (orchiectomy) + chemotherapy for metastatic disease (typically 3–4 cycles) ± RPLND **OR** Treatment of relapsing disease when treatment corresponds to surgery + 3–4 cycles of chemotherapy	Surgery (orchiectomy) + chemotherapy (>4 cycles) ± RPLND **OR** Treatment of relapsing disease containing chemotherapy > 4 cycles
Brain tumors	No treatment (radiological diagnosis) **OR** only biopsy (benign and malignant tumor)	Surgery (benign and malignant tumor)	Surgery followed by chemotherapy and/or radiotherapy **OR** Two or more treatments (e.g., radiotherapy + concomitant chemotherapy or other chemotherapy), ± surgery.	Treatment of relapsing disease **OR** Progressive disease (± craniospinal radiotherapy)

GNRH-agonist: gonadotropin-releasing hormone agonist; SOE: salpingo-oophorectomy; SD: stable disease; PD: progressive disease; RPLND: Retroperitoneal Lymph Node Dissection.

Results

ITR-YA

The final version of the ITR-YA consists of four levels of treatment intensity/extensivity (Table 1). The Level is based on diagnosis, stage and treatment modality, and stage and treatments are harmonized between diagnoses to enable comparisons between diseases. Treatment of relapsing disease is generally assessed as Level 4 except for testicular cancer, where metastatic disease can be assessed as Level 3 due to lower treatment intensity compared to relapsing disease in other diagnoses

Known-groups validation of ITR-YA

Of the participants in the Fex-Can Cohort study ($n = 1010$), 25 patients were excluded due to missing data in the registers and 985 (97.5%) were classified regarding ITR. Of the 985 patients, between one fifth and half were classified as level 1 (21% of men; 24% of women), level 2 (39% of men; 22% of women) and level 3 (35% of men; 51% of women), and few were classified as level 4 (5% of men; 2% of women). Both male and female patients classified with higher levels of the ITR-YA rated significantly worse PF and RF compared to those classified with lower levels of intensity

Table 2. Comparison of physical (PF) and role function (RF) ratings (EORTC QLQ-C30) between cancer patients ($n = 973$)[a] with different levels of treatment intensity, according to the Intensity Treatment Rating Young Adult (ITR-YA).

		Level 1 least intensive/extensive treatments mean (SD) median	Level 2 moderately intensive/extensive treatments mean (SD) median	Level 3 very intensive/extensive treatments mean (SD) median	Level 4 most intensive/extensive treatments mean (SD) median	P^b
Men ($n = 307$)	PF	**93** (12) 100	93 (10) 93	89 (17) 93	**79** (23) 87	$p = 0.014$
Men ($n = 307$)	RF	**89** (22) 100	86 (25) 100	**82** (26) 100	**67** (37) 83	$p = 0.009$
Women ($n = 666$)	PF	**89** (17) 100	**84** (20) 93	84 (16) 87	**80** (21) 83	$p < 0.001$
Women ($n = 662$)	RF	**85** (27) 100	70 (34) 83	**73** (30) 83	**60** (34) 58	$p < 0.001$

[a]Intensity treatment rating was missing for 25 patients due to missing data in the registers. Self-report of physical function (PF) was missing for 5 men and 7 women, and role function (RF) was missing for 5 men and 11 women due to incomplete responses by the patients. In total, data on ITR-YA x PF and ITR-YA x RF was missing for nine men, and for 28 and 32 women, respectively.
[b]Differences tested with Kruskall-Wallis test.
Differences in EORTC QLQ-C30 points marked with bold correspond to minimum clinically significant differences (≥5 points), $p < 0.05$.

treatment (Table 2). The most marked differences were between levels 1 and 4 with clinically significant differences (9 to 25 points), while mean values for levels 2 and 3 were similar (Table 2).

Discussion

In this study, we have developed a new rating scale for treatment intensity in young adults with cancer. To our knowledge, there is no such tool described in the literature previously for this group. We have adapted an existing rating scale for treatment intensity in pediatric oncology to classify treatments for six common cancer diagnoses during young adulthood. The newly developed ITR-YA enables the classification of patients according to treatment rated as least-, moderately-, very-, or most intensive/extensive. The ITR-YA was found to have high inter-rater reliability and to demonstrate known-groups validity. Moreover, the intensity of treatment was found to be associated with both physical and role function measured with EORTC QLQ-C30, which strengthens the validity of the ITR-YA. Previous studies have shown similar results, with more intensive treatment and a higher disease stage showing a negative effect on HRQOL [13–16]. Thus, the ITR-YA can be used to study how treatment intensity affects HRQOL among young adults with different cancer diagnoses.

The inter-rater reliability for the preliminary ITR-YA was slightly lower compared to the ITR 3.0 developed for pediatric oncology [3]. One possible explanation could be the imprecisions that were detected in the preliminary version of the ITR-YA and subsequently corrected in the final version. In addition, the fact that the physicians included in the present study were from different fields of oncology could have influenced the results as some of the diagnoses and treatments might not be familiar to all oncologists; in previous studies, everyone classifying patients was working solely with childhood cancer [2,3].

The newly developed ITR-YA seems to be a reliable tool for grading treatment intensity in six common cancer diagnoses. As young adults often are treated with similar treatment regimens as used in older patients, the ITR-YA could most likely also be used to classify treatments in older groups of patients. In addition, this classification could be extended and enable assessment of the impact of treatments on HRQOL among other tumors/cancers than the types treated in this study.

The strengths of the present study include the high coverage and good quality of the data in the national quality registries [11,12,20–22] and the close cooperation with the experienced physician representatives from each register [8–12]. In addition, the access to data from the Fex-Can Cohort study, with its population-based design, large sample size and high response rate increases the validity of the newly developed ITR-YA. Also, the low number of missing data both regarding treatment and HRQOL strengthens the results. The study also has some limitations that should be considered. Despite the high quality of the registry data, it cannot be ruled out that a few patients might have been classified to a lower level due to missing treatment information. Information on the progressive and metastatic disease was not clearly reported in all registers, which also may have affected the results.

Conclusions

The newly developed ITR-YA seems to be a reliable measure of treatment intensity in six common cancer diagnoses in young adults. The ITR-YA is recommended for use in clinical studies when comparisons of treatment intensity between diagnoses are needed.

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Disclosure statement

The authors report no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [CH], upon reasonable request.

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