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# Low Post-treatment Quality of Life and the High Incidence of Pain are Common and Significantly Exacerbated in Depressed Head and Neck Patients Treated with Definitive Accelerated Radiotherapy

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# Low Post-Treatment Quality of Life and the High Incidence of Pain Are Common and Significantly Exacerbated in Depressed Head and Neck Patients Treated with Definitive Accelerated Radiotherapy

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**Simple Summary:** Patients treated with definitive accelerated radiotherapy (DART) struggle with low quality of life, pain and persisting treatment-related symptoms even many years after the treatment. Everyday pain in the head, neck and shoulder areas is present among almost all HNC survivors treated with DART. One-third of the DART patients were depressed. The depressed group scored significantly worse in most of the quality of life subscales and suffered more intense pain than the non-depressed. Head and neck cancer survivors, especially those, who are depressed, may require additional psychosocial, physiotherapeutic and medical intervention programmes.

**Abstract:** (1) Background: The goal of the study was to evaluate psychological tolerance and health-related quality of life (QOL) in head and neck (HN) cancer patients treated with definitive accelerated radiotherapy (DART); (2) Methods: Seventy-six recurrence-free patients eligible for the study, who were treated with DART in the CAIR-2 phase III clinical study (median of follow-up=47 months), completed EORTC QLQ-C30 with H&N35 module, Hospital Anxiety and Depression Scale (HADS) and Visual–Analog Scales (VAS) of pain in HN and the neck / arm area.; (3) Results: The most dominating symptoms measured with QLQ-C30 were: fatigue (44/100), sleeplessness (39/100), financial problems (38/100) and pain (32/100). Within H&N35 the highest scores were reported on the subscales of sticky saliva (60/100), mouth dryness (65/100) and increased intake of painkillers (50/100). Pain (VAS) was reported by 87% (HN area) and 78% (shoulder) of the patients, with a mean score of 3/10. One-third reported depressive mood (HADS≥15 points) with an average score of 12.5/42 p. The depressed group, who smoked more as compared to non-depressed before DART (96% vs 78%) and required steroids treatment (85% vs 58%) during DART, also scored significantly worse on 23 of 35 subscales of QLQ-C30 and H&N35 and experienced more intense pain (VAS). Women, and less advanced patients scored better in several aspects of the quality of life; (4) Conclusions: Patients treated with DART struggle with low quality of life and persisting treatment-related symptoms including constant pain. HNC survivors, especially those, who are depressed, may require additional psychosocial, rehabilitation and medical intervention programs..

**Keywords:** definitive accelerated radiotherapy; depression; chronic pain; head and neck cancer; quality of life

## 1. Introduction

Most quality-of-life studies of head and neck cancer survivors showed that the patients are struggling with distress, depression, pain and a large variety of persisting cancer-related symptoms. Quality of life domains like the global quality of life, pain, eating and speech problems [1,2,3,4] were associated with survival in HN. Shorter overall survival is also present in the case of pre-existing depression or depressive states [5,6].

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The 3-40% prevalence of depression after treatment of HNC was noted in various studies [7]. Depression and distress were found during the first year after treatment [8] and also during the long time of follow-up [9,10,11]. The advanced disease, being unmarried, and helpless/hopeless coping strategies were predictors of depressed mood in the head and cancer [12]. More depressive symptoms in HNC survivors were also found in groups with moderate to severe dysphagia [13] and in patients with a gastrostomy tube [14].

Persisting or worsening treatment-related symptoms after treatment of HNC were reported in various prospective studies [15,16,17,18,19]. In a large cross-sectional study of 640 HNC cancer survivors (median of follow-up 4,3 years) dry mouth, sticky saliva and teeth problems were the most severe symptoms reported by the patients [20]. Intimacy problems and sexual dysfunctions were reported by 25% of patients after primary HNC treatment [21].

Modification of the standard radiotherapy (once a day for five days a week, fractionation dose of 1.8 to 2 Gy, for five to seven weeks) in head and neck cancer patients entails an increase in the severity of acute (observed during and shortly after treatment) radiation-induced toxicities, mainly mucositis. However, in most reports, the incidence and intensity of late complications (xerostomia, tissue fibrosis, taste impairment) remain similar in patients after standard radiotherapy and those treated with the use of various ways of modifying standard treatment (hyperfractionation, accelerated fractionation, accelerated hyperfractionation) [22, 23, 24, 25, 26].

Meta-analysis of 6515 head and neck cancer patients from 15 different studies who were treated with different types of altered fractionated radiotherapy showed that it can improve both survival and locoregional control [25]. Although hyperfractionated or accelerated radiotherapy with or without total dose reduction gained a lot of scientific attention, there are only a few studies that explored the detailed quality of life and/or psychological tolerance of altered fractionated radiotherapy using various measurement tools.

Several existing studies on hyperfractionated radiotherapy using different measurement methods showed no differences in most dimensions of QOL after treatment between conventionally and hyperfractionated groups [11,27,28,29]. The longitudinal study comparing accelerated versus conventional radiotherapy in 750 HNC patients showed the worse quality of life in the AR group at the end of radiotherapy, with most differences observed three, several at and six months and five years later. Oral functions have never reached the baseline level in both groups [30]. Detailed quality of life in definitive accelerated radiotherapy was also described in another two studies [31,32] but they were difficult to analyse due to group heterogeneity (several patients received chemotherapy or/and had neck dissection.

Noteworthy, the late toxicities of radiotherapy can be assessed by using various scales, such as LENT/SOMA, RTOG/EORTC, and NCI-CTC. Therefore, the observed severity of late complications may vary depending on the selected reporting method [33 Denis et al. 2003]. Subscales in the above-mentioned scales do not consider psychological and socio-economic factors. After all, the quality of life after radiotherapy is a result not only of the observed morphological or functional defects but also of accompanying diseases (somatic and mental), lifestyle (nutrition, smoking), or the already mentioned aspects related to the economic status of patients.

Although there are a few publications on detailed quality of life after hyperfractionated radiotherapy of HNC patients, up till now no such publications are focused exclusively on Definitive Accelerated Radiotherapy in HNC without any chemotherapy or surgery. There are no QOL studies concerning further psychological evaluation that would be more detailed than basic QOL in HNC patients treated with DART. The purpose of the study was to examine the quality of life and psychological tolerance of patients who were treated with definitive accelerated radiotherapy.

## 2. Materials and Methods

This is a cross-sectional survey of HNC patients with follow-ups longer than 12 months. All patients included in this study took part in the CAIR-2 phase III clinical trial [34] guided in the Ist Radiotherapy Department, Comprehensive Cancer Center Marie Skłodowska-Curie Institute of Oncology Gliwice Branch. All patients with squamous cell carcinoma of head and neck in Stage T(2-

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4)N(0-1)M(0) received two definitive radiation treatments: accelerated fractionation 7 days a week including weekends (CAIR) or 7 fractions 5 days a week (Concomitant Boost, CB). Fractionation parameters remained within the ranges: 66.6-72 Gy of the total dose, 37-40 fractions and 37-40 days. Most of the patients had received conformal radiotherapy (2D – 14%, 3D – 45%, IMRT-25%, 3D+IMRT-16%), see Table 1.

Due to results showing that weekend breaks have no impact on treatment outcome if radiotherapy is accelerated [34], with the same dose and treatment time, the quality of life scores of CB and CAIR groups were analysed as one DART group altogether. For patients' initial characteristics see Table 1.

Out of 184 patients who were treated with DART in the years 1995-2006, 24 of them were deceased at the time of the study. All the patients who agreed to take part in the study signed the written consent and agreed to fill out the set of psychological and QOL tests. Seventy-eight patients were sent back or brought filled questionnaires. Two patients were excluded from the study because of secondary cancers. The follow-up time median was 47 months after completing the treatment varying from 12 to 158 months (ibid.).

**Table 1.** Initial patients and treatment characteristics.

| **Patients & treatment characteristics** | |
|---|---|
| CAIR-2 phase III clinical trial participants | 184pts |
| Deceased at the time of the study | 24 |
| Eligible for the study | 160 |
| Patients who filled QOL tests | 78 (2 excluded due to secondary cancer) |
| Tests included into study | 76 |
| Response rate | 48% |
| Age | Median: 64 y |
| Gender | men - 70%,<br>women - 30% |
| Marital status | married - 79%,<br>widowed - 13%,<br>single - 6,7%,<br>divorced -1,3% |
| Education and overall years of education) | primary school (8y) – 20%,<br>secondary school (11y) – 39%,<br>high school (12y) – 33%,<br>master's degree (16y) – 8% |
| Smoking tobacco before DART | 84% |
| Cancer symptoms before diagnosis | median: 5,5 months (1–84) |
| Time from diagnosis to treatment | median: 49 days (15–188) |
| Tracheostomy before DART | 0 |
| Feeding tube during DART | 4% |
| Neck dissection or surgery before DART | 0 |
| ZUBROD status before DART<br>ZUBROD status after DART | 0 – 80%, 1 – 18.7%, 2 – 1.3 %,<br>0 – 70%, 1 – 28.7%, 2 –1.3% |
| Weight loss during the treatment | Mean = -2,4kg (-12,3kg +7,9kg) |
| Analgesics type during and after DART | no analgesics – 3%,<br>regional - 9%,<br>NSAIDs+tramadol - 72%,<br>opiates - 16% |
| Analgesics intake (days) | median: 21 days (5-173) |
| Dysphagia during and after DART | no dysphagia - 41%,<br>mixed food - 51%,<br>liquids only - 8% |
| Dysphagia (days | median: 20 days (6-189) |
| Corticosteroids intake during and directly after DART | 68% |
| Corticosteroids intake (days) | median: 20 days (1-50) |

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| | |
|---|---|
| Length of follow-up | Median: 47 months (12-158) |
| TNM classification<br>T<br>N | <br>T2 - 53%, T3 - 23%,T4 - 24%,<br>N0 - 69%, N1 - 31% |
| Location: | hypopharynx - 8%,<br>oropharynx - 25%,<br>larynx - 53%<br>oral cavity- 14% |
| Technique<br>Fraction schedule<br>Total dose<br>No of fractions/days | 2D - 14%, 3D - 45%, IMRT - 25%, 3D+IMRT - 16%<br>1.8Gy/fx<br>66.6-72 Gy<br>37-40 fractions and 37-40 days |

Observer-based scoring systems like the DAHANCA toxicity score or CTCAE are not recognizing many symptoms of HN patients contrary to the quality of life scales which refer to their own complaints [35]. Therefore detailed QOL research in head and neck cancer requires the usage of patient-based surveys, especially in clinical trials. Quality of life research on head and neck cancer may be currently measured with 13 measurement tools designed exclusively for HNC patients [36]. Researchers are also using general quality-of-life questionnaires like for example the EORTC QLQ-C30 for cancer patients or SF-36 for the general population.

Instruments selected for this study are well-known tools measuring the quality of life, pain and psychological status of patients. Health-related quality of life of HNC patients was measured with the EORTC QLQ-C30 with head and neck module H&N35 [37,38]. Scores of QLQ-C30 and H&N35 range from 0 to 100. The higher are scores on functional subscales of QLQ-C30, the better the patient's functioning. Scores of H&N35 are symptom scales, so a higher result means that the symptom is more severe.

Baseline T and N status and patient's gender were used as independent data to compare the intergroup differences in QOL and treatment-related data. Quality-of-life outcomes of the DART group were compared to the results of 640 HNC patients with a similar median follow-up [20] who completed QLQ-C30 and H&N35 and were treated with different types of radiotherapy with doses ranging from 54 to 79 Gy. A subgroup of 359 patients (67%) received the dose>70,2 GY, 371 patients were treated by 2DRT and 269 patients by conformal RT (3DCRT: 127 patients, IMRT: 142 patients). The clinically significant differences – of 10 points and more [38] between the groups in all QLQ-C30 subscales were analysed.

Two VAS scales, ranging from 0 to 10 points [40] were used to evaluate pain intensity in the head/neck area and, separately, in the shoulder area.

Depression and anxiety were examined with HADS - Hospital Anxiety and Depression Scale [41, 42]. HAD scale is recognized as a sensitive instrument to screen for depressive symptomatology in HNC [43] Sum of anxiety and depression subscales was also examined, 15 points are the cut-off score for recognizing major depression in HNC patients (ibid.). Patient's QOL and VAS outcomes, initial characteristics including age, gender, marital status, education, smoking, TNM, presence of cancer symptoms before diagnosis, time from diagnosis to treatment ZUBROD, dose, irradiation method, corticosteroids and analgesics intake, dysphagia (see tab1) were analysed using the HADS cut-off score. Data were analysed with the non-parametric method – the Mann-Whitney U test.

## 3. Results

Patients reached the highest scores in role (85/100), social (79/100) and cognitive functioning (73/100) subscales. Fatigue (44/100), insomnia (39/100) and financial problems (38/100) were the most severe symptoms of QLQ-C30 reported by the patients. Out of the scores of H&N35, mouth dryness (65/100), sticky saliva (61/100) and painkillers intake (50/100) were the most severe symptoms, see Table 2. As compared to the large HNC survivors group who completed radiotherapy with similar time of the follow-up [20], DART group scored worse significantly worse with 10 points or more - a

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clinically significant difference, [39] in physical, emotional and financial functioning, the intensity of fatigue, insomnia, sexuality, dry mouth, sticky saliva and coughing.

**Table 2.** Results of QLQ-C30 and H&N35 of DART survivors with a follow-up median of 47 months compared with 640 HNC survivors with a similar median of follow-up who had various radiotherapy treatments from Leung et al [20].

| **QLQ-C30 and H&N 35 Subscales** (range 0-100) | **DART survivors** n=76 (sexuality scale n=63) median of follow-up: 47m. | | **Leung et al, 2011g** n=640 median of follow-up 51m | | **Clinically significant difference - 10 points or more between the means** |
|---|---|---|---|---|---|
| | Mean (sd) | Median | Mean (sd) | Median | |
| **QLQ-C30 Functional scales:** | | | | | |
| Global health status | 58,6 (23,1) | 58,3 | 54.6 (19.9) | 50 | ↑4 |
| Physical functioning | 68,9 (20,2) | 68,7 | 84.5 (16,5) | 86.7 | ↓**15,6** |
| Role functioning | 85,7 (19,4) | 100 | 86,4 (21) | 100.0 | ↓0,7 |
| Emotional functioning | 62,9 (23,2) | 66,7 | 77,9 (20) | 75.0 | ↓**15** |
| Cognitive functioning | 73,1 (21,2) | 66,7 | 78,4 (19,8) | 83.3 | ↓5,3 |
| Social functioning | 80,1 (25) | 83,3 | 75,1 (24,2) | 66.7 | ↑5 |
| **QLQ-C30 Symptom scales:** | | | | | |
| Fatigue FA | 43,6 (25,6) 8,9 | 44,3 | 29,2 (20,04) | 33.3 | ↓**14,4** |
| Nausea and vomiting NV | (15,1) | 0 | 9.3 (17,5) | 0.0 | ↑0,4 |
| Pain PA | 32,40(28,4) | 33,3 | 21,9 (22,4) | 16.7 | ↓**10,5** |
| Dyspnea DY | 20,4 (26,2) | 0 | 15,2 (21,16) | 0.0 | ↓5,2 |
| Insomnia | 38,8 (33,8) | 44,4 | 26,3 (25,9) | 33.3 | ↓**12,4** |
| Appetite loss AP | 29,7 (26,9) | 30 | 19,9 (24,6) | 0.0 | ↓2,6 |
| Constipation CO | 22,5 (28,2) | 0 | 19,1 (23,7) | 33.3 | ↓3,4 |
| Diarrhea DI | 10,3 (15,3) | 0 | 14 (19,9) | 0.0 | ↓3,7 |
| Financial difficulties FI | 37,6 (38,8) | 33,3 | 26,4 (27,1) | 33.3 | ↓**11,2** |
| **H&N35 (symptoms scales)** | 28,2 (21,5) | | | | ↓9,1 |
| HN pain HNPA | 26,7 (25,4) | 25 | 19,1 (20,6) | | ↓3,5 |
| Swallowing problems HNSW | 31,2 (30,6) | 16,7 | 30,2 (24,4) | 16.7 | ↓4,39 |
| Senses problems HNSE | 28,9 (23,7) | 33 | 26,9 (27,7) | 25.0 | ↓0,9 |
| Speech HNSP | 28,7 (26,6) | 22 | 28 (25,9) | 25.0 | ↓0,9 |
| Social eating HNSO | 19,6 (19,9) | 25 | 28,5 (26,9) | 22.2 | ↓0,8 |
| Social contact HNSC | 38,6 (34,9) | 13 | 20,4 (23,5) | 25.0 | ↓**12,6** |
| Less sexuality HNSX | 26 (36,5) | 33 | 26 (27,7) | 13.3 | ↑**12,9** |
| Teeth HNTE | 27,4 (37,8) | 0 | 38,9 (29,8) | 33.3 | ↑5,4 |
| Opening mouth HNOM | 64,8 (32,3) | 0 | 32,8 (31,6) | 33.3 | ↓**16,5** |
| Dry mouth HNDR | 60,7 (34,8) | 66,7 | 48,3 (31) | 33.3 | ↓**20** |
| Sticky saliva HNSS | 42,7 (31) | 66,7 | 40,7 (30,6) | 33.3 | ↓**13,4** |
| Coughing HNCO | 36,5 (32,5) | 33,3 | 29,3 (25,4) | 33.3 | ↓7,2 |
| Feeling ill HNFI | | 33,3 | 29,3 (25,3) | | |
| **H&N35 single items** | | | Not analysed | | |
| Painkillers HNPK | 50 (50) | | - | - | - |
| Nutritional supplements HNNU | 18,9 (39,4) | 50 | - | - | - |
| Feeding tube HNFE | | 0 | - | - | - |
| Weight loss HNWL | 0 | 0 | - | - | - |
| Weight gain HNWG | 24,3 (43) | 0 | - | - | - |
| | 36 (48,3) | 0 | - | | - |

Inter-group differences were analysed in all treatment-related, biological, QOL, and psychosocial variables (see tab 1) using such grouping factors as gender, T and N stage and cut off score for the depression (clinically relevant overall HADS score ≥15 points). All statistically

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significant results are presented in Table 3. Results for all groups are presented as means, not medians, due to the character of single-item questions of QLQ-C30 and H&N35 modules where the median is always 1 or 0.

Women initially lost less weight during radiotherapy as compared to men. They reported a lower frequency of pain in the head and neck area measured by the H&N35 subscale ($p<0,05$), fewer swallowing problems ($p<0,01$), and fewer problems with eating in the public ($p<0,05$). Men reported also more severe appetite loss ($p<0,05$) and more problems with sticky saliva ($p<0,05$, Table 3).

Two groups of 42 patients with T2 and 34 patients with T3 and T4 categories were analysed. Patients with a more advanced T category reported significantly worse cognitive functioning ($p<0,05$), more problems with opening the mouth ($p<0,01$), with speech ($p<0,02$) and also with social eating ($p<0,02$). They also reported more frequent pain in the head and neck area ($p<0,05$). Patients with N0 advancement (n=52) were compared to the N1 group (n=24). Nodal advancement was associated with worse cognitive functioning ($p<0,05$), problems with the opening mouth ($p<0,02$) and feeling senses ($p<0,01$), trouble with social eating ($p<0.01$) and dysphagia ($p<0,05$) during the treatment (see Table 3).

**Table 3.** Statistically significant differences in mood, pain, QoL and medical data depending on gender, T and N status.

| Variables | Test type (if relevant) | Grouping variable vs mean/ median results for analyzed groups | | p value Mann-Whitney U-test |
|---|---|---|---|---|
| | | **Gender** | | |
| | | **men (M/ME)** | **women (M/ME)** | |
| Appetite loss AP | QLQ-C30 | 33 / 33,3 | 23 / 0 | <0,05 |
| Pain of H&N area – HNPA | H&N35 | 32 / 33,3 | 20 / 16,7 | <0,05 |
| Sticky saliva HNSS | H&N35 | 32 / 33,3 | 16 / 8,3 | <0,01 |
| Swallowing problems HNSW | H&N35 | 67/ 66,7 | 47 / 33,3 | <0,05 |
| Social eating HNSO | H&N35 | 33 / 25 | 20 / 16,7 | <0,05 |
| Weight loss during RT (kg) | - | -2,9 / -2,7 | -1,2 / -0,8 | <0,05 |
| | | **T-stage** | | |
| | | **T2 (M/ME)** | **T3+T4 (M/Me)** | |
| Cognitive functioning CF | QLQ-C30 | 78 / 83 | 66 / 66,7 | <0,01 |
| Opening mouth HNOM | H&N35 | 17 / 0 | 42 / 33,3 | <0,01 |
| Pain of H&N area – HNPA | H&N35 | 23 / 25 | 35 33,3 | <0,05 |
| Speech problems HNSP | H&N35 | 25 / 22,2 | 34 / 33,3 | <0,05 |
| Social eating HNSO | H&N35 | 23 / 16,7 | 37 / 33,3 | <0,05 |
| | | **N-stage** | | |
| | | **N0 (M/ME)** | **N1 (M/ME)** | |
| Cognitive functioning CF | QLQ-C30 | 77 / 83,3 | 64 / 66,7 | <0,05 |
| Opening mouth HNOM | H&N35 | 18 / 16,7 | 45 / 33,3 | <0,05 |
| Senses problems HNSE | H&N35 | 24 / 16,7 | 44 / 37,5 | <0,01 |
| Social eating HNSO | H&N35 | 23 / 16.7 | 40 / 33,3 | <0,01 |
| Dysphagia during DART (mixed food or liquids only) | - | 58% | 87% | <0,05 |

The intensity of pain in the head and neck (HN) area scored 3.4 on the VAS scale (1-3 points pain on 0-10 VAS is considered a weak pain). The pain in the shoulder area both scored 2,9. Only 10 patients (13%) didn't report any pain. That suggests that the majority of patients experienced some kind of HN pain. A very intense HN pain (7-10p) was reported by 10% of patients. Pain in the shoulder was reported by 78% of patients. In most cases, the intensity of pain was weak or moderate (see Table 4).

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**Table 4.** The mood (HADS) and intensity of the pain (VAS) in the DART group.

| Mood (HADS) | Results | Std dev | Median/ quartiles |
|---|---|---|---|
| Depression (0-21p.) | mean=6 | 4,53 | |
| Anxiety (0-21p.) | mean=7 | 4.41 | 5 (2-9) |
| Sum of depression + anxiety | mean=12,5 | 8,37 | 6 (2.5-10) |
| % of possible major depression outcomes (≥15 points) | 27% | | 10.5 (6-18) |
| **Intensity of Pain (VAS, 0-10p.)** | | | |
| Pain of the head and neck area | mean=3.4 | | |
| no pain (0 points) | 13% | | 3(1-5) |
| weak pain (1-3 p) | 37% | 2,46 | |
| moderate pain (4-6p) | 40% | | |
| strong pain (7-10p) | 10% | | |
| Pain of the shoulder area | mean=2.9 | | |
| no pain (0 points) | 22% | | |
| weak pain (1-3 p) | 41% | 2,44 | 3 (1-5) |
| moderate pain (4-6p) | 32% | | |
| strong pain (7-10p) | 4,5% | | |

The analysis revealed a low average level of depression and anxiety in the whole group (below 8 points - 6/21p and 7/21p respectively). The clinically significant level of overall HADS score (15 points and more, [37] signifying possible major depression was reached by 27% of patients. The mean result was 12.25 points – below the cut-off score (Table 4).

Comparing the depressed group (27%) to the non-depressed has revealed many significant differences within variables like smoking before treatment, corticosteroids intake during and directly post-treatment, quality of life data, emotional states and traits and pain. They reported worse social, emotional and cognitive functioning and lower global health status. The intensity and frequency of pain were greater in the depressed group. Treatment-related symptoms except the pain were also more frequent in the depressed group including fatigue, insomnia, appetite loss, swallowing, speech, social eating and contact, mouth opening, mouth dryness, sticky saliva, deterioration of sexuality, coughing, painkillers intake and weight loss, scoring worse in 23 subscales out of 35 in QLQ-C-30 and H&N35. The depressed were smoking before DART and they had to take corticosteroids during and right after DART more often than non-depressed. Patients' initial biological characteristics and medical status 3,5y after the survey timeline didn't differ in both subgroups. Statistically significant differences are listed in Table 5.

**Table 5.** Significant differences between depressed and non-depressed group (Mann-Whitney's U Test).

| Variables | Test type | Mean results for analyzed groups | | | | p value |
|---|---|---|---|---|---|---|
| | | Depressed group (27%) | | Non-depressed (73%) | | |
| Pretreatment/treatment data | | | | | | |
| Smoking tobacco before RT | - | 96% | | 78% | | <0,05 |
| Steroids intake during RT | - | 85% | | 58% | | <0,05 |
| | | mean | median | mean | median | |
| Intensity of pain of head/neck (0-10) | VAS | 4,7 | 5 | 2,6 | 2 | <0,001 |
| Intensity of shoulder pain (0-10) | VAS | 4,4 | 5 | 2 | 2 | <0,001 |
| **Functional scores (0-100)** | | | | | | |
| Global health status QL2 | | 41,3 | 45 | 66,2 | 66,7 | <0,000001 |
| Physical functioning PF | | 60 | 60 | 74,2 | 80 | <0,001 |
| Emotional functioning EF | QLQ-C30 | 44,7 | 41,7 | 73,7 | 75 | <0,000001 |
| Cognitive functioning CF | | 65,9 | 66,7 | 77,4 | 83.3 | <0,05 |
| Social functioning SF | | 70,2 | 66,7 | 85 | 100 | <0,05 |
| **Symptom scores (0-100)** | | | | | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Fatigue FA | | 53,9 | 55,6 | 37,6/ | 33,3 | <0,01 |
| Pain (frequency) PA | | 53,2 | 50 | 20,9 | 16,7 | <0,000001 |
| Dyspnea DY | | 28 | 33,3 | 15,9 | 0 | <0,05 |
| Insomnia SL | | 58,8 | 66,7 | 27,5 | 33,3 | <0,001 |
| Appetite loss AP | | 44,7 | 33,3 | 21 | 33,3 | <0,01 |
| **Symptom scores (0-100)** | | | | | | |
| HN pain (frequency) HNPA | H&N35 | 40,4 | 33,3 | 21 | 16.7 | <0,001 |
| Swallowing problems HNSW | | 40,7 | 33,3 | 18,4 | 8.3 | <0,001 |
| Speech HNSP | | 38,3 | 33,3 | 23,4 | 22,2 | <0,05 |
| Social eating HNSC | | 40,7 | 26,7 | 21,7 | 6,7 | <0,01 |
| Social contact HNSO | | 29,6 | 33,3 | 13,7 | 16,7 | <0,001 |
| Less sexuality HNSX | | 53,6 | 50 | 29,9 | 16,7 | <0,05 |
| Opening mouth HNOM | | 45,7 | 33,3 | 16,7 | 0 | <0,01 |
| Dry mouth HNDR | | 81,5 | 100 | 55 | 33,3 | <0,01 |
| Sticky saliva HNSS | | 74,1 | 100 | 52,9 | 33,3 | <0,05 |
| Coughing HNCO | | 53,1 | 66,7 | 36,8 | 33,3 | <0,05 |
| Feeling ill HNFI | | 57,7 | 33,3 | 24,8 | 33,3 | <0,0001 |
| Painkillers HNPK | | 74,1 | 100 | 34,8 | 0 | <0,01 |
| Weight loss HNWL | | 44,4 | 0 | 12,7/ | 0 | <0,01 |

## 4. Discussion

The experience of persisting pain dominates among other symptoms despite using painkillers and coming to follow-up visits. A large majority of DART-treated patients reported pain in the head/neck and shoulder area (87% and 78% respectively). Other studies on quality of life in HNC also showed that pain and other treatment-related symptoms are persisting or worsening during follow-ups longer than 1 year [15,17,18,19]. The pain in the DART group both in the HN area and arm and shoulder after cancer treatment persisted or possibly deteriorated over the years after the treatment. A meta-analysis of 82 studies evaluating pain in HNC patients treated according to various schemes estimated the incidence of any pain in 57% of patients before treatment and 42% after the treatment [44]. This result shows a much better outcome than the results of DART patients, where intensification of pain in the head and neck area concerned almost all of the examined patients. The intensity of pain in the analysed DART group was also found to be higher than in another study of the severity of pain in patients with HNC before and after radiation treatment with VAS up to 24 months after the treatment [45].

Persisting treatment–related symptoms are consistent with already existing research on QOL in H&N. Patients scored high on QOL dimensions such as functioning in the role, social and cognitive areas. Fatigue, insomnia and financial difficulties were the most common symptoms from QLQ-C30 subscales reported by patients treated with DART. Sticky saliva, mouth dryness and painkillers intake had the highest scores out of all subscales from the H&N35 module. Generally, the patients were functioning better in social, emotional and cognitive dimensions as compared to treatment-related ailments.

As compared to a large sample of HNC survivors from the Leung et al. study (see tab. ) with a similar median of follow-up but with several different irradiation types [20], DART patients reported worse functioning in most analysed QoL dimensions except for global health status, social functioning and mouth opening. DART patients scored significantly worse – with more than 10 points [39] on subscales of physical functioning, emotional functioning, fatigue, pain, insomnia, and financial difficulties. The largest, clinically relevant differences within treatment-specific symptoms (H&N35) between DART and the other group were found on subscales evaluating sticky saliva, dry mouth, coughing, and diminished sexuality.

These results might be corresponding to a quality of life study comparing accelerated fractionation to conventional by Nyqvist et al [30]. The reduction of the treatment time resulting in dose intensification is directly related to persistently low quality of life outcomes.

Reasons for gender differences in quality of life and psychological outcome remain unclear. Different QoL studies present contradictory results while comparing the QoL of men and women

treated for HNC [46, 47]. Inter-group differences depending on T and N status seem to be mostly associated with more intensive treatment in case of more advanced disease.

Although the mean results on depression, anxiety or overall HADS score were below the clinically relevant score, one-third (27 % of the patients) scored more than 15 points of the major depression cut-off score. That shows that one-third of this group had a poor psychological outcome. Results comparing depressed and non-depressed groups revealed many significant differences in quality of life subscales, emotional states and pain. Deterioration of quality of life and increased pain are linked to depression in cancer. [48,49,50].

More common corticosteroid intake during DART in the depressed group suggests that their treatment caused more intensive symptoms of acute mucositis and might have been more difficult to bear. Previous intake of corticosteroids by cancer patients is linked to depressive symptomatology following such treatment. [51].

The depressed DART group significantly admitted more often to smoking before the treatment. Prevalence of depressive symptoms is also often related to fear of recurrence in head and neck cancer survivors which might be one of the possible reasons [52,53]. Level of cigarette consumption was a predictor of psychological distress 15 months after treatment in head and neck cancer survivors. Smoking was also linked to baseline distress and fear of recurrence [54].

A review of existing research on the comorbidity of pain and depression showed that pain and depression occur simultaneously in approximately 35% of patients (22-49%) [55]. A longitudinal study examining the relationship between the occurrence of pain and mood disorders in cancer patients also showed the interdependence of both symptoms. Patients responding well to analgesic treatment (61%) had significantly lower HADS scores within a few weeks, unlike people who had no improvement in pain [56]

## 5. Conclusions

All results from this cross-sectional study allow drawing limited conclusions only. Nevertheless, patients treated with DART struggle with low quality of life and persisting treatment-related symptoms including constant pain. Pain and multifaceted psychological and somatic ailments dominate the profile of self-rated quality of life.

The intensity of distress/depression strongly affects patients' perception and reception of post-treatment symptoms and general functioning. Both facts are consistent with the quality of life research on HNC survivors after different kinds of treatment. The presence of depression in DART co-exists with intensive post-treatment oral symptoms, weight loss, and lower QOL. The level of self-rated depression and distress might be the factor distinguishing between the patient who can receive standard and the one who needs non-standard, more intensive care. Screening for distress/depression should become part of conventional follow-up visits after DART. HNC survivors, who are depressed, may require additional psychosocial, physiotherapeutic and medical intervention programmes.

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