

An international and multidisciplinary EORTC survey on resectability of stage III non-small cell lung cancer

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ABSTRACT

Introduction: The EORTC-Lung Cancer Group initiated a Delphi consensus process to establish a consensual definition of resectable stage III non-small cell lung cancer (NSCLC) for the use in clinical trials, including a systematic review, survey, and review of clinical cases. Here, the survey results are presented, aimed to identify areas of controversy.

Methods: A survey was distributed among the members of six international organizations related to lung cancer. Respondents were interrogated on the resectability (not limited to the technical resectability) of all stage III NSCLC TNM-subsets (8th edition). Additionally, four N2-subdivisions were used. The threshold for agreement was 75%. Answers with “yes” were considered upfront resectable. “Yes” and “maybe” were grouped together and considered potentially resectable. Answers with “no” were considered unresectable.

Results: 558 responses were collected from thoracic surgeons (38%), radiation oncologists (27%), medical oncologists (17%), pulmonologists (14%), and others (4%). Most worked in a specialized center (80%), had >5 years of experience (80%), were European (76%), male (73%), and treated >20 patients with stage III NSCLC annually (77%). Agreement was found in 26 (70%) out of 37 TNM-subsets: 9 (24%) were considered (potentially) resectable, and 17 (46%) unresectable. There was no agreement for 11 (30%) TNM-subsets: smaller tumors with N2-multistation, larger tumors with N2-single station, and invasive T4-tumors with maximum N2-single station involvement.

Conclusions: This international and multidisciplinary survey showed agreement on the resectability for the majority of stage III NSCLC TNM-subsets, but also identified several TNM-subsets for which no agreement was found.

1. Introduction

Stage III non-small cell lung cancer (NSCLC) accounts for approximately 30% of NSCLC cases worldwide.[1] Although grouped together as stage III, there is significant heterogeneity in tumor size, local infiltration, and nodal involvement. The management of patients with stage III NSCLC is complex and comprises multimodal strategies, combining locoregional and systemic therapy.[2,3] With the rapidly evolving treatment landscape and emerging treatment options such as immunotherapy and targeted therapy, the management of stage III NSCLC is becoming increasingly complex.

Results from the phase III trials CheckMate-816, KEYNOTE-671, IMpower010, and PEARLS/KEYNOTE-091 have led to European marketing approval, and represent new treatment options incorporating immunotherapy into the neoadjuvant, perioperative, or adjuvant setting for patients with resectable NSCLC undergoing surgery.[4–8]

For fit patients with unresectable stage III NSCLC, concurrent chemoradiotherapy followed by consolidation durvalumab is the recommended treatment.[3,9] However, a clear definition of resectable or unresectable stage III NSCLC is lacking. Current guidelines exhibit significant variation in their resectability criteria, and recently completed as well as ongoing studies lack explicit definitions of resectability in their inclusion criteria. Consequently, the absence of uniform patient inclusion criteria results in difficulty comparing results of different trials and impairs the identification of patient subgroups that will benefit most from specific neoadjuvant treatments.

To address this issue, the European Organisation for Research and Treatment of Cancer Lung Cancer Group (EORTC-LCG) initiated a Delphi consensus process, aiming to agree on a consensual definition of resectable stage III NSCLC that could be used in future clinical trials.[10] A multidisciplinary consensus group was formed. Preparatory work, including a systematic review, survey, and review of real-world clinical cases, was performed to identify areas of agreement and controversy regarding the definition of resectable stage III NSCLC.[11,12] Here, we report the survey results.

2. Material and methods

2.1. Study design and population

An online (SurveyMonkey) survey developed by the EORTC-LCG was distributed to its members and Radiation Oncology Group members of the EORTC. Members of four European scientific societies (ESTS,

ESTRO, ETOPIBCSG, ERS; full names in [Supplementary Data](#)) and one global scientific society (IASLC) were also approached for, and agreed on participation. Responses were collected between 13/FEB/2023 and 20/MAR/2023.

2.2. Description of the survey

An initial draft of the survey was designed by a multidisciplinary consensus definition working group consisting of a panel of international experts in the field, which was then reviewed and validated by the EORTC-LCG board members. The survey was strictly confidential and anonymous and was designed to be completed in approximately 12 min. The questionnaire was divided into two sections: 7 general questions and 6 questions related to resectability. Out of 13 questions, 3 were check box questions, 1 open question, and for all other questions, only one answer could be selected. Clinical staging was according to the 8th Tumor, Node, Metastasis (TNM) edition.[13] Additionally, 4 N2-subdivisions (N2_{single}, N2_{multi}, N2_{bulky}, and N2_{invasive}; definitions provided in [Table S1](#)) were used in this survey. 37 stage III (non-N3) NSCLC TNM-subsets were possible with the subdivisions used. In the resectability assessment, which was not limited to technical resectability (i.e. a treatment that was expected to provide a meaningful benefit in terms of cancer outcome/alter the course of the disease; all assumptions are provided in [Supplementary Data](#) Survey format question 8), respondents could answer for each TNM-subset with “yes” (resectable), “no” (unresectable), or “maybe” regarding resectability. Resectability of N3-tumors was assessed separately. A copy of the full survey is available in the [Supplementary Data](#).

2.3. Agreement level and analysis

A percentage of 75% was used as the threshold for agreement among the respondents. If a TNM-subset was not considered as “resectable” in 75% or more of the answers, then the “maybe”-answers were added up to the “yes”-answers and, this TNM-subset was then considered as “potentially resectable”. For the final analysis, TNM-subsets considered as “resectable” or “potentially resectable” were grouped together and considered as “potentially resectable”. Exploratory subgroup analyses were performed in “no agreement” TNM-subsets based on specialty (thoracic surgery vs. others) and center volume in the all-respondents group and thoracic surgeons group (low- vs. high-volume; definitions provided in [Supplementary Data](#)). Multidisciplinary Tumor Board (MDT) composition differences between low- and high-volume centers

in the all-respondents group were also described.

3. Results

3.1. General questions

A total of 558 responses were collected from thoracic surgeons (38%, n=213), radiation oncologists (27%, n=152), oncologists (17%, n=95), pulmonologists (14%, n=76), and others (4%, n=22) (Table 1). The majority of respondents were male (73%, n=406) and worked in Europe (76%, n=425). The most common working environment was specialized center (university hospital or cancer center; 80%, n=448), followed by community hospital (12%, n=65), private clinic (6%, n=34), and others (2%, n=11). Most respondents had more than 5 years of working experience (80%, n=448), and about half (47%, n=260) had more than 15 years of experience. Most specialists treated more than 20 patients with stage III NSCLC, regardless of resectability, in their center annually (77%, n=428), and almost half treated more than 50 patients (high-volume center: 45%, n=250). Team members regularly participating in MDT's were thoracic surgeons (98%, n=549), radiation oncologists (94%, n=525), medical oncologists (90%, n=503), pulmonologists (90%, n=501), radiologists (90%, n=504), and pathologists (85%, n=475) (Fig. S1). Low-volume centers had a comparable MDT composition to high-volume centers (Figs. S2a and S2b).

3.2. Resectability of TNM subsets in stage III NSCLC

Out of 37 possible stage III (non-N3) NSCLC TNM-subsets, agreement was found in 26 TNM-subsets (70%) while there was no agreement on 11 TNM-subsets (30%) (Fig. 1).

Nine TNM-subsets (24%) were considered as (potentially) resectable: 1 out of these 9 was considered as resectable (T3_{size}N1, 83% 'yes') and the remaining 8 were considered as potentially resectable ($\geq 75\%$ 'maybe' or 'yes'). These 9 TNM-subsets were T1-2-, T3- or T4_{size}-tumors with involvement of N0, N1, or N2_{single}. Seventeen TNM-subsets (46%) were considered as unresectable. These were T4N2_{multi} and tumors with N2_{bulky} or N2_{invasive} involvement. N3-tumors were also considered as unresectable by agreement (77%, n=432). No agreement was found for T4-tumors with limited nodal disease (T4_{invasion}N0, T4_{satellite}N1, and T4_{invasion}N1) and tumors with N2 involvement, specifically N2_{single} (with T3_{invasion}, T4_{size}, T4_{satellite}, or T4_{invasion}) and N2_{multi} (with T1-2, T3_{size}, T3_{satellite}, or T3_{invasion}). A summary of detailed responses is provided in the Supplementary Data (Figs. S3-S8).

A subgroup analysis by specialty regarding 'no agreement' TNM-subsets demonstrated that thoracic surgeons considered more TNM-subsets as potentially resectable compared to others (13 (35%) vs. 9 (24%) TNM-subsets). Four cases in which no agreement was found by others (T4_{invasion}N0, 45%; T4_{satellite}N1, 64%; T4_{invasion}N1, 43%; T3_{invasion}N2_{single}, 67%) were judged as potentially resectable by thoracic surgeons (89%, 83%, 80%, and 77%, respectively). In addition, in the thoracic surgeons group, no agreement was found on the resectability of 2 TNM-subsets (T4_{invasion}N2_{single}, 50%; T3_{invasion}N2_{multi}, 36%), which were considered as unresectable by others (76% and 77%, respectively, answered 'no'). In the all-respondents group there were no differences when analyzed by center volume. When analyzing responses from thoracic surgeons only, no agreement could be found regarding the resectability of T4_{invasion}N1-tumors (74%) in low-volume centers, while this TNM-subset was considered as potentially resectable (89%) by agreement in high-volume centers.

3.3. Unresectable invasive T3 and T4 tumors

The respondents were asked to indicate their views on resectability for T3- or T4-tumors invading a surrounding structure. No agreement was found in case of T3-tumors invading the parietal pleura (25.3%, n=141), chest wall (30%, n=168), phrenic nerve (37%, n=205), or

Table 1
Demographical data of 558 respondents.

	n (%)
Specialty	
Thoracic surgery	213 (38)
Radiation oncology	152 (27)
Oncology	95 (17)
Pulmonology	76 (14)
Pathology	16 (3)
Radiology	5 (1)
Nuclear medicine	1 (<1)
Hospital type	
University	321 (57)
Cancer center	127 (23)
General	65 (12)
Private	34 (6)
Other	11 (2)
Years of clinical experience in NSCLC	
0-5 years	110 (20)
6-10 years	84 (15)
11-15 years	104 (18)
>15 years	260 (47)
Number of treated patients with stage III NSCLC in their center annually¹	
0 – 10	32 (6)
11 – 20	98 (17)
21 – 50	178 (32)
>50	250 (45)
Country²	
European	
Italy	66 (11)
Spain	45 (8)
Germany	37 (7)
Belgium	33 (6)
Netherlands	28 (5)
United Kingdom	28 (5)
France	27 (5)
Turkey	22 (4)
Switzerland	20 (4)
Austria	13 (2)
Denmark	13 (2)
Slovenia	11 (2)
Greece	10 (2)
Romania	10 (2)
Hungary	8 (1)
Portugal	8 (1)
Poland	5 (1)
Others (<5 responses per country)	42 (8)
Non-European	
United States	38 (7)
Canada	14 (3)
Brasil	11 (2)
Australia	10 (2)
Japan	9 (2)
India	8 (1)
Egypt	6 (1)
Others (<5 responses per country)	36 (6)
Gender	
Male	406 (73)
Female	147 (26)
Preferred not to answer	5 (1)

(1) Regardless of resectability; (2) Countries falling partially under any common geographical or political definitions of Europe are counted as European.

	N0	N1	N2_SINGLE	N2_MULTI	N2_BULKY	N2_INVASIVE
T1-2	N/A	N/A	POTENTIALLY RESECTABLE (95%)	NO AGREEMENT (50%)	UNRESECTABLE (75%)	UNRESECTABLE (84%)
T3_SIZE	N/A	RESECTABLE (83%) ^a	POTENTIALLY RESECTABLE (87%)	NO AGREEMENT (39%)	UNRESECTABLE (80%)	UNRESECTABLE (88%)
T3_SATELLITE	N/A	POTENTIALLY RESECTABLE (94%)	POTENTIALLY RESECTABLE (79%)	NO AGREEMENT (34%)	UNRESECTABLE (84%)	UNRESECTABLE (91%)
T3_INVASION	N/A	POTENTIALLY RESECTABLE (89%)	NO AGREEMENT (71%) ^b	NO AGREEMENT (28%) ^c	UNRESECTABLE (87%)	UNRESECTABLE (92%)
T4_SIZE	POTENTIALLY RESECTABLE (94%)	POTENTIALLY RESECTABLE (90%)	NO AGREEMENT (66%)	UNRESECTABLE (77%)	UNRESECTABLE (88%)	UNRESECTABLE (93%)
T4_SATELLITE	POTENTIALLY RESECTABLE (78%)	NO AGREEMENT (71%) ^b	NO AGREEMENT (44%)	UNRESECTABLE (85%)	UNRESECTABLE (92%)	UNRESECTABLE (94%)
T4_INVASION	NO AGREEMENT (62%) ^b	NO AGREEMENT (57%) ^b	NO AGREEMENT (34%) ^c	UNRESECTABLE (90%)	UNRESECTABLE (95%)	UNRESECTABLE (94%)

Fig. 1. Survey agreement summary of the resectability assessment of 37 TNM-subsets in stage III NSCLC.

Please take note that these results do not reflect the consensual definition of resectable stage III NSCLC. The threshold for agreement among respondents is 75%. If a TNM-subset was not considered as resectable in 75% or more of the answers, then the maybe-answers (=maybe upfront resectable) were added up to the yes-answers (=upfront resectable) and, this TNM-subset was then considered as potentially resectable. Staging was according to the 8th edition of the TNM classification. Working definition of N2 (ipsilateral mediastinal and/or subcarinal nodes) subdivision used: N2 single = single station, non-bulky (≤ 3 cm), discrete; N2 multi = multi-level, non-bulky (≤ 3 cm), discrete; N2 bulky = bulky (> 3 cm), discrete; N2 invasive = invasive growth.

(a) 83% of respondents answered yes. In potentially resectable and no agreement cases, the percentage comprises yes + maybe-answers. In unresectable cases, the percentage comprises no-answers; (b) Considered as potentially resectable by thoracic surgeons vs. no agreement among others, based on the subgroup analysis by specialty (thoracic surgery vs. others) regarding no agreement TNM-subsets in the overall group; (c) No agreement among thoracic surgeons vs. unresectable by others. *Abbreviations:* NSCLC =non-small cell lung cancer; N/A =not applicable, not stage III disease.

parietal pericardium (37%, n=208) (Fig. 2a). For T4-tumors invading the heart, the respondents agreed that these tumors should be considered unresectable (76%, n=422). No agreement was found in case of invasion of the esophagus (71%, n=396), great vessel (65%, n=365), trachea (58%, n=325), spine (57%, n=320), carina (52%, n=290), mediastinum (48%, n=267), recurrent laryngeal nerve (43%, n=241), or diaphragm (36%, n=203) (Fig. 2b).

3.4. Surgery after downstaging with neoadjuvant chemoimmunotherapy

When the respondents were asked “Would you recommend surgery after downstaging with neoadjuvant chemoimmunotherapy, assuming available in your country, in cases that were answered with maybe” (assessed by the respondent in the resectability assessment of the TNM-subsets in stage III NSCLC), the respondents agreed on recommending surgery (83%, n=463). A similar question with unresectable cases showed no agreement between the respondents (49%, n=275).

4. Discussion

Here, we present the results of what is, to date, the largest international and multidisciplinary survey conducted on the resectability of stage III NSCLC. This survey was designed to contribute to a consensual definition of resectable stage III NSCLC for the use in clinical trials. The results of our survey reveal both substantial agreement and disagreement on the resectability of TNM-subsets in stage III disease. Agreement was found for smaller tumors with maximum N2_{single} involvement but

also for larger tumors with maximum N1 involvement. These tumors were considered as (potentially) resectable (T3_{size}N1 resectable, the others potentially resectable), while tumors with N2_{bulky}, N2_{invasive}, or N3 involvement and T4-tumors with N2_{multi} involvement were considered as unresectable. No agreement was found for smaller tumors with N2_{multi} involvement, larger tumors with N2_{single} involvement, and invasive T4-tumors with maximum N2_{single} involvement.

Common categories of N2 involvement reported by guidelines are N2 single-station, N2 multi-station, N2 bulky, and N2 invasive.[2,14] However, the node category of the 8th TNM edition is determined by the location of the involved lymph nodes and does not differentiate between small-volume and extensive, bulky, or infiltrative nodal disease.[13] For instance, patients with single-station N2 disease are grouped in the same category as those with multi-station, bulky, or invasive nodal disease. We used an N2 subdivision working definition which considered these characteristics. The IASLC recently proposed to subdivide N2 disease into N2a and N2b for the revisions of the N-descriptors in the forthcoming 9th TNM edition, differentiating between single-station (N2a) and multi-station (N2b) disease, which is in line with the subdivision used in our study.[15] Separating this category aligns with long-standing clinical perception that single-station, non-bulky N2 disease has a better prognosis. This is reflected in the 9th TNM edition with, for example, T1-tumors with single-station N2 involvement now considered as stage IIB disease compared to T1-tumors with multi-station N2 involvement considered as stage IIIA disease. As no clear differences in results between station-level and zone-level analyses were observed for the 9th TNM edition, in addition to other factors, the station-based

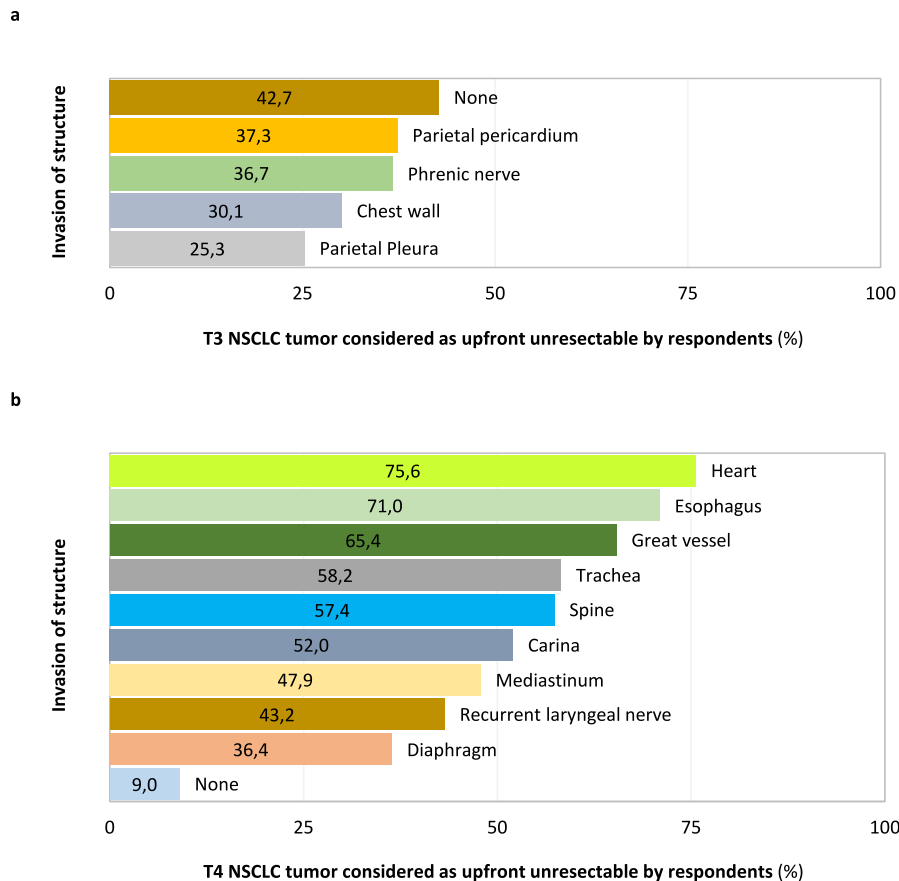


Fig. 2. Survey agreement summary of unresectable invasive T3 or T4 NSCLC tumors according to anatomical structures invasion. The invasion of surrounding structures is in accordance with the 8th edition of the TNM classification. The threshold for agreement among respondents is 75%. (a) Proportion of respondents (n=558) that considered an invasive T3 NSCLC tumor as upfront unresectable. (a) Proportion of respondents (n=558) that considered an invasive T4 NSCLC tumor as upfront unresectable. *Abbreviation:* NSCLC =non-small cell lung cancer.

classification remained unchanged. Nodal size, invasive/infiltrative growth, and extracapsular extension were among the proposed variables of interest but these analyses were not feasible at the time and could be an area for future research.

A multidisciplinary approach, involving a range of specialists including thoracic surgeons, radiation oncologists, oncologists or pulmonologists, pathologists, and imaging specialists, is critical in the management of stage III NSCLC, with MDT discussions playing a central role. This approach has been shown to improve disease staging, guide treatment decisions, enhance adherence to guidelines, and ultimately lead to better clinical outcomes. [16–18] While technical resectability of stage III NSCLC is primarily determined by the thoracic surgeon, the boundaries of resectability can sometimes be unclear. In cases of borderline resectability, the assessment can benefit from further refinement through MDT discussions, particularly with experienced radiologists and pulmonologists, to ensure a more accurate evaluation. [19] Most respondents in our study were from specialized centers, and we therefore analyzed the MDT composition in both low- and high-volume centers. Our comparison revealed that the MDT compositions in these different settings were similar.

The results of this survey emphasize the different perspectives of the specialties involved in thoracic oncology regarding resectability of stage III NSCLC tumors. This is further evidence of the relevance of MDT discussions to resolve such discrepancies. For example, the thoracic surgeons were more likely to consider certain TNM-subsets as potentially resectable or found no agreement in cases that were considered as unresectable by others. Differences were not only observed between

specialties, but also within specialties such as between thoracic surgeons, depending most probably on institutional traditions and experiences. Notably, T4_{invasion}N1-tumors were considered as potentially resectable by thoracic surgeons from high-volume centers, while in low-volume centers no agreement was found. This result underlines the importance to seek second opinion in high-volume or specialized centers as recommended in official guidelines. [9]

Strengths of this work include the large number of respondents, the multidisciplinary approach when designing the survey, the representation of both European and non-European countries, and the range and balance of specialists involved. Approximately two third of respondents had a specialty other than thoracic surgery. For those respondents and also for surgeons not specializing in thoracic oncology surgery only, the determination of resectability may be challenging. For instance, the parietal pericardium is generally considered as resectable by dedicated thoracic surgeons, while in this survey close to 40 % of respondents defined T3-tumors invading the parietal pericardium as unresectable. Nevertheless, we find that our results obtained from a group of specialists from different disciplines is one of the major strengths of this study, resulting in valuable information for the discussions during the subsequent Delphi consensus process. Another strength of this study is that most respondents worked in a specialized high-volume center. Although this could affect the generalizability of the survey results, it may indicate that the respondents are experienced and have the expertise on this topic, which will be favorable for obtaining more reliable results, especially in more complex stage III NSCLC cases. Moreover, with the advent of neoadjuvant chemoimmunotherapy, the

difficulty relating to the decision to resect or not is likely to increase, highlighting the importance of an experienced MDT and highly experienced thoracic surgeon.

Some limitations of this survey should be acknowledged. First, the response rate (respondents/total number of specialists contacted) could not be calculated because the survey was circulated by scientific societies to a large email list with unknown denominator, and specialists are often member of several scientific societies. Secondly, morphological characteristics of the lymph nodes were categorized into simplified categories: bulky and non-bulky N2 disease. Bulky mediastinal N2 disease has mostly been defined as metastatic lymph nodes larger than 3 cm in the smallest diameter, easily measurable and free from major mediastinal structures.[9,20] We used a similar definition, however, a consensual definition is currently lacking and could introduce potential bias. Additionally, the lack of a precise definition of invasive N2 disease may introduce bias. Selection bias is also a possible limitation in our study as interested thoracic surgeons were more likely to respond to the survey, however, we did have many respondents from various specialties.

Future work could further explore the differences within specialties. For example, distributing a similar survey to thoracic surgeons could offer insights in the differing perspectives regarding the technical resectability decision, as well as other influencing factors, such as the type of center, center volume, and availability of facilities and expertise. Especially with the introduction of new systemic therapies, resulting in improved survival, future research should emphasize the difference between technical and oncological resectability, as the latter also takes into account whether the surgical removal of the tumor provides a meaningful benefit in terms of treatment outcomes.

5. Conclusion

This survey found agreement on resectability for certain stage III NSCLC TNM-subsets. However, it also identified several TNM-subsets where agreement is lacking. By using the Delphi consensus method, these survey results combined with the results of a systematic review and review of real-world clinical cases are intended to inform the development of a consensual definition of resectable stage III NSCLC, standardizing patient inclusion criteria in future clinical trials.

CRedit authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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