

Neo-adjuvant Chemo-Radiation to 60 Gray Followed by Surgery for Locally Advanced Non-Small Cell Lung Cancer Patients: Evaluation of Trimodality Strategy

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ABSTRACT: **Background:** Neoadjuvant chemo-radiation therapy (CRT) dosages in locally advanced non-small cell lung cancer (NSCLC) were traditionally limited to 45 Gray (Gy).

Objectives: To retrospectively analyze outcomes of patients treated with 60 Gy CRT followed by surgery.

Methods: A retrospective chart review identified patients selected for CRT to 60 Gy followed by surgery between August 2012 and April 2016. Selection for surgery was based on the extent of disease, cardiopulmonary function, and response to treatment. Pathological response after neoadjuvant CRT was scored using the modified tumor regression grading. Local control (LC), disease free survival (DFS), and overall survival (OS) were estimated by the Kaplan–Meier method.

Results: Our cohort included 52 patients: 75% (39/52) were stage IIIA. A radiation dose of 60 Gy (range 50–62Gy) was delivered in 82.7%. Surgeries performed included: lobectomy, chest-wall resection, and pneumonectomy in 67.3%, 13.4%, and 19.2%, respectively. At median follow-up of 22.4 months, the 3 year OS was 74% (95% confidence interval [CI] 52–87%), LC was 84% (95%CI 65–93), and DFS 35% (95%CI 14–59). Grade 4–5 postoperative complications were observed in 17.3% of cases and included chest wall necrosis (5.7%), bronchopleural fistula (7.7%), and death (3.8%). A major pathologic regression with < 10% residual tumor occurred in 68.7% of patients (36/52) and showed a trend to improved OS ($P = 0.1$). Pneumonectomy cases had statistically worse OS ($P = 0.01$).

Conclusions: Major pathologic regression was observed in 68.7% with 60 Gy neoadjuvant CRT with a trend to improved survival. Pneumonectomy correlated with worse survival.

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KEY WORDS: locally advanced non-small cell lung cancer (NSCLC), neoadjuvant chemo-radiation therapy (CRT), completion lobectomy, pathologic response, trimodality

Neoadjuvant chemo-radiation therapy (CRT) followed by surgery in resectable locally advanced non-small cell lung cancer (NSCLC) was used in physically fit patients in an attempt to improve their survival. This trimodality approach was based on the randomized intergroup trial (INT 0139) in which neoadjuvant CRT of 45 Gray (Gy) was followed by surgery. This approach was compared to CRT alone with a higher radiation dose of 61 Gy. The group that was treated with CRT followed by surgery demonstrated longer progression free survival (PFS) compared to the group that was treated to 61 Gy without surgery: median 12.8 months (range 5.3–42.2) vs. 10.5 months (range 4.8–20.6), hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.62–0.96, $P = 0.017$. Median overall survival (OS) was not statistically changed in the groups. The OS was 23.6 months in the group with trimodality vs. 22.2 months (9.4–52.7) in group with CRT to 61 Gy without surgery (HR 0.87, 95%CI 0.70–1.10, $P = 0.24$). In an exploratory analysis, OS was improved for patients who underwent lobectomy, but not pneumonectomy vs. CRT alone, suggesting that it is the extent of surgery that may offset the benefit of surgery [1].

While 45 Gy was the conventional radiation dose for neoadjuvant CRT prior to surgery, not all patients underwent surgery, either due to the patient's medical condition or at the patient's request. These patients were then referred back for completion of a course of radiotherapy, in which case a prolonged treatment break may have caused accelerated repopulation of tumor cells, resulting in suboptimal treatment. Since the INT 0139 trial [1], several investigators have hypothesized that higher radiation doses delivered with modern techniques would be safe and may further improve outcomes [2,3]. RTOG 0229 was a phase II trial that confirmed other retrospective reports of the safety of higher dose CRT followed by surgery [4].

Based on reports of the safety of higher doses of neoadjuvant and the intent to avoid treatment breaks, we were motivated to begin this in-house protocol of neoadjuvant CRT, with definitive-dose radiotherapy at 60 Gy. We hypothesized

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that modern CRT followed by surgery can be safely combined and will result in an improved pathologic response. We also reported on the overall survival (OS), local control (LC), and disease free survival (DFS) of a modern trimodality approach.

PATIENTS AND METHODS

Figure 1 shows the treatment schema in the trimodality approach.

INCLUSION CRITERIA

Patients referred by a multi-disciplinary tumor board for neoadjuvant CRT followed by surgery between August 2012 and April 2016 were included. Inclusion criteria were biopsy proven NSCLC, clinical stage IIB-IIIIB according to the American Joint Committee on Cancer (AJCC) 7th edition [5] including T3 N0 or T3 N1 (N1 includes hilar lymph node metastasis) or T1–3 N2 (N2 includes ipsilateral mediastinal nodal metastasis). Additional selection criteria for surgery were a World Health Organization performance status of 0–1, no major co-morbidities, no additional malignancy, and adequate cardiopulmonary function as assessed by pulmonary function tests. Further selection criteria included echocardiography showing a predicted postoperative forced expiratory volume in 1 second and carbon monoxide lung diffusion capacity of more than 40% of the calculated expected value, cardiac ejection fraction of more than 35%, and pulmonary artery pressure of less than 40 mmHg. Excluded from surgery and from analysis were patients with bulky,

multi-station or diffuse mediastinal disease, contra-lateral mediastinal lymphatic spread, or T4 primary tumor. Patients with tumor progression or persistent grade 3–4 radiation induced pulmonary toxicity (radiation pneumonitis) were excluded as well.

Prior to treatment, all patients were staged with an ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), and brain magnetic resonance imaging (MRI). Mediastinal lymph nodes were sampled either before or after CRT to exclude contra-lateral mediastinal metastasis. Response to CRT was assessed with a chest and abdomen CT or a whole body ¹⁸F-FDG PET/CT performed 2 to 4 weeks after CRT. This retrospective analysis was approved by the institutional ethical review board.

CHEMOTHERAPY

One of five different chemotherapy regimens was used concomitantly with radiotherapy, according to the treating medical oncologist’s recommendation:

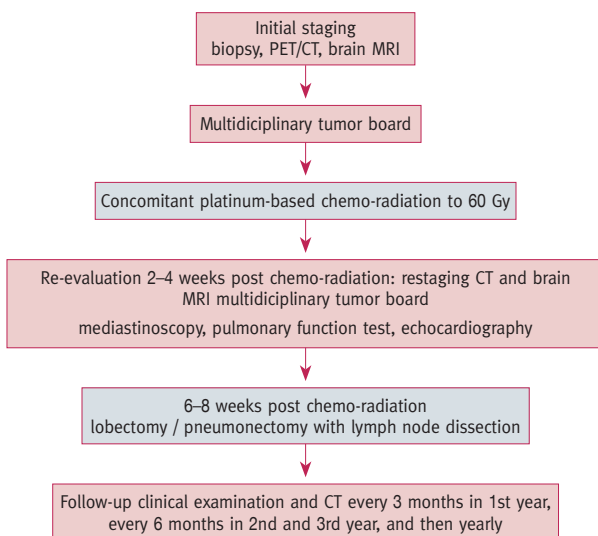
- Cisplatin (CN) (37.5 mg/m² D1, D8, D22, D38) and vinorelbine (12.5 mg/m² D1, D8, D22, D38)
- Carboplatin at AUC 2 with paclitaxel at 45 mg/m² both given every week (CT qw)
- Carboplatin at AUC 5 with paclitaxel 175 mg/m² every three weeks q3w (CTq3w)
- Etoposide (EP) at 100 mg/m² D1-3 with cisplatin at 75 mg/m² q3w or etoposide 50 mg/m² D1-5 with cisplatin 50 mg/m² D1,D8 q4w
- Pemetrexate at 500 mg/m² with cisplatin 75 mg/m²

Consolidation chemotherapy was not planned.

RADIATION THERAPY

The radiation therapy goal was to deliver 30 fractions of 2 Gy for a total dose of 60 Gy. PET/CT scans were co-registered with the simulation scan and used for target delineation. Treatment targets included the gross tumor and mediastinal lymph nodes that were FDG-avid, and/or enlarged lymph nodes (short axis larger than 1 cm) defined as gross tumor volume (GTV). Elective node irradiation was not applied. For clinical target volume (CTV), added margins were 0.5 cm circumferentially and for planning target volume (PTV). Margins were 0.5 cm in the axial dimension and 0.8–1 cm in the longitudinal dimension, added over the CTV. Planning constraints were: lung V20 < 32% and dose to spine < 50 Gy. When constraints could not be met, the prescription dose was decreased. Dose calculations were performed using the analytical anisotropic algorithm (AAA) in the Eclipse (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system. AAA was developed to improve the dose calculation accuracy, especially in heterogeneous media. Treatment

Figure 1. Treatment schema in the trimodality approach



MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography, Gy = Gray

was delivered using daily image-guidance radiation therapy (IGRT) prior to each fraction.

SURGERY

A complete anatomical resection with hilar and mediastinal lymph node dissection was performed 6 to 8 weeks following completion of CRT. The preferred surgical approach was muscle sparing lateral thoracotomy. A single dose of steroids, limited ventilation volume and ventilation pressure, and careful fluid administration were used to minimize pulmonary trauma during surgery. The surgical procedure of choice was lobectomy, but in some cases, chest wall resection or pneumonectomy was required. Postoperative treatment protocol included continuous epidural anesthesia combined with intravenous non-steroidal anti-inflammatory medications, early mobilization, and respiratory physiotherapy.

PATHOLOGIC RESPONSE

The treatment effect was evaluated on the pathologic specimen according to protocol recommended by the College of American Pathologists and based on the modified tumor regression grading, as suggested by Junker and colleagues [6]. Favorable pathologic responses included major tumor regression (MTR), defined as residual vital tumor estimated to be less than 10% of suspected area, and complete pathologic response (pCR) in which there were no viable tumor cells identified. Unfavorable pathologic responses included residual tumor of more than 10% and no response.

FOLLOW-UP

Follow-up included clinical examination and CT scans of the thorax and upper abdomen every 3 months during the first year, every 3 to 6 months during the second year, and then annually.

OUTCOME AND STATISTICAL ANALYSIS

The analysis endpoints were OS, LC, DFS, pathologic response to treatment, and toxicity. OS was defined as the time from the beginning of radiation until death by any cause. DFS was defined as the time from the beginning of radiation until disease progression, local recurrence, or death by any cause. Patients without failure at the last follow-up were censored at that date. Major surgical complication rates were determined from patient medical charts 90 days post-surgery. Mortality rates were recorded at 30 days and 90 days post-surgery. Adverse events were retrospectively graded using common terminology criteria for adverse events (CTCAE) version 4.03 [7].

Data collection stopped at the end of April 2016. OS, LC, and DFS were estimated using the Kaplan–Meier method. Univariate analysis was performed with a log rank test. A two-sided *P* value of < 0.05 was used to indicate statistical significance. Statistical

analysis was performed using STATA13 software (StataCorp LP, College Station, Texas, USA).

RESULTS

Fifty-two patients were included in the analysis [Table 1]. The mean age was 63 years (range 45–79.7). Adenocarcinoma comprised 58% of cases (30/52) and stage IIIA was found in 75% (39/52). Chemotherapy was delivered in full intensity to 90% of patients and dose reduction to 10%.

The mean radiation dose was 58 Gy (range 50–62 Gy), 43 patient (82.7%) were treated with 60 Gy. One patient did not complete the radiation course due to chest pain, and seven patients were treated to doses between 50–56 Gy to respect lung dose constraints. Median radiation treatment lasted 41 days (range 37–49, standard deviation ± 3.8). Treatment was interrupted for 4–7 days in three patients due to esophagitis.

The surgical procedure performed was lobectomy in 67.3% (35/52), chest wall resection in 13.4% (7/52), and pneumonectomy in 19% (10/52). The median interval between the end of CRT to surgery was 67 days (range 30–136). Surgical margins were negative in 90.4% (47/52) and positive in 9.6% (5/52).

At a median follow-up of 22.4 months, the estimated 3 year OS was 74%, 95% confidence interval (CI) 52–87% [Figure 3A].

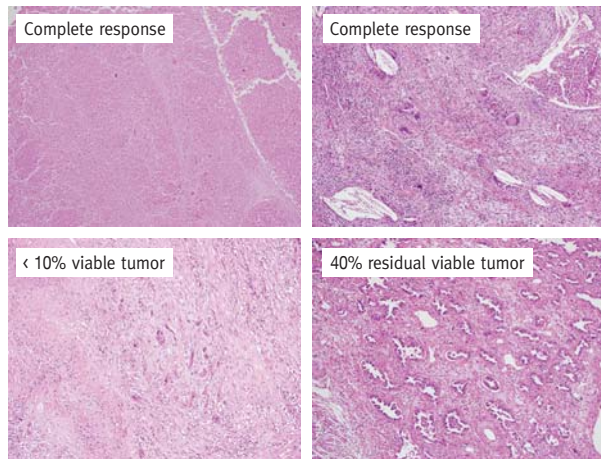
Table 1. Patients characteristics (N=52)

	Number	Percent
Age (mean, range)	63	45–79
Male	39	75%
Female	13	25%
Stage IIB*	10	19%
Stage IIIA*	39	75%
Stage IIIB*	3	6%
Adenocarcinoma	30	58%
Squamous cell cancer	17	33%
Other histology	5	9%
Radiation dose 60 Gy	43	82.7%
Radiation dose 48–56 Gy	9	17.3%
Lobectomy	35	67.3%
Chest wall resection with lobectomy	7	13.4%
Pneumonectomy	10	19.2%
Surgical margins negative	47	90.4%
Surgical margins positive	5	9.6%
Pathologic response		
No response	3	5.8%
> 10% vital tumor	13	25%
< 10% vital tumor	17	32.7%
Complete tumor regression (pCR)	19	36%

*clinical stage, pretreatment

pCR = complete pathologic response

Figure 2. Example of pathologic response to concomitant chemoradiation



Local control at 3 years was 84% (95%CI 65–93%) and estimated DFS at 3 years was 35% (95%CI 14–59%) [Figure 3B].

A complete pathologic response was evident in 36% (19/52) and MTR was found in 32.7% (17/52) of the patients (See Figure 2 for examples of the pathologic responses). In the cases with favorable pathologic response including MTR or pCR, the 3 year OS was 75.7% (95%CI 42–91%) while for the unfavorable pathologic response the OS at 3 years was 66.6% (95%CI 33–86%) (log rank test $P = 0.1$) [Figure 3D]. For pneumonectomy patients, OS was statistically significantly worse (log rank test $P = 0.043$) [Figure 3C].

Positive margins were associated with increased risk of local recurrence (log rank test $P = 0.004$) and shorter DFS (log rank test $P = 0.07$).

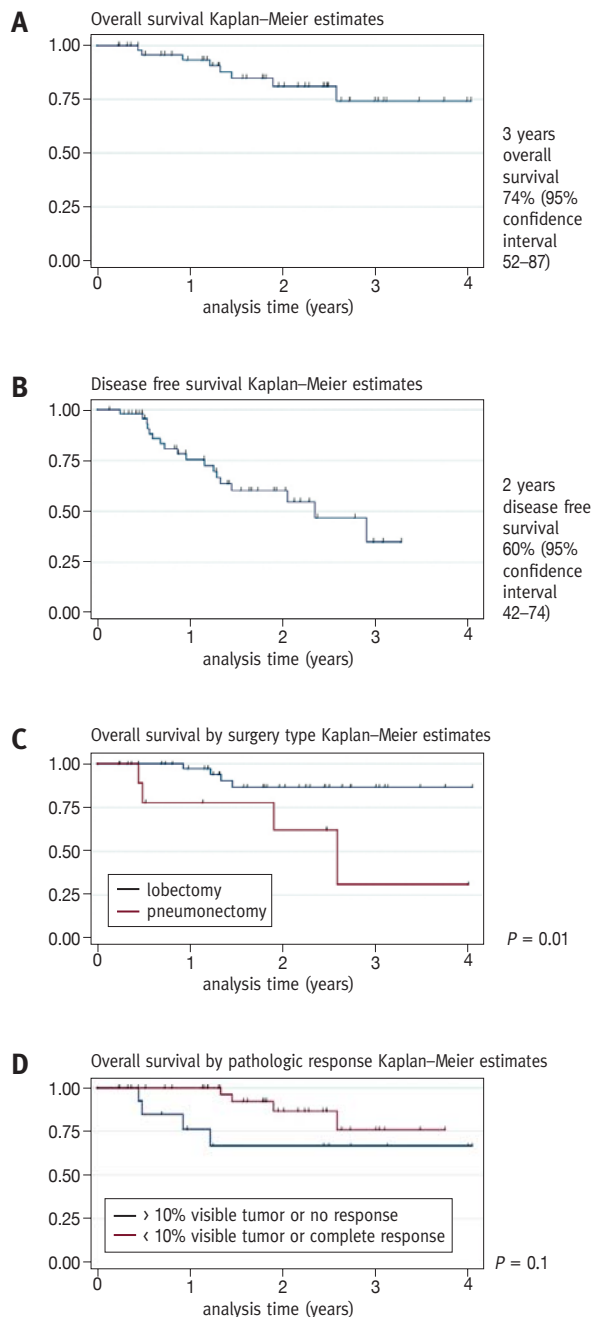
POSTOPERATIVE TOXICITIES

Grade 4–5 were seen in 17.3% including three patients (5.7%) with chest wall necrosis and four cases of broncho-pleural fistula (7.7%). In addition, two cases of post-operative death (3.8%), both underwent right sided pneumonectomy. Low grade toxicities included dyspnea grade 2–3 in 12 patients (23%). The atrial fibrillation grade 2 was 3.8% (2/52).

DISCUSSION

We report the feasibility of a trimodality approach in a selected cohort of locally advanced lung cancer patients with definitive dose neoadjuvant chemo-radiation followed by surgery. We demonstrate encouraging early oncologic results with 3 years OS of 74%, LC of 84%, but the DFS remained dismal at 35% at 3 years. In the RTOG 0229 study with chemo-radiation at 61.2 Gy followed by surgery, the 2 years OS was 54% and median PFS was 12.9 months [4]. In the INT 0139 [1] study, the addition of surgery to CRT improved local controls (10% local recurrence vs. 22% in the non-operative arm). Positive margins were found

Figure 3. Kaplan–Meier survival estimates of locally advanced non-small cell lung cancer treated with concomitant chemo-radiation followed by surgery. **[A]** overall survival, **[B]** disease free survival, **[C]** overall survival by surgery type, **[D]** overall survival by pathologic response



in five patients (9.6%), thus suggesting that selection of patients was appropriate.

The toxicity profile of the trimodality approach included a 3.8% mortality rate (2/52, both cases in right sided pneu-

monectomy). Chest wall necrosis in 5.7% and bronchopleural fistula in 7.7% are debilitating side effects, requiring prolonged hospitalizations and sometimes re-operations. Probable causes of these complications include delayed wound healing due to radiation therapy. Other authors have reported comparable 9–14% grade 3 complications with the trimodality approach. Our 90 day mortality in patients undergoing pneumonectomy in our analysis was 3.8%, which is comparable to 3–3.7% in other series [2,4].

We observed favorable pathologic regression with less than 10% residual viable tumor in 68.7% of patients, and pCR was found in 36%. Other authors reported similar results with 81–82% tumor regression and 40–45% pCR [3,8] following CRT with radiation given to 60 Gy.

Different pathologic responses did not correlate significantly with the 3 year OS (log rank test $P = 0.1$) [Figure 3D]. This may be due to the small cohort size or to the highly metastatic tendency of this cancer, with 3 years expected DFS of only 35% (95%CI 14–59). For the patients who underwent pneumonectomy the OS was statistically significantly worse than other patients (log rank test $P = 0.043$), which is consistent with previously published reports [1], confirming that this procedure remains a high-risk operation that should be used cautiously [see Figure 3C]. The LC was found to correlate significantly with the positive margins (log rank test $P = 0.004$), thus we recommend against surgery if positive margins are anticipated.

We hypothesized that neoadjuvant CRT with a radiation dose of 60 Gy would be advantageous due to a higher probability of down-staging compared to 45 Gy. Furthermore, an unnecessary treatment break after 45 Gy would be avoided in patients deemed unsuitable for surgery. Radiation dosage was shown by some authors to have impact on the pathologic response: pCR rate was 28% following a dose of 60 Gy as compared to 10% following 45 Gy ($P = 0.04$) [2]. In another retrospective analysis [9], pCR was 50% following a dose of 60 Gy vs. 15% following a lower dose ($P = 0.016$). A recently published meta-analysis compared neoadjuvant chemo-radiation at three dose groups: low dose radiation therapy LD-RT (36–45Gy), standard dose radiation therapy SD-RT (45–54Gy), and high dose radiation therapy HD-RT (54–74 Gy). Indeed they showed that higher radiation doses had an impact on the residual nodal disease with residual disease in 25.5% in HD-RT as compared to 37.5% residual in SD-RT. Yet, this improved pathologic response did not translate to improvement in survival: on the contrary, patients treated with standard dose (45–54 Gy) experienced prolonged overall survival (median 38.3 vs. 31.8 vs. 29.0 months for SD-RT, LD-RT, and HD-RT, respectively, $P = 0.0089$) [10]. Another factor that may contribute to tumor regression is IGRT that allows better accuracy, lower geographical miss, and smaller radiation fields, thus offering safer treatments. In a retrospective analysis of trimodality treatment, authors

found improvement of pCR in patients treated with IGRT as opposed to those who were not treated with IGRT (pCR 60% vs. 35%, $P = 0.0728$) [8]. Our cohort was treated with daily IGRT as well as high radiation doses, thus, optimizing both accuracy and dose.

One limitation of our study is the short follow-up (22.4 months), thus limiting the survival analysis; however, this time is adequate for toxicity analysis since most complications appear in the first 3 months after surgery. Another limitation is the small cohort size and the inherent selection bias associated with retrospective analysis. Our cohort was comprised of carefully selected patients with potentially resectable tumor and a good general medical condition.

Chemo-radiation at 60 Gy with modern planning technique and daily IGRT may result in pathologic regression in the majority of cases, with higher chances of mediastinal lymph nodes clearance, making more patients resectable with clear margins and improved oncologic outcomes. However, thoracic surgery after chemo-radiation is much more complex than upfront surgery and thus, the potential added benefit of surgery should be weighed against the morbidity and risk of mortality with this trimodality strategy, especially in right sided pneumonectomy. These recommendations are consistent with finding from the INT 0139 [1]. Trimodality strategy should be practiced in high volume centers with a highly qualified and an experienced thoracic surgical team, and only in appropriately selected patients as recommended by the National Comprehensive Cancer Network® (NCCN) guidelines [11].

CONCLUSION

We have demonstrated the feasibility of trimodality approach with high dose neoadjuvant chemo-radiation followed by surgery for locally advanced NSCLC in specifically selected patients. Modern radiation techniques with IGRT to radiation dose of 60 Gy induced a favorable pathologic regression in a majority of the patients. We recommend avoiding surgery in cases in which positive margins or right sided pneumonectomy are anticipated.

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Capsule

No escape for KRAS mutant tumors

RAS mutant tumors are usually resistant to PARP inhibitors, one of the newest classes of anti-cancer therapeutics. Sun et al. discovered that inhibition of MEK or ERK (proteins in the RAS pathway) reversed PARP inhibitor resistance in KRAS mutant tumors in mouse models of aggressive tumors such as ovarian

and pancreatic cancer. Because MEK and PARP inhibitors are clinically approved drugs, they provide a readily translatable therapeutic combination to treat human cancer patients.

Sci Transl Med 2017; 9: eaal5148
Eitan Israeli

Capsule

Cancer immunotherapy according to GARP

Cancer, like microbes, can adapt to become resistant to a single therapy, making combination therapies the approach of choice. Complementary therapies that decrease immunosuppression may boost the efficacy of immunotherapies. Rachidi and colleagues found that targeting platelets improved adoptive T cell therapy of multiple cancers in mice. Transforming growth factor β (TGFβ)

from platelets decreased T cell function, largely through the expression of the TGFβ docking receptor, GARP (glycoprotein A repetitions predominant). Thus, combining immunotherapy with platelet inhibitors may improve cancer therapy.

Sci Immunol 2017; 2: eaai7911
Eitan Israeli

Capsule

Personalized physical therapy versus usual care for patients with systemic sclerosis: a randomized controlled trial

To compare a physical therapy program to usual care of systemic sclerosis (SSc) patients on disability, a 12-month follow-up, parallel-group randomized controlled trial involving a modified Zelen design was conducted in four tertiary-care hospitals. Patients were enrolled if they had a disability rating ≥ 0.5 on the Health Assessment Questionnaire disability index (HAQ DI) or symptoms of decreased mouth opening or limited range of motion of at least one joint. The experimental intervention (n=112, of which 110 were analyzed) was a 1-month personalized supervised physical therapy program provided by trained care providers followed by home sessions. The control parameter (n=108, all 108 were analyzed) was usual care that could include ambulatory physical therapy. The primary outcome was the HAQ DI score. Rannou and co-

authors found statistically significant differences in disability at 12 months. HAQ DI score between-group difference was -0.01, 95% confidence interval (95%CI) -0.15–0.13, P = 0.86. Disability was reduced at 1 month for patients in the physical therapy group (HAQ DI between-group difference -0.14, 95%CI -0.24– -0.03, P = 0.01, at 6 months the HAQ DI score between-group difference was -0.12, 95%CI -0.23–0.01, P = 0.054. There was a statistically significant difference for hand mobility and function, and for pain, at 1 month. Microstomia was lower in the physical therapy group at 1, 6, and 12 months (between-group difference at 12 months 1.62, 95%CI 0.32–2.93, P = 0.01). No differences in adverse effects were observed.

Arthritis Care & Res 2017; 69: 1050
Eitan Israeli