Oncology Gold Standard Consensus Recommendation

ICON 2013: Practical consensus recommendations for hormone receptor-positive Her2-negative advanced or metastatic breastcancer

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On Behalf of Breast Cancer Expert Group of Indian Cooperative Oncology Network (ICON Trust)

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Abstract

The management of hormone receptor-positive Her2-negative breast cancer patients with advanced or metastatic disease is a common problem in India and other countries in this region. This expert group used data from published literature, practical experience, and opinion of a large group of academic oncologists, to arrive at practical consensus recommendations for use by the community oncologists.

Key Words: Chemotherapy, developing countries, endocrine therapy, guidelines, women

Introduction

The Indian Cooperative Oncology Network (ICON Trust) Expert Group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines on the management of hormone receptor-positive Her2-negative breast cancer patients with advanced or metastatic disease. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.[1,2]

The discussion was based on domain expertise of the international faculty, published evidence and practical experience in real life management of such patients. Opinion of the 300 participants in the 28th meeting of ICON Trust was also taken into consideration by the expert panel. The expert group was chaired by Dr Sudeep Gupta whereas the discussions were moderated by Dr Shaheenah Dawood and Dr Purvish Parikh.

The core expert group discussed over several sessions about the possible methodologies. It was decided to use a series of questions on key practical issues and management challenges with each question answerable in the form of selection from multiple choice options. The consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.[3-5] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the 28th ICON Trust meeting. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements.

A total of seven broad question categories were part of the expert group discussions [Table 1].

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This manuscript is the outcome of the expert group discussion and consensus arrived at in 2013.

Defining clinical cohort and practice of expert group panel members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared.

Breast cancer is the commonest cancer among women in India, the age-adjusted incidence being 32.4 per 100,000 in Maharashtra in the year 2010 with a 2.5% increase predicted annually upto 2021.[5]

To the question, what is the fraction of advanced/metastatic breast cancer patients with ER +ve/Her2 –ve phenotype disease in their practice, the answers were as follows [Table 2].

In one study of 11,780 breast tumors (age range 18 to 102 years), hormone receptor positivity was 53.9%.[6] A total of 41.8% tumors were positive for both estrogen and progesterone receptors, 10.6% positive for estrogen receptors alone and 3.4% positive for progesterone receptors alone. Overall hormone receptor positivity increased steadily with age, it being 10% in patients less than 19 years of age and 90% in those 71 years or older. As far as grade of tumor was concerned, there was an inverse correlation with respect to the hormone receptor positivity, it being 93% for grade 1 tumors and 39.5% for grade 3 tumors. With the median age of breast cancer in India being 49 years, the majority tend to be in the pre-menopausal group.[5] This is a significant difference from patients seen in the western world.[7]

Triple negative phenotype is 42% at initial presentation for all comers. In advanced and metastatic setting will be less since they have better prognosis and less chance of relapse. In a study of 2001 patients, Her2 positivity by IHC was seen in 498 (24.8%) patients and triple negative breast cancers formed 29.8% (n = 596) of all invasive cancers.[8] HER2 over-expression did not differ significantly with age (incidence being 17.7% for those below the age of 35 years and 17.0% for those above, P = 0.825). On the other hand

hormone receptor expression (ER and/or PR) increases and triple negative phenotype decreases with increasing age.

To the question regarding the fraction of above patients with visceral involvement, the expert group agreed with the polls that it is between 20 and 40% of hormone-sensitive Her2-negative patients have visceral involvement when they present with metastatic disease. In tier 2 cities, where access to oncology centers may be a challenge, this incidence is slightly higher. This is applicable to the one fifth of the poll participants who are seeing visceral involvement in upto 60% of their patients at metastatic presentation [Table 3].

The standard adjuvant endocrine therapy in pre-menopausal breast cancer patients is clearly tamoxifen. The consensus was to use it for 5 years. Perception of higher risk (e.g. lymph node positive patients) was associated with longer use of tamoxifen. In fact some patients had a tendency to get attached to their "regular medication" and were not averse to continuing the same. Additional of ovarian suppression for patients who did not have complete suppression during previous therapy (for non-metastatic disease) is accepted as standard of care and that option in fact reflects the current practice in the community. This is particularly for patients who are strong ER-positive or aggressive disease. In case where ovarian suppression is commenced but is not effective, oophorectomy is the next recommendation [Table 4].

Common practice of adjuvant endocrine therapy in post-menopausal hormone-sensitive Her2-negative breast cancer patients is aromatase inhibitors for 5 years, as selected by the majority of oncologists in the poll. Tamoxifen is recommended for older patients and those with poor PS where the risk of skeletal related toxicity of AI is a cause for concern. The expert group agreed that the meta-analysis data showed that the best outcome (balance of efficacy and toxicity) is with a combination of Tamoxifen and AI for 5 years, as selected by 32% in the poll[9] [Table 5].

Table 1: Question categories addressed by the ICON trust expert group

Broad question title	Number of subquestions
Clinical cohort and practice setting	4
Endocrine resistance	2
Visceral disease	3
Hormone receptor-positive, her2-negative post-menopausal breast cancer patients	6
Treatment approach	2
Role of evorolimus	1
Role of re-biopsy	2

ICON: Indian Cooperative Oncology Network

Table 2: Question 1 (i): What is the fraction of advanced/metastatic breast cancer patients with HR+ve/Her2 –ve phenotype in your practice?

Options (%)	–40	41-50	51-60	>60
% of polled oncologists	32	32	37	0

Expert group consensus: 40 to 50% in most settings; increases with age, HR: Hormone receptor

Table 3: Question 1 (ii): What fraction of your patients with HR+ve/Her2 –ve breast cancer in the first-line metastatic setting have visceral involvement?

Options (%)	<20	21-40	–60	>60
% of polled oncologists	11	61	22	6

Expert Group Consensus: Less than 40% in urban setting; more in tier 2 cities, HR: Hormone receptor

Defining endocrine resistance

Any patient who has received endocrine therapy and then has progressive disease is considered to have endocrine resistance in the broad sense. The group also agreed that there was no standard definition of what constitutes endocrine resistance. However, as the Bolero2 study has shown, several practical considerations have emerged.[10] Their importance relates to the consensus about subsequent management of patients. For patients relapsing while on endocrine therapy there is no debate about defining it as absolute endocrine resistance. However, the oncologists participating in the poll were split about what amounts to a significant off therapy period - upto 6 months or upto 12 months. Voting for secondary endocrine resistance also revealed an identical split [Tables 6 and 7].

The expert group agreed that distinction between primary and secondary endocrine resistance was not important for practical management of the patient. Just as a patient who progresses after one line of chemotherapy is still given a second line of chemotherapy, so also should be the approach to the patient with hormone receptor-positive breast cancer. The discussion ended with the consensus that for patients who relapse while on endocrine therapy, the next choice should be everolimus or exemestane. On the other hand for patients who progress while off therapy, it was reasonable to continue with alternate endocrine therapy – irrespective of the off therapy duration.

Significant visceral disease

Various trials have used different definition of impending visceral crisis (e.g. Tamrad v/s Bolero) and these trials

Table 4: Question 1 (iii): What is your standard adjuvant endocrine therapy for pre-menopausal patients?

Options	Tamoxifen for 5 years	Tamoxifen for >5 years	Tamoxifen for 5 years plus ovarian suppression
% of polled oncologists	47	18	35

Expert Group Consensus: Tamoxifen for 5 years; additional ovarian suppression only if required

Table 5: Question 1 (iv): What is your standard adjuvant endocrine therapy for post-menopausal patients?

Options	Tamoxifen for 5 years	Tamoxifen for 5 years followed by AI	Tamoxifen and AI in a switch strategy for a total of 5 years	AI for 5 years
% of polled oncologists	0	5	32	63

Expert group consensus: Tamoxifen and AI in a switch strategy for a total of 5 years

also represent different patient populations.[10,11] Hence, for this practical recommendations expert group, it was decided to explore the meaning of significant visceral disease as opposed to impending visceral crisis. Almost all the oncologists participating in the poll required associated symptoms to define that their patient had significant visceral metastasis. The expert group discussed three hypothetical scenarios to have a clearer understanding. Scenario one represented an asymptomatic patient with liver metastasis in four regions, multiple lung metastasis, and extensive bone involvement. In scenario two, the patient was considered as having 60% of the liver affected by metastasis, multiple lung metastasis, was still asymptomatic and biochemical parameters showed liver and renal profile that was within normal limits. Scenario three envisaged a patient with multiple lung metastases, evidence of lympangitis and being symptomatic with shortness of breath on exertion, though involvement of liver by metastasis was less than 20%. There was unanimous consensus by the expert group for the use of chemotherapy (with endocrine therapy) for scenario one and three. For scenario two while use of endocrine therapy was considered as a reasonable option, the majority still recommended chemotherapy [Tables 8-10].

Hormone Receptor-Positive, Her2-Negative Post-menopausal Breast Cancer Patients

The discussions then shifted to patients without significant visceral disease or visceral crises. For patients with *de novo* stage IV disease, the polled oncologists and the expert group had no hesitation in recommending AI as the treatment of first choice. The expert groups added that the only reason to use Tamoxifen would be if AI was contraindicated in any particular patient [Table 11].

For a similar patient who has progressed on an AI, the expert group examined three groups of studies. These included results from Bolero (Exemestone 25 and Everolimus 10 + Exemestone 25), Tamrad (Tamoxifen 20 and Everolimus 10 + Tamoxifen 20) and Horizon (Letrozole 2.5 and Letrozole 2.5 + Temsirolimus 30) Studies. In all of them the PFS was about 9 months[10-12] [Table 12].

The choice of therapy for patients progressing on AI is also quite clear and the voting of the polled oncologists showed their familiarity with the current published literature. The expert group, while taking into consideration that Fulvestrant 500 mg is now shown to be better than 250 mg, still concurred that the strength of the data from BOLERO2 shows that Everolimus is the better option.

To explain further, data from 18 month pre-planned analysis showed a doubling of PFS (Progression Free Survival) in patients receiving Everolimus plus Exemestane compared to Exemestane alone (11 vs 4.1 months; P = 0.0001; HR 0.38; 95% CI 0.31-0.48).[10] Everolimus Plus Exemestane has also demonstrated a beneficial effect on bone marker assessments; C-terminal cross linking telopeptide of type I collagen (CTX), amino terminal propeptide of type 1 collagen (P1NP), and bone-specific alkaline phosphatase (BSAP) all showed reduction at 6 and 12 weeks for patients receiving Everolimus plus Exemestane (irrespective of prior bisphosphonate use), whereas the group on Exemestane alone actually had increase of bone turnover markers.[13] This is evidence of protective effect of Everolimus on bone health, of particular importance in such patients who have high incidence of bony metastasis. Everolimus plus Exemestane was also associated with a longer time to definitive deterioration (TDD) in global HRQOL measured using EORTC QLQ-C30) which strengthens the evidence further.[10,14,15]

This, rightly so, also highlights the fact that neither the expert group nor the polled oncologists considered the use of chemotherapy for patients at this stage in their disease [Table 13].

For this specific scenario, there is little published evidence. Hence, the expert group decided that there is no single correct answer. The reason for the polled oncologists to select option b was data from the phase 2 TAMRAD study, which is currently the most promising option. The rationale for this is that a key adaptive change leading to endocrine resistance is activation of the mTOR signaling pathway[16-18] [Table 14].

Table 6: Question 2 (i): How would you define primary endocrine resistance in the adjuvant setting?

Options	Relapse while on adjuvant endocrine therapy	Relapse while on adjuvant endocrine therapy or within 6 months of its discontinuation	Relapse while on adjuvant endocrine therapy or 6 to 12 months of its discontinuation	Other
% of polled oncologists	10	45	40	5

Expert group consensus: Relapse while on adjuvant endocrine therapy

Table 7: Question 2 (ii): How would you define secondary endocrine resistance in the adjuvant setting?

Options	Relapse more than 6 months following endocrine therapy	Relapse more than 12 months following endocrine therapy	Other
% of polled oncologists	44	44	11

Expert group consensus: Relapse at any time following endocrine therapy

Table 8: Question 3 (i): What is the definition of significant visceral disease?

Options	Any visceral involvement	More than on viscera involved	Visceral organ involvement associated with symptoms	>20 to 30% of the viscera involving by disease	Other
% of polled oncologists	0	0	95	5	0

Expert group consensus: Visceral organ involvement with symptoms or more than 30% of organ involvement

A clear majority of the polled oncologists and the entire expert group were of the opinion that, at present, there is no data to support continuation of everolimus beyond progression [Table 15].

The expert group discussed and agreed that number or type of visceral organs involved by metastatic disease did not prevent the use of everolimus and exemestane in this group of patients. Even among patients with metastasis involving more than three visceral organs, there was no hesitation in recommending this combination [Table 16].

The expert group was unanimous in voting yes. While the updated investigator assessment of the progression-free survival (PFS) rate for patients treated with exemestane and everolimus was 7.8 months, independent reviewers assessed PFS at 11.0 months – strengthening the confidence and statistics.[19] When this data represents 724 post-menopausal women with hormone receptor-positive metastatic breast cancer who had progressed on a nonsteroidal aromatase inhibitor (AI), it clearly affirms the superior value of the exemestane and everolimus combination.

The benefit is in terms of PFS was also associated with better bone health and QoL. The risk reduction is identical for patients with visceral metastasis (53%) and those without visceral metastasis (59%). In fact, the 61% risk reduction in patients who had progressed after adjuvant therapy also suggests that this combination is likely to be of greater benefit in the first-line setting.[10,19]

Treatment approach [Table 17]

In the poll of oncologists, 85% selected Tamoxifen as the best option in this situation, with or without ovarian suppression. The expert group agreed that both of these are valid options. Without compelling evidence, the rationale for combining tamoxifen with ovarian suppression was considered as the better practical recommendation [Table 18].

The expert group agreed that there is no strong evidence for selecting any one of the choices. The poll results reflect the current practice of using AI for such patients. The expert consensus was that chemotherapy is also an option, even in the absence of visceral crisis. For instance when patients having speedy progress of the disease or significant symptoms.

Role of everolimus refined [Table 19]

There were arguments on both sides for the approach to appropriate use of everolimus. Based on the evidence from pivotal data the consensus was to start with the labeled dose of 10 mg and de-escalate if necessary.[20] This is supported by the study in metastatic renal cell carcinoma that predicted median change in single largest diameter (SLD) of the disease will be increase of 22.4 ± 17.2% with 5 mg of Everolimus and reduction of 15.7 ± 11.5% with 10 mg.[21] For frail patients a fraction of oncologists may still continue to start with a lower dose and escalate if no toxicity, but this is without evidence and not recommended.[22]

Measures to prevent and minimize toxicity used in clinical trials are often neglected in routine clinical practice. Application of such measures will ensure that toxicity remains manageable in most patients.[23] Hence the following are recommended for all patients receiving Everolimus: Proper counseling and patient information, prophylactic measures for maintaining oral hygiene, more frequent follow up in the first few weeks (when toxicity are most likely to develop) and communicating early onset of specific symptoms to the healthcare team (to allow appropriate intervention that can prevent the toxicity from

Table 9: Question 3 (ii): What is the appropriate choice of therapy for HR+ve/ Her2–ve breast cancer in the presence of significant visceral disease in the first-line metastatic setting

Options	Chemotherapy	CT in the major and endocrine therapy in the minor	Endocrine therapy in the major and CT in the minor	Endocrine therapy
% of polled oncologists	60	35	5	0%

Expert group consensus: Chemotherapy with or without endocrine therapy, CT: Chemotherapy, HR: Hormone receptor

Table 10: Question 3 (iii): What is the appropriate choice of therapy for HR +ve/Her2 –ve breast cancer in the presence of significant visceral disease in the second-line metastatic setting

Options	Chemotherapy	CT in the major and endocrine therapy in the minor	Endocrine therapy in the major and CT in the minor	Endocrine therapy
% of polled oncologists	75	25	0	0

Expert group consensus: Chemotherapy with or without endocrine therapy, CT: Chemotherapy, HR: Hormone receptor

Table 11: Question 4 (i): What is the most appropriate choice of therapy for HR +ve/ Her2 –ve breast cancer post-menopausal patients with newly diagnosed stage IV *de novo* disease and no visceral crisis?

Options	Tamoxifen	AI	Fulvestrant 500 mg	Everolimus plus exemestane	CT
% of polled oncologists	0	85	6	6	0

Expert group consensus: AI, HR: Hormone receptor

Table 12: Question 4 (ii): What is the most appropriate choice of therapy for HR +ve/ Her2 –ve breast cancer post-menopausal patients who have progressed on previous therapy with an AI and have no visceral crisis?

Options	Fulvestrant 500 mg	Everolimus plus exemestane	Everolimus plus tamoxifen	CT
% of polled oncologists	17	78	6	0

Expert group consensus: Everolimus plus exemestane, HR: Hormone receptor

Table 13: Question 4 (iii): In a post-menopausal patient with HR +ve/Her2 –ve breast cancer who has progressed on exemestane and who is a candidate for further endocrine therapy what would you consider as the most appropriate line of therapy?

Options	Everolimus plus another AI	Everolimus plus Tamoxifen	Everolimus plus Fulvestrant	Endocrine agent alone	Any of these options
% of polled oncologists	25	38	6	6	25

Expert group consensus: All the options are reasonable choices. Everolimus plus tamoxifen is the most promising choice, HR: Hormone receptor

Table 14: Question 4 (iv): In a patient with no visceral crisis who has progressed on everolimus and exemestane and in whom you are considering next line endocrine therapy, would you continue everolimus beyond progression?

Options	Yes	No
% of polled oncologists	17	83

Expert group consensus: No

Table 15: Question 4 (v): Would you consider the combination of everolimus and exemestane among post-menopausal patients with HR +ve/Her2 –ve breast cancer who have >3 visceral organs involved by metastatic disease?

Options	Yes	No
% of polled oncologists	89	11

Expert group consensus: Yes, HR: Hormone receptor

Table 16: Question 4 (vi) Given the BOLERO-2 trial data, can the combination of everolimus and exemestane be considered as standard treatment option in patients with HR +ve/Her2 –ve breast cancer that has progressed on a previous AI in the post-menopausal setting?

Options	Yes	No
% of polled oncologists	85	15

Expert group consensus: Yes, HR: Hormone receptor

worsening). Interventions for common clinically relevant toxicities include use of non-alcohol containing mouth wash, topical corticosteriods and anti-fungal agents (for stomatitis), routine anti-diabetic agents (for hyperglycemia), statins (for hyperlipidemia) and correction of anemia, optimized hydration and restricted physical activity (for fatigue). It is also important to check for and correct hypophosphatemia (which can lead to muscle weakness and is often mistaken for fatigue).[23]

Value and need for rebiopsy [Table 20]

Among the polled oncologists, 15% were reluctant to do a rebiopsy for any patient. On the other hand 60% would biopsy in all patients. Neither of these extreme positions was recommended by the expert group. A rebiopsy is recommended in specific circumstances. One is to confirm that the patient actually has a relapse rather than a lesion due to other causes, like infections. The other is when the clinical picture or behavior of the patient is not in tune with what is expected from a hormone-sensitive Her2-negative disease. An example of this would be development of liver metastasis within 3 months of starting tamoxifen. This was particularly important since the earlier laboratory methodology or tumor block processing may have been using techniques that have undergone significant improvement over time. The group also understood that a patient with recurrences in an easily accessible location is more likely to agree to undergo a rebiopsy. Hence counseling skills are vital for such a discussion with patients and family members [Table 21].

There is evidence about change in receptor status either way.[24,25] While the question pertained to changes that would indicate the need to use chemotherapy, the expert group was of the opinion that the reverse is equally important.

Conclusions

The ICON 2013 expert group hormone receptor-positive Her2-negative advanced or metastatic breast cancer had the specific mandate to develop practical consensus recommendations for easy application by the community oncologist. It took into consideration data as well as the current practices in India, in addition to international data that conventional panels look at, making it the perfect blend of evidence, clinical expertise, and real life preference.

The options for treatment of such patients include tamoxifen, aromatase inhibitors, exemestane, everolimus, fulvestrant, chemotherapy, and ovarian suppression.

Common factors to be considered while selecting therapy in individual patients include previous therapy, disease-free interval, tumor biology, underlying medical and social issues (age, PS and co-morbidities), patient preferences (convenience vs compliance), risk of toxicities and their implications, menopausal status and presence/absence of visceral crisis or significant visceral metastasis.

This practical consensus recommendation allows for optimal sequencing if the effective therapeutic interventions available today. While both Everolimus Exemestane combination as well as Fulvestrant 500 mg result in better outcome as compared to their control arms, the magnitude of clinical benefit as well as the robustness of currently available data favors the use of the Everolimus Exemestane combination. Benefit to individual patients can be optimized (response as well as quality of life) by paying adequate attention to proactively minimizing toxicity.

Unresolved issues of importance include value of ovarian suppression, systematic segregation of visceral organ involvement (nature, speed, number), identification of co-morbidities of significance.

Table 17: Question 5 (i): Assuming absence of visceral crisis, what is the most appropriate choice of therapy for pre-menopausal patients with newly diagnosed stage IV *de novo* HR +ve/Her2 –ve breast cancer?

Options	Tamoxifen	Tamoxifen plus ovarian suppression	AI or Fulvestrant plus ovarian suppression	Everolimus plus Exemestane plus ovarian suppression	CT
% of polled oncologists	30	55	0	5	10

Expert group consensus: Tamoxifen plus ovarian suppression, HR: Hormone receptor

Table 18: Question 5 (ii): Assuming absence of visceral crisis, what is the most appropriate choice of therapy for pre-menopausal patients who have progressed on Tamoxifen?

Options	AI plus ovarian suppression	Fulvestrant 500 mg plus ovarian suppression	Everolimus plus exemestane plus ovarian suppression	CT
% of polled oncologists	70	10	0	20

Expert group consensus: All the options are reasonable choices, CT: Chemotherapy

Table 19: Question 6: What is the appropriate way of using everolimus for advanced breast cancer in your practice?

Options	Start with dose of 10 mg and de-escalate if toxicity	Start with dose of 5 mg and escalate if no toxicity
% of polled oncologists	70	30

Expert group consensus: Start with dose of 10 mg and de-escalate if toxicity develops

Table 20: Question 7 (i): Do you routinely rebiopsy a breast cancer patient with recurrence?

Options	Yes, for all patients	Yes, only for Her2-negative/ HR-negative patients	Yes, only for Her2-positive,/ HR-positive patients	No, for any patient
% of polled oncologists	60	20	5	15

Expert group consensus: Rebiopsy is recommended in specific circumstances

Table 21: Question 7 (ii): Among patient with Her2-negative and HR-positive breast cancer patients, changes of concern that will significantly impact treatment decision making will include?

Options	From Her2–ve to Her 2+ve	From HR+ve to HR–ve	Both	Neither
% of polled oncologists	45	5	50	0

Expert group consensus: Both, HR: Hormone receptor

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Organizing Chairman : Prof. Raghunadhrao D.,
Organizing Secretary & Program Director : Dr. Senthil Rajappa
27th - 29th June, 2014
Web: www.bestofascoindia.com
Mail: indiabestofasco@gmail.com

31st ICON Conference.
Organizing Secretary : Dr. T. P. Sahoo,
12th - 14th September, 2014
Web: www.iconconferences.com
Mail: 31sticon@gmail.com

9th SFO (SAARC Federation of Oncologists), conference 2014
Organizing Chairman : Dr. Ashok Vaid
Web: www.sfo2014.com
Mail: saarconcology14@gmail.com

Author Help: Reference checking facility

The manuscript system (www.journalonweb.com) allows the authors to check and verify the accuracy and style of references. The tool checks the references with PubMed as per a predefined style. Authors are encouraged to use this facility, before submitting articles to the journal.

- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
  Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. Otolaryngol Head Neck Surg 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.